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Objective—Insulin resistance is associated with chronic subclinical inflammation, and both conditions are linked with increased risk for type 2 diabetes mellitus and atherothrombotic cardiovascular disease.

Methods and Results—In a cross-sectional study conducted among participants in the Women's Health Study, an ongoing US primary prevention trial of cardiovascular disease and cancer, we evaluated the correlates of elevated fasting insulin, a marker of insulin resistance, among 349 healthy, nondiabetic women who remained free from clinically diagnosed type 2 diabetes mellitus during a 4-year period from biomarker assessment. Fasting insulin was strongly associated with body mass index (BMI) ($r=0.53$, $P<0.001$), C-reactive protein (CRP) ($r=0.38$, $P<0.001$), and interleukin-6 ($r=0.33$, $P<0.001$). Physical activity level, alcohol consumption, and use of hormone replacement therapy were also related to fasting insulin. However, in multivariable linear regression analysis, BMI and CRP were the only independent correlates of log-normalized fasting insulin. Overall, the final model explained 32% of the variance in log insulin level. In multivariable logistic regression, the fully adjusted odds ratio (OR) for elevated fasting insulin (≥51.6 pmol/L) increased with tertile of BMI, CRP, and IL-6, such that the ORs in the highest versus lowest tertile of each parameter were 9.0 (95% confidence interval [CI], 4.4 to 18.7), 4.4 (95% CI, 1.9 to 10.1), and 2.0 (95% CI, 0.9 to 4.2), respectively. Furthermore, increasing levels of CRP were associated with a stepwise gradient in odds for elevated fasting insulin among both lean and overweight women.

Conclusions—CRP is independently associated with fasting hyperinsulinemia in nondiabetic women. These data provide additional support for previously reported associations between subclinical inflammation and the risk of type 2 diabetes and cardiovascular disease. **(*Arterioscler Thromb Vasc Biol*. 2003;23:650-655.)**

Key Words: fasting insulin ■ C-reactive protein ■ women

Although insulin resistance is a common antecedent of impaired glucose tolerance and type 2 diabetes and has more recently been linked with the development of cardiovascular disease, the underlying biologic mechanisms remain incompletely understood. C-reactive protein (CRP) is an acute-phase reactant and a sensitive marker of subclinical inflammation. Elevated levels of CRP are known to predict the development of type 2 diabetes[1–5] and cardiovascular disease[6–10] in otherwise healthy populations. Interleukin-6 (IL-6) is a major proinflammatory cytokine and primary determinant of hepatic CRP production. Experimental studies have shown that ≈25% to 30% of circulating IL-6 originates in subcutaneous adipose tissue.[11] In addition, cells deriving from omental as opposed to subcutaneous fat have been shown to secrete 2 to 3 times more IL-6 in vitro,[12] and abdominal adiposity is strongly linked to insulin resistance.[13] These findings suggest that upregulation of the inflammatory response might be an early event in the development of insulin resistance.

We, and others, have previously reported prospective associations between baseline elevations of CRP and IL-6 and the subsequent development of clinically overt type 2 diabetes.[1–5] Among nondiabetic subjects, fasting insulin levels are moderately well correlated with more direct measures of insulin resistance.[14,15] To further examine the relation between inflammation and incipient glucose metabolic disorders, we evaluated the association between CRP, IL-6, and fasting insulin in a cross-sectional study of apparently healthy nondiabetic women.

Methods

Study Population

The Women's Health Study (WHS)[16] is an ongoing, randomized, clinical trial initiated in 1992 to evaluate the role of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer among female health professionals aged 45 years and older. Among participants in this trial, 27 628 individuals (69% of the WHS cohort) were also free of diagnosed diabetes and provided

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Drs Ridker and Manson are listed as coinvestigators on patents filed by the Brigham and Women's Hospital that related to inflammatory markers in vascular disease and diabetes mellitus.

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whole-blood samples at enrollment. These samples were centrifuged and then stored in liquid nitrogen (−80°C) until the time of laboratory analysis. Plasma samples collected in EDTA were used for CRP, IL-6, and insulin determination. Packed red blood cells were used for measurement of hemoglobin A1c (HbA1c).

The study population comprised nondiabetic controls involved in a previous case-control study of incident type 2 diabetes.[1] Controls were age- and fasting-matched with cases in that prospective analysis but otherwise randomly selected from the cohort. Among 576 women remaining free of type 2 diabetes during follow-up, 400 provided fasting blood specimens. Fasting was defined as 10 hours or longer since the last meal before specimen collection. Because insulin levels might be falsely lowered in the presence of hemolysis,[17] we excluded women with blood specimens showing evidence of significant hemolysis, defined as free hemoglobin levels >50 mg/dL (n=37). In addition, we excluded participants with missing values for baseline clinical characteristics of main interest (n=13). One subject with a HbA1c level >6.5% was excluded owing to possible undiagnosed diabetes mellitus at baseline. Our study population thereby comprised 349 healthy, nondiabetic, middle-aged women who remained diabetes-free during a period of 4 years subsequent to assessment of baseline clinical and biochemical parameters.

Exposure Variables

Clinical exposure variables were determined from participant responses to mailed questionnaires at enrollment into the WHS. Body-mass index was calculated as the self-reported weight in kilograms divided by the square of self-reported height in meters (kg/m^2). In secondary analyses, waist-to-hip ratio (WHR) and waist circumference were used as alternate indexes of adiposity. These measurements were available for 79.1% of the population from responses on the 72-month follow-up questionnaire. The average absolute percent change in weight from baseline to WHR ascertainment was 7.4%. A positive family history of diabetes was determined by self-report of diabetes mellitus in a first-degree relative. Smoking status (nonsmoker, former smoker, or current smoker) was classified according to lifetime smoking of at least 100 cigarettes. Frequency of regular strenuous (aerobic) physical activity was categorized as rarely/never, less than once per week, 1 to 3 times per week, or 4 or more times per week. Alcohol consumption was categorized as rarely/never, monthly, weekly, or daily from reported alcoholic beverage consumption within the year before enrollment. Postmenopausal status was identified as premenopausal, postmenopausal, or perimenopausal/unknown according to history of natural cessation of menses or surgical menopause. Hormone replacement therapy (HRT) status was classified as never, past, or current use of unopposed estrogen or estrogen plus progestin from pills, patches, or vaginal preparations.

Laboratory Procedures

Baseline plasma samples were thawed and assayed for specific insulin, CRP, and IL-6 levels. Double antibody systems (Linco Research) with <0.2% cross-reactivity between insulin and its precursors were used to quantify concentrations of plasma insulin. CRP, IL-6, free plasma hemoglobin, and HbA1c were measured as previously described.[1] Blinded quality-control specimens were analyzed simultaneously with the study samples. The coefficients of variation for insulin, CRP, and IL-6 were 14.7%, 12.0%, and 12.7%, respectively.

Statistical Analysis

We used the *t* test for 2-group comparisons and ANOVA for comparisons between >2 groups to assess for difference in fasting insulin among participants with and without diabetes risk factors. Because the distribution of fasting insulin is skewed, this variable was natural log–transformed to meet normality assumptions of parametric tests of group means. Spearman correlation coefficients were calculated for fasting insulin and other continuous covariates.

Linear regression models were constructed with natural log (ln) fasting insulin as the dependent variable and clinical and biochemical risk factors for diabetes as independent variables. To improve symmetry and comparability of per-unit-effect estimates, BMI, CRP, and IL-6 were transformed to the ln scale, and effect estimates are presented in SD units. To assess for nonlinear relations between BMI, CRP, and IL-6 with fasting insulin, we first modeled these parameters using regression spline functions and tested for nonlinearity by ANOVA methods in SPLUS. Because we found no evidence for nonlinearity, subsequent models incorporated simple linear parameterization of these ln-transformed covariates. The final fitted linear regression model was constructed by using a stepwise regression algorithm with an entry probability value criterion of 0.20 and stay criterion of 0.05 for identifying independent correlates of fasting insulin levels. In secondary analyses confined to individuals providing waist and hip measurements (n=276), waist circumference and WHR were added to the final models to assess for residual confounding by alternate indexes of obesity. Linear regression lines were plotted for BMI and CRP against fasting insulin levels. Axes are labeled on the linear scale for ease of interpretation of graphs.

Because insulin resistance is a central component of the metabolic syndrome and to examine whether the relation between inflammatory biomarkers and fasting insulin is limited to individuals with the metabolic syndrome who might be considered at high risk for subsequent diabetes, we duplicated our analysis in the subgroup of women *without* clinical evidence of the metabolic syndrome. As previously defined in this cohort,[18] subjects with 3 or more of the following attributes were defined as having the metabolic syndrome: obesity (BMI>26.7 kg/m^2), hypertriglyceridemia (triglycerides≥150 mg/dL), low HDL cholesterol (<50 mg/dL), high blood pressure (≥130/85), and abnormal glucose metabolism (diagnosed diabetes). Stepwise linear regression (probability value criterion of 0.20 and stay criterion of 0.05) was used to evaluate the independent contributions of all clinical and biochemical variables of interest.

The odds ratios (ORs) for elevated fasting insulin according to tertiles of BMI, CRP, and IL-6 were estimated by logistic regression models adjusted for other clinical risk factors and each other. Elevated fasting insulin was defined by a value greater than the upper tertile cutpoint for the study population, ≥51.6 pmol/L. Ordinal variables corresponding to tertiles of BMI, CRP, and IL-6 were used in regression models to assess for linear trends. To evaluate multiplicative effects of BMI and CRP, we divided the study population into 6 groups based on the upper tertile cutpoint for BMI (>26.7 kg/m^2) and all 3 tertiles of CRP. Subgroup-specific ORs were estimated from logistic regression models simultaneously controlling for clinical covariates.

Results

Characteristics of the study population are presented in Table 1. Subjects had a mean BMI similar to the average for comparably aged women in the US population.[19] The median fasting insulin level was similar to levels anticipated for an unselected sample of healthy, predominantly white, middle-aged, nondiabetic women.[20] However, within this group, we found statistically significant differences in geometric mean fasting insulin among subjects with and without several putative diabetes risk factors (Table 2). Specifically, higher insulin levels were associated with increased BMI, lower frequency of exercise, lower alcohol consumption, noncurrent HRT, and higher CRP and IL-6 levels. Spearman correlation coefficients for fasting insulin with BMI, CRP, and IL-6 were 0.53, 0.38, and 0.33, respectively (all $P<0.001$).

In multivariable linear regression models, although exercise frequency and HRT use were significant determinants of ln fasting insulin in age-adjusted analysis, these associations were attenuated and nonstatistically significant after adjustment for BMI. Although IL-6 levels remained significantly associated

TABLE 1. Clinical and Biochemical Characteristics of the Study Population

No. of subjects	349
Age, y, mean (SD)	55.3 (7.1)
BMI, kg/m^2, mean (SD)	25.7 (4.9)
Race, n (%)	
White	326 (93.4)
Nonwhite/unknown	23 (6.6)
Family history of diabetes mellitus, n (%)	94 (26.9)
Smoking status, n (%)	
Nonsmoker	186 (53.3)
Former smoker	119 (34.1)
Current smoker	44 (12.6)
Frequency of exercise,* n (%)	
Rarely or never	131 (37.5)
<1 time/wk	60 (17.2)
1–3 times/wk	114 (32.7)
>4 times/wk	44 (12.6)
Frequency of alcohol consumption,† n	
Rarely or never	145 (41.6)
Monthly	48 (13.8)
Weekly	117 (33.5)
Daily	39 (11.2)
Postmenopausal status, n (%)	
Premenopausal	82 (23.5)
Postmenopausal	211 (60.5)
Perimenopausal/unknown	56 (16.1)
Use of hormone replacement therapy,‡ n (%)	
Never	63 (29.9)
Past only	27 (12.8)
Current	121 (57.4)
Fasting insulin, pmol/L, median (IQR)	39.9 (28.8–58.9)
C-reactive protein, mg/dL, median (IQR)	0.25 (0.09–0.60)
Interleukin-6, pg/mL, median (IQR)	1.38 (0.90–2.11)
Hemoglobin A1c, %, median (IQR)	5.5 (5.3–5.7)

*Frequency per week of strenuous (aerobic) physical activity.

†Frequency of alcoholic beverage consumption within the year prior to enrollment.

‡Among postmenopausal women.

with fasting insulin in models adjusting for BMI, the association of fasting insulin with CRP was more pronounced. Indeed, in final prediction models (Table 3), ln-normalized BMI and CRP were the only factors independently associated with fasting insulin. A 1-SD unit increase in ln BMI and ln CRP was associated with a 0.26 ($P<0.001$) and 0.09 ($P=0.001$) unit increase, respectively, in ln fasting insulin. Overall, this model explained 32% of the variability in insulin levels. In the subgroup of participants for whom WHR and waist circumference were available (n=276), control for these alternate indexes of adiposity did not alter the observed risk associations (β per SD unit ln CRP=0.10, $P=0.001$). Figure 1 A and 1B show estimated linear regression lines and confidence bands for ln-normalized BMI and CRP against ln-normalized fasting insulin.

TABLE 2. Association Between Geometric Mean Fasting Insulin Levels and Clinical and Biochemical Characteristics Among Nondiabetic Women

Characteristic	Geometric Mean Fasting Insulin Level, pmol/L	Standard Error	*P* Value
Age			0.36
≥55 years	41.0	1.9	
<55 years	43.2	2.2	
BMI tertile			<0.001
1: <23.1 kg/m^2	32.2	1.5	
2: 23.1–26.7 kg/m^2	39.4	2.0	
3: >26.7 kg/m^2	59.0	3.2	
Ethnicity			0.92
White	41.7	1.5	
Nonwhite/unknown	42.1	5.9	
Family history of diabetes			0.67
Yes	41.2	2.7	
No/Unknown	42.4	1.7	
Smoking status			0.20
Nonsmoker	44.1	2.3	
Former smoker	39.4	2.3	
Current smoker	41.3	3.8	
Frequency of exercise			0.001
Rarely or never	47.1	2.8	
<1 time/wk	41.9	3.1	
1–3 times/wk	40.0	2.4	
>4 times/wk	34.6	3.1	
Frequency of alcohol consumption			0.04
Rarely or never	45.8	2.6	
Monthly	38.6	3.4	
Weekly	40.1	2.3	
Daily	39.4	3.9	
Postmenopausal status			0.76
Premenopausal	41.9	3.1	
Postmenopausal	41.6	1.8	
Perimenopausal/unknown	44.2	3.7	
HRT use†			0.02
Never	45.1	3.7	
Past only	50.5	6.1	
Current	38.2	2.1	
CRP tertile			<0.001
1: <0.14 mg/dL	32.7	1.7	
2: 0.14–0.44 mg/dL	41.4	2.2	
3: >0.44 mg/dL	54.7	3.1	
IL-6 tertile			<0.001
1: <1.05 pg/mL	34.5	1.9	
2: 1.05–1.75 pg/mL	40.5	2.2	
3: >1.75 pg/mL	53.2	3.1	

BMI indicates body mass index; HRT, hormone replacement therapy; CRP, C-reactive protein; IL-6, interleukin-6.

TABLE 3. Multiple Linear Regression Analysis With Ln (Insulin) as the Dependent Variable

	Total Study Population				Women Without Metabolic Syndrome			
Independent Variables	β	SE (β)	*P* Value	Partial R^2, (%)	β	SE (β)	*P* Value	Partial R^2, (%)
Ln BMI, per SD unit	0.26	0.03	<0.001	29.5	0.19	0.04	<0.001	14.2
Ln CRP, per SD unit	0.09	0.03	0.001	2.1	0.07	0.03	0.02	1.8

A final predictive model was derived by stepwise linear regression analysis. After age was forced into the model, the following candidate independent variables were assessed: body-mass index (BMI), ethnicity, family history of diabetes, smoking status, physical activity, alcohol consumption, menopausal status, use of hormone replacement therapy, C-reactive protein (CRP), and interleukin-6 (IL-6). BMI, CRP, and IL-6 were transformed to the natural log scale in order to improve symmetry and comparability of effect estimates. Only those variables with a *P* value of <0.05 were included in the final fitted model. β indicates linear regression coefficient; Ln, natural logarithm; SE, standard error. The model R^2 for the total population was 31.9% and for women without the metabolic syndrome was 16.1%.

Insulin resistance is a major feature of the metabolic syndrome. To determine whether the association between CRP and fasting insulin is limited to individuals with this clinical syndrome who are at high risk for imminent progression to type 2 diabetes, we duplicated our multivariate linear regression analysis among women without the metabolic syndrome at baseline. In this subgroup (n=270), as among all subjects, BMI and CRP remained the only statistically significant independent factors associated with fasting insulin (Table 3).

In analyses evaluating categories of risk as specified by tertiles of BMI, CRP, and IL-6, we found a consistent graded response (Table 4). The fully adjusted OR for elevated insulin, defined as the highest tertile for the population, was 1.0, 1.6, and 9.0 for increasing tertiles of BMI (*P* trend=0.001); 1.0, 3.7, and 4.4 for increasing tertiles of CRP (*P* trend <0.001); and 1.0, 1.4, and 2.0 for increasing tertiles of IL-6 (*P* trend=0.08). To assess for a potential joint role of BMI and CRP as determinants of fasting insulin, we divided the study sample into 6 groups based on low and high BMI, characterized by the upper tertile cutpoint for the population, and CRP tertiles (Figure 2). In both BMI strata, increasing levels of CRP were associated with increasing odds for elevated fasting insulin. In particular, among individuals with a BMI >26.7 kg/m^2, elevated CRP discriminated between individuals having a low OR for hyperinsulinemia from those with 4- to 6-fold relative odds.

Discussion

In this cross-sectional study of the association between markers of systemic inflammation and fasting insulin level among nondiabetic women, we observed an independent association between elevated levels of CRP and relative hyperinsulinemia. The relation between both BMI and CRP with insulin appeared to be linear on the ln scale and undiminished by adjustment for other clinical risk factors for type 2 diabetes. Although we found similar associations for IL-6, the magnitude was weaker and not statistically significant after adjustment for CRP. In the subgroup of women without metabolic syndrome, CRP remained independently associated with insulin levels. A stepwise gradient in odds for elevated fasting insulin was noted across tertiles of both BMI and CRP. Furthermore, the increase in odds for elevated insulin corresponded with increasing CRP within both low- and high-BMI strata.

The current findings confirm previous reports of an association between CRP and insulin resistance and are in accord with prior hypotheses suggesting that an acute-phase response might be an important contributor to the development of glucose tolerance disorders.[21] In an earlier prospective nested case-control analysis of the WHS cohort, we have shown that increased levels of CRP and IL-6 predict the subsequent development of type 2 diabetes.[1] Elevated CRP (>0.61 mg/dL) remained strongly associated with a 4-fold increase in diabetes risk after controlling for BMI, fasting insulin, and HbA1c. A subsequent report from the Cardiovascular Health Study[2] found similar associations in elderly individuals with normal glucose tolerance at baseline. Among several markers of systemic inflammation, CRP was the only independent predictor of risk for type 2 diabetes (OR in the highest vs lowest quartile, 2.03, 95% confidence interval, 1.44 to 2.86). Similarly, nondiabetic men in the West of Scotland Coronary Prevention Study[4] having a CRP level >0.42 mg/dL had a 3-fold increase in 5-year risk of diabetes. However, in the Insulin Resistance Atherosclerosis Study[3] and MONICA Augsburg Cohort Study,[5] the risk associated with elevated CRP was not statistically significant in models adjusting for BMI or waist circumference. Indeed, in the majority of clinical studies evaluating this hypothesis, the observed risk relations are

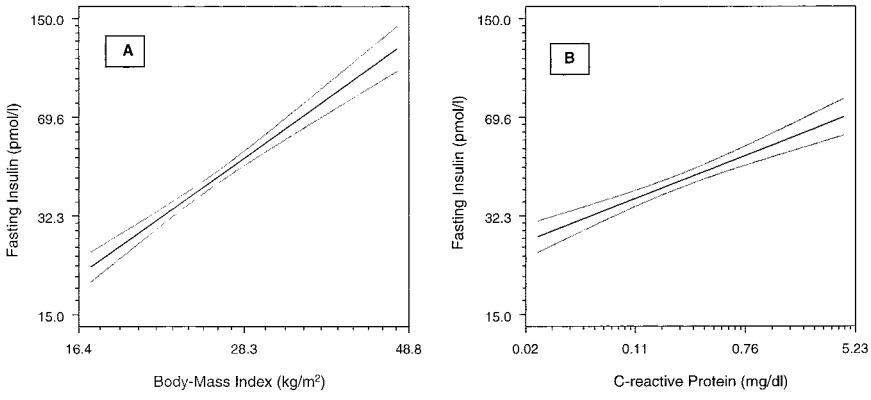

Figure 1. Linear regression lines and confidence bands for (a) ln-normalized BMI and (b) ln-normalized CRP against ln-normalized fasting insulin.

TABLE 4. Multivariable Adjusted Odds Ratio* for Elevated Fasting Insulin† According to Body Mass Index and Inflammatory Markers

	Tertile of Risk Factor			
Risk Factor	1	2	3	*P* Trend
Body mass index				
Odds ratio	1.0	1.6	9.0	0.001
Confidence interval		(0.8–3.5)	(4.4–18.7)	
P value		0.2	<0.001	
C-reactive protein				
Odds ratio	1.0	3.7	4.4	<0.001
Confidence interval		(1.7–8.1)	(1.9–10.1)	
P value		0.001	0.001	
Interleukin-6				
Odds ratio	1.0	1.4	2.0	0.08
Confidence interval		(0.7–2.8)	(0.9–4.2)	
P value		0.4	0.08	

*Adjusted for all risk factors in Table 1 and each other.

†Elevated fasting insulin is defined by a level greater than the upper tertile for the population, >51.6 pmol/L.

attenuated after adjustment for obesity. This finding concurs with experimental observations that adipocyte activation and release of IL-6,[11,12] tumor necrosis factor-α,[22] and potentially other inflammatory mediators might represent a potent, nonvascular source of chronic low-grade inflammation.

Our current findings that CRP is independently associated with hyperinsulinemia in nondiabetic subjects have several important implications. First, our data suggest that subclinical inflammation might play an early role in the progression to insulin-resistant states. Although fasting insulin levels less accurately reflect insulin sensitivity than more invasive methods, among nondiabetic individuals fasting insulin is moderately well correlated with glucose clamp[14] and minimal model techniques.[15] Although we found a stronger relation for CRP than for IL-6, this difference might be due to a considerably shorter plasma half-life of IL-6 as opposed to CRP, which might thereby be a better indicator of ongoing subclinical inflammation.

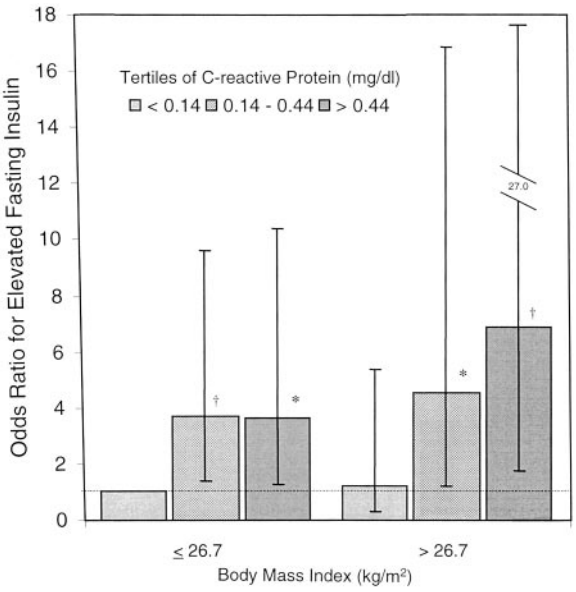

Figure 2. ORs and 95% confidence intervals for elevated fasting insulin (≥51.6 pmol/L) according to lower 2 tertiles vs upper tertile of BMI and increasing tertiles of CRP. Adjusted for age, race, family history of diabetes, smoking status, exercise frequency, use of alcohol, postmenopausal status, use of HRT, and continuous BMI within strata. Number of women in each group according to BMI and increasing CRP: for BMI ≤26.7 kg/m^2, 99, 78, and 55; for BMI >26.7 kg/m^2, 17, 32 and 63. *P<0.05, †P<0.01

Second, although BMI is perhaps the most important clinically recognized risk factor for type 2 diabetes, obesity is neither a sufficient nor a necessary determinant of diabetes incidence. Indeed, as many as 20% of adult women who develop diabetes on long-term follow-up are lean, as defined by a BMI <25 kg/m^2.[23] Our findings of significant associations among both lean and overweight subjects suggest that CRP assessment might identify a broader subgroup of individuals, irrespective of weight, who might be at high risk for conversion to clinically overt type 2 diabetes.

Third, several longitudinal studies of initially nondiabetic individuals have found fasting hyperinsulinemia to be predictive of future cardiovascular events.[24] It is therefore possible, given well-described relations between subclinical inflammation and the development of atherosclerosis, that CRP elevation and coincident systemic inflammation in hyperinsulinemia might at least partially account for the previously reported associations between elevated insulin levels and cardiovascular risk.

Several alternative explanations for our results might exist. For instance, it is possible that CRP and IL-6 elevations in our study population might largely reflect underlying atherosclerosis. However, in this regard, it is important to note that only 1 study subject developed a clinical cardiovascular endpoint (incident stroke, myocardial infarction, or coronary revascularization) during the 4-year period from time of exposure determination. In addition, as the primary associations described are cross sectional in nature, the direction of causality cannot be clearly established from these data alone. It is therefore possible that insulin resistance might lead to a heightened inflammatory response rather than being a result of chronic inflammation. However, given (1) the observed risk gradient in both linear and logistic regression models, (2) the consistency of our results in the absence of the metabolic syndrome, (3) the existence of plausible biologic mechanisms, and (4) the availability of prospective clinical outcomes data, we believe our findings more likely reflect an influence of inflammation on hyperinsulinemia.

Previous cross-sectional studies of the relation between fasting insulin, other measures of insulin resistance, and inflammatory biomarkers, including CRP and IL-6, among nondiabetics[25–29] have shown that subclinical inflammation is associated with insulin sensitivity in nondiabetic or prediabetic individuals. The current results demonstrate an association between inflammation and hyperinsulinemia independent of other putative clinical risk factors while further indicating a clear relation between plasma CRP and fasting insulin among both lean and overweight individuals and among those without clinically manifest metabolic syndrome.

Several important limitations of our study merit further discussion. First, we did not measure glucose tolerance status at baseline. However, the estimated prevalence of impaired glucose

tolerance (IGT) among previous studies of nonselected white populations over the age of 50 is 20%,[30,31] and the expected prevalence of IGT among our study subjects who remained diabetes-free during a 4-year period of observation is likely to be low. Additionally, hyperinsulinemia as an index of progressive insulin resistance appears to be an important predictor of subsequent diabetes among individuals with either normal or impaired glucose tolerance.[31] Second, the use of BMI in our main analyses does not account for the metabolic effects of central obesity, which might play a prominent role in insulin resistance. However, inclusion of WHR and waist circumference in regression models did not alter our findings, although these latter indexes nonetheless do not distinguish visceral from subcutaneous adipose depots. Third, as this study was conducted among middle-aged women, our results might not be generalizable to other age groups or to men.

In conclusion, in this cross-sectional study of markers of systemic inflammation as independent predictors of fasting insulin in nondiabetic women, we provide further evidence of a role for inflammation in the development of insulin resistance. Our findings, coupled with those of previous investigators, suggest that targeted interventions aimed at modulation of the inflammatory response might prove beneficial in the prevention or treatment of insulin resistance disorders.

Acknowledgments

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