Independent Role of Conventional Cardiovascular Risk Factors as Predictors of C-Reactive Protein Concentrations in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** We elucidated whether factors that determine systemic inflammation in the general population independently contribute to C-reactive protein (CRP) concentrations in rheumatoid arthritis (RA).
Methods. The association between factors known to be associated with systemic inflammation in the general population (age, sex, lifestyle variables, metabolic syndrome features, and estrogen use) and high sensitivity CRP (hs-CRP) concentrations independent of the Disease Activity Score 28 (DAS28) was determined in 94 patients with RA.
Results. In all patients, the DAS28 ($p < 0.0001$), ever smoking ($p \leq 0.006$), waist circumference ($p = 0.03$), and the homeostasis model assessment of insulin resistance (HOMA-IR; $p = 0.03$) were independently associated with hs-CRP. Although in patients without central obesity (n = 53, 56%), the DAS28 was the only independent predictor of inflammation and contributed 28%–30% to the variability of hs-CRP, in patients with National Cholesterol Education Program (NCEP) defined central obesity (n = 41, 44%), smoking contributed 13%, the HOMA-IR 21%, and the DAS28 21% to the variability of hs-CRP. In centrally obese patients, the standardized regression coefficient for the independent relationship between HOMA-IR and hs-CRP (0.401 ± 0.132) was similar to that for DAS28 and hs-CRP (0.432 ± 0.144); and the HOMA-IR ($p = 0.04$) was associated with hs-CRP independent of waist circumference.
Conclusion. In patients with RA with NCEP-defined central obesity, insulin resistance explains a degree of the variability of CRP concentrations equivalent to that of disease activity. These findings have potential implications for the use of CRP as an RA disease activity marker, and in understanding the reported relationship of CRP with cardiovascular disease in RA. (First Release Jan 31 2007; J Rheumatol 2007;34:681–8)

Key Indexing Terms:
RHEUMATOID ARTHRITIS SMOKING INSULIN RESISTANCE
METABOLIC SYNDROME C-REACTIVE PROTEIN

The markedly increased risk for coronary heart disease (CHD) in patients with rheumatoid arthritis (RA) is well documented[1]. Although traditional risk factors contribute to CHD in RA[2-4], joint-derived cytokine-mediated high-grade systemic inflammation is strongly implicated in the excess CHD experienced by these patients[2-5]. Indeed, in 506 patients with inflammatory polyarthritis recruited from the Norfolk Arthritis Register and followed for 10 years, baseline CRP concentrations (an index of high-grade systemic inflammation) predicted death from cardiovascular disease (CVD) independent of age, sex, smoking status, functional impairment, rheumatoid factor positivity, and swollen joint counts (hazard ratio 3.3, 95% CI 1.4–7.6)[6]. Additionally, an independent association between ultrasonographically determined carotid atherosclerosis and CRP concentrations in RA was reported[7]. Consequently, in RA, CRP, which is generally considered to be induced by circulating interleukin 6 derived from inflamed joints[2,8], is not only frequently used as a disease activity marker[8,9], but also constitutes a promising tool in the assessment of cardiovascular risk[6,7].

In the general population, markers of systemic inflammation also predict cardiovascular events independent of traditional risk factors[10-12]. Adiposity explains a substantial proportion of CRP concentrations in population studies[2,13]. Other metabolic syndrome features including insulin resistance and hypertension, dyslipidemia and hyperglycemia, and age, male sex, cigarette smoking, estrogen use and chronic infections are further associated with inflammation in the general population[10-12,14-17]. However, there are presently no data to indicate to what extent factors that determine inflammation in the general population contribute to CRP concentrations in RA. If

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such factors substantially contribute to CRP concentrations in RA, the use of this inflammatory marker may overestimate disease activity in these patients[8,9]. Moreover, elucidation of the relative contribution of disease activity and other factors as predictors of the degree of inflammation in RA may improve our understanding of the relationship between CRP and CVD[6,7]. In our investigation, we calculated the previously validated composite index, the Disease Activity Score 28 (DAS28), as a measure of disease activity[9]; and using the DAS28 for comparison, determined the extent to which factors known to induce inflammation in the general population are associated with CRP concentrations independent of the DAS28 in 94 patients with RA.

MATERIALS AND METHODS

Patients. Ninety-four consecutive patients that met the American College of Rheumatology criteria for RA were investigated[18]. Demographic characteristics are shown in Table 1; socioeconomic status was not recorded. As a consequence of the historic systemic exploitation of Apartheid in South Africa, only around 1% of RA patients in this clinic (private care) are African[19]. Most patients seen in our setting are Caucasian[19]. In view of this and the fact that ethnic groups show differences in visceral obesity, insulin resistance, and CRP concentrations[20], only Caucasians were included in the current investi-

Table 1. Characteristics in patients with low waist circumference (< 88 cm in women and < 102 cm in men) and in patients with high waist circumference (n = 41). Results are expressed as mean (95% CI) unless indicated otherwise, and compared between patients with low and high waist circumference by Mann-Whitney U test, Fisher's exact test, or chi-squared test.

Characteristic	Low Waist Circumference (n = 53)	High Waist Circumference (n = 41)	p
Age, yrs	55 (51–58)	56 (52–59)	0.8
Women, n (%)	43 (81)	39 (95)	0.04
Disease duration, yrs	5.6 (3.7–8.3)	6.2 (4.1–9.1)	0.9
Lifestyle factors			
Ever smokers, n (%)	16 (30)	18 (44)	0.2
Ex-smokers, n (%)	7 (13)	7 (17)	0.4
Current smokers, n (%)	9 (17)	11 (27)	0.2
Current smoking, cigarettes/day	2 (1–2)	2 (1–3)	0.4
Alcohol, units/wk	2 (1–3)	2 (2–3)	0.3
Alcohol users, n (%)	18 (34)	22 (49)	0.06
Exercise, hours/wk	2.0 (1.6–2.5)	1.1 (1.0–1.3)	0.002
Exercisers, n (%)	24 (45)	4 (10)	0.0001
Rheumatoid factor-positive, n (%)	42 (79)	29 (71)	0.3
Metabolic syndrome features			
Waist circumference, cm	79 (77–81)	99 (96–102)	< 0.0001
BMI, kg/m^2	22.3 (21.6–23.0)	29.8 (28.4–31.1)	< 0.0001
Systolic BP, mm Hg	127 (123–131)	135 (128–142)	0.08
Diastolic BP, mm Hg	81 (78–83)	88 (85–92)	0.001
Hypertension, n (%)	19 (36)	29 (71)	0.001
Triglycerides, mmol/l	1.0 (0.9–1.1)	1.3 (1.1–1.4)	0.02
HDL cholesterol, mmol/l	1.7 (1.5–1.8)	1.4 (1.3–1.6)	0.05
Triglycerides/HDL cholesterol	0.6 (0.6–0.7)	0.9 (0.7–1.2)	0.008
Glucose, mmol/l	4.4 (4.2–4.5)	4.7 (4.5–5.0)	0.0009
HOMA-IR, μU. mmol/ml.l	0.9 (0.8–1.1)	1.9 (1.5–2.4)	< 0.0001
IFG or diabetes, n (%)	3 (6)	5 (12)	0.2
Current estrogen users, n (%)	17 (32)	9 (22)	0.2
Systemic inflammation			
Hs-CRP, mg/l	7.6 (4.3–10.7)	12.0 (8.1–17.4)	0.04
Disease activity			
DAS 28	4.0 (3.4–4.6)	4.7 (4.1–5.4)	0.08
ESR, mm/h	13 (9–18)	19 (14–26)	0.2
Swollen joints, n	4 (3–5)	5 (4–7)	0.1
Tender joints, n	4 (3–6)	6 (4–8)	0.3
VAS patient disease activity, mm	44 (35–52)	54 (43–64)	0.3
Antirheumatic agent use			
Current prednisone users, n (%)	8 (15)	5 (12)	0.5
Current DMARD users, n (%)	35 (66)	20 (49)	0.09

BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; HOMA-IR: homeostasis model for insulin resistance; IFG: impaired fasting glucose; hs-CRP: high sensitivity C-reactive protein; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; VAS: visual analog scale; DMARD: disease modifying antirheumatic drugs.

gation. In our clinic, patients are systemically examined at each consultation and we excluded cases in which symptoms or clinical signs of any infection had been recorded. Since insulin sensitivity and dyslipidemia were assessed as predictors of inflammation, patients taking glucose or lipid-lowering agents were excluded. Included were cases with impaired fasting glucose or type 2 diabetes mellitus treated with dietary intervention only. We also excluded patients with hypothyroidism, since we have previously found an independent association of hypothyroidism with insulin resistance in RA[21]. Patients in whom any intervention had been changed or initiated over the previous month were also excluded. This included the use of parenteral (intraarticular, intramuscular, or/and intravenous) glucocorticoids.

The study was approved by the Ethics Committee for Research on Human Subjects (Medical) of the University of the Witwatersrand.

Outcome characteristic. Routine CRP testing methods often have a lower detection limit of 8 mg/l or more[22]. We previously reported that around 40% of RA patients in our setting have a CRP of 2 to 8 mg/l, a value that was associated with active disease as reflected by physician disease activity scales and swollen joint counts[22]. In the present investigation, systemic inflammation was therefore assessed by high sensitivity CRP (hs-CRP) measurement determined on fasting blood samples taken between 8:00 AM and 10:00 AM and using an immunoturbidimetric assay performed with an Olympus OSR6185 (Olympus Diagnostics, Lismeehan, Ireland). The intraassay and interassay coefficients of variance for CRP were 0.43% and 1.34%, respectively.

Baseline characteristics. The baseline recorded variables included the following: age; sex; disease duration; smoking status (current smokers, ex-smokers, never smokers) and number of cigarettes smoked per day; alcohol intake (average number of units per week over the previous month); exercise (average number of hours per week over the previous month); rheumatoid factor status; metabolic syndrome features; current estrogen use; and disease activity variables[9,10,23,24]. Blood pressure (BP) measurements were made in accord with reported guidelines on the evaluation and treatment of hypertension[25]. Hypertension was diagnosed in patients with BP ≥ 130/85 mm Hg and in those employing antihypertensive agents[26]. In accord with recommendations of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III[26], we diagnosed central obesity in women with a waist circumference ≥ 88 cm and in men with waist circumference ≥ 102 cm. Impaired fasting glucose and diabetes were diagnosed in accord with recent recommendations of the American Diabetes Association[27]. Erythrocyte sedimentation rate (ESR), plasma glucose and serum insulin (Abbott Laboratories, Chicago, IL, USA), and serum high-density lipoprotein (HDL) cholesterol and triglycerides (Olympus Diagnostics) were also determined on fasting blood samples. Insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) using the formula [insulin (μU/ml) × glucose (mmol/l)]/22.5[28]. Disease activity variables consisted of the tender joint count 28, swollen joint count 28, ESR, and patient disease activity measured on a 100 mm visual analog scale (VAS). We calculated the DAS28 using the formula $0.56 \times \sqrt{(\text{tender joint count 28})} + 0.28 \times \sqrt{(\text{swollen joint count 28})} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{VAS}$ patient disease activity[9].

Data analysis. Results are expressed as mean (95% confidence interval) or number (%) unless indicated otherwise. For non-normally distributed data, the geometric means (95% CI) are given and these data were log-transformed prior to entering them in regression models.

Since central obesity is a main determinant of CRP concentrations in the general population, we first compared the recorded variables in patients without central obesity with those recorded in patients with central obesity using the Mann-Whitney U-test (continuous variables) and Fisher's exact test or chi-square test as appropriate (for dichotomous variables). The association of hs-CRP concentrations with central obesity was further assessed in logistic regression models with adjustment for potentially confounding variables. In these models, obesity status (high waist = 1, normal waist = 0) was used as the dependent variable, whereas hs-CRP and potentially confounding variables were entered as independent variables.

The relationships between age, sex, lifestyle factors, metabolic syndrome features, estrogen, disease modifying antirheumatic drug (DMARD) use, prednisone and antihypertensive agent use, and disease activity versus the hs-CRP were determined using simple linear regression analysis or the Mann-Whitney U-test as appropriate. Subsequently, the most explanatory multivariable mixed regression models for hs-CRP were constructed based on the strength of associations in univariate analysis, interactions, and causality. Although age and current prednisone and DMARD use were not associated with hs-CRP in univariate analysis, these variables were forced into each of the models as potential confounders. Separate models were constructed in all patients, in patients without central obesity, and in patients with central obesity in order to discern whether determinants of inflammation differ in patients with abdominal obesity and in those without abdominal obesity. Statistical significance was set at 0.05.

RESULTS

Hs-CRP concentrations, disease activity, and disease remission and drug therapy. The hs-CRP was < 2 mg/l in 11 (12%), 2 to 8 mg/l in 38 (40%), and > 8 mg/l in 45 (48%) patients. In all patients, the mean DAS28 was 4.3 (SD 3.9–4.7, range 0.2–8.9), a value that reflects moderate disease activity[29]. In patients with hs-CRP ≤ 8 mg/l, DAS28 was 3.1 (SD 0.2–6.9, range 0.2–6.7), whereas it was 5.5 (SD 1.4–6.9, range 1.4–8.9) in patients with hs-CRP > 8 mg/l. The hs-CRP was as strongly associated with the DAS28 in patients with hs-CRP ≤ 8 mg/l ($R = 0.44$, $p = 0.003$) as it was in patients with hs-CRP > 8 mg/l ($R = 0.39$, $p = 0.006$). According to recent recommendations, 20 (21%) patients were in remission (DAS28 ≤ 2.4)[29], 16 (36%) of the patients with hs-CRP ≤ 8 mg/l and 4 (8%) patients with hs-CRP > 8 mg/l.

Thirty-one (33%) patients were taking one or more antihypertensive agents, i.e., diuretics (n = 19, 20%), beta-blockers (n = 3, 3%), calcium channel blockers (n = 8, 9%), angiotensin-converting enzyme inhibitors (n = 12, 13%), and angiotensin type II receptor blockers (n = 13, 14%). As 40 (42%) patients were assessed for the first time at our clinic at the time of the study, only 55 (59%) patients were using one or more DMARD. The DMARD comprised methotrexate (n = 47, 50%), chloroquine (n = 23, 25%), minocycline (n = 12, 13%), leflunomide (n = 5, 5%), and azathioprine (n = 5, 5%). No patient was treated with biologic agents at the time of the study. Thirteen (14%) patients were receiving prednisone at the time of the study: the prednisone dose was 1 mg/day in 3, 2 mg/day in 1, 2.5 mg/day in 1, 3 mg/day in 2, 4 mg/day in 1, 5 mg/day in 3, and 10 mg/day in 2 patients.

Characteristics in patients with and without central obesity. The characteristics recorded in patients with and without central obesity are shown in Table 1. Patients with central obesity were more often women, exercised less, were more hypertensive, dyslipidemic and insulin resistant, and had higher fasting plasma glucose and hs-CRP concentrations. The higher hs-CRP in patients with central obesity was not attenuated after adjustment for sex ($p = 0.04$). By contrast, centrally obese patients did not have a higher hs-CRP after controlling for the potentially confounding variables of exercising status ($p = 0.2$), diastolic BP ($p = 0.1$), triglycerides/HDL cholesterol ratios ($p = 0.3$), glucose ($p = 0.2$) or HOMA-IR ($p = 0.06$).

Factors correlated with hs-CRP. The log hs-CRP and log ESR were strongly correlated with each other (R = 0.68, p < 0.0001). Hs-CRP concentrations were associated with ever smoking [mean 17.7 mg/l (95% CI 11.3–27.8) in ever smokers (n = 34) and 5.8 mg/l (3.9–9.6) in never smokers (n = 60; p = 0.0007)], current smoking status [17.2 mg/l (8.9–33.2) in current smokers (n = 20) and 7.2 mg/l (5.1–10.1) in current nonsmoking patients (n = 74; p = 0.04)], and impaired fasting glucose or diabetes [25.7 mg/l (9.6–68.9) in patients with impaired fasting glucose or diabetes (n = 8) and 7.8 mg/l (5.7–10.7) in patients without impaired fasting glucose or diabetes (n = 86; p = 0.02)]. Log hs-CRP was also associated with waist circumference (R = 0.32, p = 0.0005), body mass index (BMI; R = 0.23, p = 0.02), log triglyceride/HDL cholesterol ratios (R = 0.32, p = 0.0005), log HOMA-IR (R = 0.30, p = 0.004), and the DAS28 (R = 0.60, p < 0.0001). Hs-CRP was not associated with age (p = 0.09), sex (p = 0.4), alcohol intake (p = 0.3), exercise (p = 0.06), current estrogen use (p = 0.2), systolic BP (p = 0.08), glucose (p = 0.07), diastolic BP (p = 0.2), current prednisone use (p = 0.1), current DMARD use (p = 0.08), and current use of antihypertensive agents (p = 0.1).

Independent determinants of hs-CRP in all patients. The metabolic syndrome features of waist circumference, log triglyceride/HDL cholesterol ratios, and log HOMA-IR were strongly interrelated (R = 0.46 to 0.67, p < 0.0001). Contributions of these variables to hs-CRP were therefore assessed in separate regression models. In multivariable regression models, DAS28, waist circumference, and the HOMA-IR were independent predictors of hs-CRP (Table 2, models 1 and 2). The regression coefficient in multivariable regression models reflects the average amount that the dependent variable increases when the independent variable increases by 1 unit and other dependents are held constant. In all patients, the DAS28 explained 28% to 30%, smoking 8% to 10%, waist circumference 6%, and the HOMA-IR 5% of the variability of hs-CRP (see partial R^2 in Table 2, models 1 and 2). Triglyceride/HDL cholesterol ratios were not independently associated with hs-CRP (data not shown).

Independent determinants of hs-CRP in patients without central obesity. In patients without central obesity, the DAS28 was the only independent predictor of hs-CRP, which explained 27% of its variability (Table 2, model 3). Waist circumference and triglyceride/HDL cholesterol ratios were not independently associated with hs-CRP (data not shown).

Independent determinants of hs-CRP in patients with central obesity. In patients with central obesity, the DAS28 explained 21%, the HOMA-IR 21%, and smoking 13% of the variability of hs-CRP (Table 2, model 4). Waist circumference and triglyceride/HDL cholesterol ratios were not independently associated with hs-CRP (data not shown).

After additional adjustment for waist circumference in model 4 of Table 2, the log HOMA remained associated with hs-CRP (ß ± SE = 0.616 ± 0.283, p = 0.04).

Further adjustment for the use of antihypertensive agents in each of the models in Table 2 did not materially alter the results.

There was an interaction between the log HOMA-IR and the DAS28 in patients with central obesity (R = 0.32, p = 0.04).

Size effects of determinants of hs-CRP in patients with central obesity. We further quantified the size effects of increases in DAS28 and HOMA-IR on hs-CRP concentrations in patients with central obesity. After adjustment for covariates (age, ever smoking, HOMA-IR, current prednisone use, current

Table 2. Mixed regression models for high-sensitivity C-reactive protein (log transformed). The first 2 models were constructed using data obtained from all patients, with waist circumference and HOMA-IR being entered in separate models (model 1 and model 2, respectively) in view of the collinearity between these 2 characteristics. Model 3 was constructed using data obtained in patients with low and model 4 in patients with high waist circumference. Waist circumference was not included in models 3 and 4.

	All Patients						Patients with Low Waist Circumference			Patients with High Waist Circumference		
	Model 1			Model 2			Model 3			Model 4		
	ß ± SE	p	R^2 of Model	ß ± SE	p	R^2 of Model	ß ± SE	p	R^2 of Model	ß ± SE	p	R^2 of Model
Age	0.005 ± 0.005	0.3	0.01	0.006 ± 0.005	0.2	0.02	0.008 ± 0.007	0.3	0.03	0.002 ± 0.007	0.8	0.00
Ever smoking	0.301 ± 0.106	0.006	0.08	0.336 ± 0.106	0.002	0.10	0.305 ± 0.188	0.1	0.05	0.294 ± 0.132	0.03	0.13
DAS	0.169 ± 0.028	< 0.0001	0.30	0.162 ± 0.028	< 0.0001	0.28	0.189 ± 0.046	0.0002	0.27	0.110 ± 0.037	0.005	0.21
Waist circumference	0.009 ± 0.004	0.03	0.06									
HOMA-IR*				0.351 ± 0.161	0.03	0.05	0.088 ± 0.332	0.8	0.00	0.628 ± 0.207	0.005	0.21
Current prednisone use	0.220 ± 0.144	0.1	0.03	0.211 ± 0.145	0.2	0.02	0.285 ± 0.210	0.2	0.04	0.092 ± 0.202	0.7	0.01
Current DMARD use	0.104 ± 0.114	0.4	0.01	0.076 ± 0.115	0.5	0.01	0.105 ± 0.186	0.6	0.01	0.045 ± 0.143	0.8	0.00

ß ± SE: regression coefficient ± standard error; R^2: squared partial correlation coefficient. For other abbreviations, see Table 1. * Log-transformed.

DMARD use), an increase in DAS28 of 2.1 (roughly 1 SD) was associated with an increase in hs-CRP of 1.2 mg/l (95% CI 0.6 to 2.0) (p = 0.005). By comparison, an increase in HOMA-IR of 2.2 μU.mmol/ml.l (roughly 1 SD) was independently associated with an increase in hs-CRP of 2.6 mg/l (95% CI 0.6 to 4.1) (p = 0.005).

We further tested for potential effect modifications between the independent variables in all patients (Table 2, model 2) by including a low waist × prednisone and an ever-smoking × HOMA-IR (each variable was standardized) as additional independent variables in separate models. No effect modifications could be identified (p > 0.4).

Relative contribution of disease activity and insulin resistance to hs-CRP in all patients, in patients with low waist, and in patients with high waist circumference (Figure 1). Figure 1 shows the standardized regression coefficients (SE) between the DAS28 and HOMA-IR versus hs-CRP after adjustment for covariates (see Table 2, models 2 to 4). The SE reflects the average amount that the dependent variable increases when the independent variable increases by 1 SD and other dependent variables are held constant. For example, the SE for the DAS in all patients was 0.52 in Figure 1, indicating that a 1 SD increase in DAS increased the hs-CRP by 0.52 × 1 SD of hs-CRP. The HOMA-IR contributed more to hs-CRP in patients with high waist circumference compared to those with low circumference (p = 0.03, unpaired Student t test). In all patients and in patients with low circumference, the DAS28 contributed more to the hs-CRP than did the HOMA-IR (p = 0.004 and p = 0.003, respectively). By contrast, the contributions of the DAS28 and HOMA-IR to hs-CRP were equivalent in patients with high waist circumference.

We verified the statistical assumptions for the multivariable regression models that were constructed in this study. Residuals for each model were normally distributed (Shapiro-Wilk W = 0.974 to 0.986, p = 0.3 to 0.5).

DISCUSSION

In our investigation in patients with RA, we found that current or ever smoking, waist circumference, and HOMA-IR were associated with hs-CRP concentrations independent of disease activity as assessed by the DAS28. Importantly, in patients with central obesity, despite the presence of moderately active disease, the HOMA-IR and DAS28 accounted for an equivalent proportion of the variability (21%) of CRP. We found that in patients with central obesity, a 1 SD increase in HOMA-IR was associated with a numerically larger increment in CRP (2.6 mg/l) than the increment in CRP (1.2 mg/l) that was associated with a 1 SD increase in DAS28. These results indicate that if target values for CRP that confirm control of RA disease activity are to be determined, such values should be substantially different in patients with abdominal obesity compared to patients without abdominal obesity. Further, smoking made an additional contribution of 13% to the variability of CRP in patients with central obesity.

In clinical practice, measures of acute-phase reactants may add little information to a disease activity score that includes purely clinical variables (tender and swollen joint count and patient and physician global assessments)[30]. However, meas-

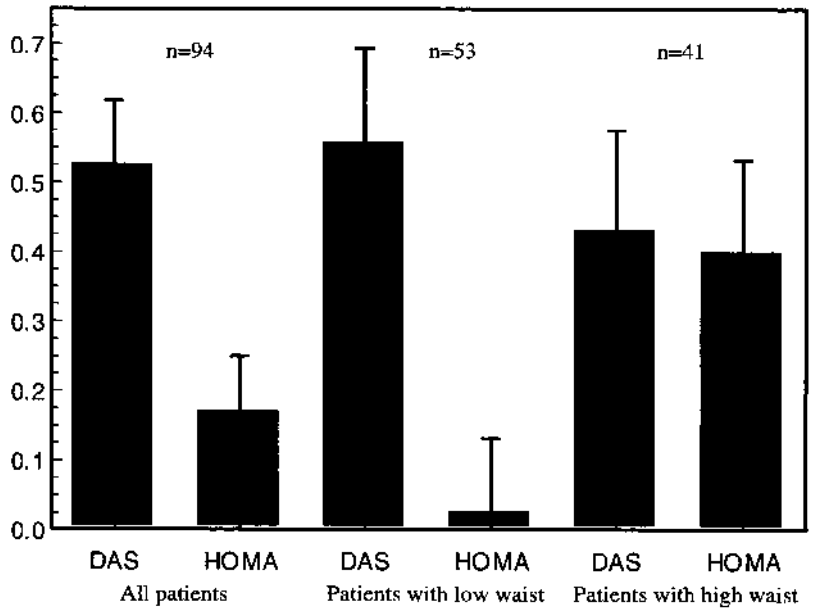

Figure 1. Standardized regression coefficients (SE) between disease activity and insulin resistance versus high sensitivity CRP in all patients and in patients with low and high waist circumference. These were adjusted for the covariates age, ever smoking, current prednisone use, and current DMARD use (see Table 2, models 2, 3, and 4). DAS: Disease Activity Score; HOMA: homeostasis model assessment.

ures of acute-phase reactants generally form part of disease activity assessment in research settings. We found a strong association of the DAS28 with CRP in patients with an hs-CRP ≤ 8 mg/l, a value that is often below the detection limit of routine CRP testing methods[22]. Importantly, in our cohort, the majority of patients (64%) were not in remission according to recent recommendations[29]. Moreover, others have demonstrated that baseline CRP concentrations can predict radiographically documented joint damage for as long as 10 years in RA[31]. Therefore, whether hs-CRP testing outperforms routine CRP testing in clinical trials on disease activity control warrants further study.

The DAS28 explained only about 30% of the variation in CRP in our cohort. This may not be surprising, since the DAS28 is a composite score that includes subjective measures and the ESR, another acute-phase reactant that is highly correlated with CRP. Also, the DAS28 may not fully capture all facets of RA disease activity. However, similar or even weaker associations between single disease activity variables or composite disease activity scores and acute-phase reactants were previously reported in RA[8,22,30].

With respect to the influence of factors that determine CRP concentrations in the general population, waist circumference has been found to explain 10%–20% of the variability in CRP in univariate analysis[13,32], compared to 9% (6% in multivariable analysis) in patients with RA in our study. The contribution of HOMA-IR to the variability of CRP in the general population was reported to be 5% in univariate analysis in a population study[16], whereas it was 9% (5% in multivariable analysis) in patients with RA in our study. Smoking was found to be associated with a 2- to 3-fold increase in CRP concentrations in subjects who did not have RA[17]. In our cohort, CRP values were 3 times higher in smokers compared to nonsmokers with RA. The association between cardiovascular risk factors and CRP in RA suggests that adjustment for these characteristics should not be indicated when using CRP as a marker of cardiovascular risk in RA, even in patients with central obesity.

In all patients, we could account for not more than about 50% of the variability of CRP. This is not unexpected, as the characteristics that account for all the variability in CRP concentrations in the general population are also not fully known at present[11]. Of likely importance in this context, subclinical infections (e.g., periodontal disease) contribute to CRP concentrations both in the general population[11] and in RA[33].

We found waist circumference was more strongly associated with CRP than the BMI. A low BMI is paradoxically associated with increased cardiovascular and total mortality in RA[34,35]. These findings are not unique to RA — in the Interheart study (a case-control study of myocardial infarction with 12,461 cases and 14,637 controls from 52 countries), measures of abdominal obesity (waist circumference and waist-to-hip ratio) were independently associated with myocardial infarction, whereas BMI was not[36]. Moreover, the association between waist-to-hip ratio and myocardial infarction was present even in subjects with a low BMI[36].

Insulin resistance is a common feature of RA. Excess adiposity, disease activity, glucocorticoid therapy, and hypothyroidism are thought to contribute to insulin resistance in RA[2,19,37-40]. Disease activity suppression markedly improves insulin resistance in RA[38,39]. Our study was cross-sectional and therefore did not allow for inferences to be drawn about causality between recorded baseline variables and the degree of inflammation. However, we excluded hypothyroid patients, and in patients with NCEP-defined abdominal obesity, the HOMA-IR remained associated with hs-CRP even after adjustment for waist circumference, DAS28, and glucocorticoid therapy. In support of the notion that insulin resistance determines the degree of inflammation, in a controlled study of 38 obese women without RA, calorie restriction resulted in reductions in CRP that were independently predicted by decreased insulin resistance but not by the extent of weight loss[41]. Also, the insulin-sensitizing agents metformin and troglitazone can decrease CRP concentrations in the absence of weight loss[42]. We found a positive interaction between the HOMA-IR and the DAS28 in patients with abdominal obesity, indicating that these factors act synergistically to increase the inflammatory burden in such patients. Our current findings together with previous reports suggest that RA patients with pronounced abdominal adiposity may experience mutually reinforcing interactions between insulin resistance and inflammation.

Smoking increases the production of inflammatory mediators including prostaglandin F2-alpha, interleukin 6, and F2-isoprotane[43]. In our cohort, the presence of abdominal obesity enhanced the association of smoking with inflammation. Also, our finding of an independent association of smoking with inflammation adds to previous reports on the adverse effects of smoking in RA[44-46].

Our study has potential limitations. Longitudinal investigations are needed to confirm a role of smoking cessation, weight management, and other measures aimed at reducing insulin resistance (e.g., exercise and use of insulin-sensitizing agents) in attenuating systemic inflammation and CVD in RA. Whether hs-CRP testing is superior to routine CRP evaluation in predicting CVD in RA also awaits confirmation. We did not perform a power analysis before initiating this study and investigated only 94 patients with RA. Our study may therefore have been underpowered to identify an association of some of the baseline recorded variables with inflammation. However, of those variables that were significantly associated with hs-CRP in univariate analysis, only the triglyceride/HDL cholesterol ratio was not associated with hs-CRP in mixed regression models. In order to obtain results that apply to the RA population at large, we did not exclude patients taking angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, beta-blockers, and diuretics, agents that have the potential to affect insulin sensitivity[48-50]. When we

adjusted for the use of antihypertensive agents in multivariable analyses, our outcomes were not altered. Our findings may still not be generalizable to the RA community at large, since 45% of patients were not taking DMARD, prednisone use was uncommon, and all patients were Caucasian. We did, however, control for the use of DMARD and prednisone in multivariable analysis.

We have shown that ever smoking, waist circumference, and insulin resistance were associated with CRP concentrations independent of the DAS28 in 94 patients with RA. In the 41 (44%) patients with NCEP-defined central obesity, insulin resistance explained an equivalent degree of the variability in CRP concentrations as did disease activity. These findings have potential implications in the use of CRP as an RA disease activity marker and in the understanding of the relationship of CRP with cardiovascular disease in RA.

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