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Cross-Sectional Associations of Resistin, Coronary Heart Disease, and Insulin Resistance

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Context: Recently, resistin was found to be present in atherosclerotic lesions in apoE$^{-/-}$ mice. Resistin may be associated with inflammation and atherosclerosis in humans; however, the role of resistin in human disease remains controversial.

Objective: This study assesses cross-sectional relationships of resistin with coronary heart disease (CHD).

Design, Setting, and Participants: Blood samples from the third examination of the Strong Heart Study (SHS)—the largest study of CHD in American Indians—were used. Cases who had suffered previous myocardial infarction (n = 100) were selected randomly from the three SHS sites and matched for study site and sex with controls who had no history of cardiovascular disease (CHD or stroke) (n = 100).

Main Outcome Measure: Resistin levels by enzyme-linked immunosorbent assay method in cases and controls was the main outcome measure.

Results: Resistin levels were higher in cases than controls [median (interquartile range): 3.4 (2.5–4.7) *vs.* 2.8 (2.1–4.0) ng/ml; $P = 0.003$] and had univariate correlations with age (Spearman r = 0.21; $P < 0.002$), fasting insulin (r = 0.21; $P = 0.003$), insulin resistance by homeostasis model (r = 0.22; $P = 0.04$), albumin to creatinine ratio (r = 0.19; $P = 0.01$), and fibrinogen (r = 0.34; $P < 0.0001$). Cases were more likely to have diabetes (cases 67%; controls 41%; $P < 0.0001$) but had similar body mass index (cases 31.4 ± 5.4; controls 30.7 ± 6.3; $P = 0.85$). Resistin levels were higher in participants with established nephropathy (albumin to creatinine ratio >300 mg/g, n = 26) compared with those with normo- (n = 122) or microalbuminuria (n = 42). In multivariate analysis, nephropathy ($P = 0.0013$) but not previous myocardial infarction ($P = 0.12$) was significantly associated with resistin.

Conclusions: Resistin is not independently associated with CHD. Resistin is elevated in survivors of myocardial infarction; however, this reflects a novel association of raised resistin with diabetic nephropathy. **(*J Clin Endocrinol Metab* 91: 64–68, 2006)**

RESISTIN BELONGS TO a family of cysteine rich secretory proteins known as resistin-like molecules or FIZZ (found in inflammatory zones) proteins. Resistin was originally found to be induced during adipocyte differentiation and down-regulated in mature murine adipocytes cultured in the presence of thiazolidinediones, a class of insulin-sensitizing drugs (1). Further studies in rodents have suggested that resistin mRNA levels are higher in abdominal fat depots, compared with depots from the thigh (2), and that serum resistin levels are positively correlated with body mass index (BMI) (3). Additionally, resistin has been found to modulate hepatic insulin action (4, 5) and possibly play a role in maintaining fasting blood glucose levels (6).

Confirmation of these findings in human populations has been difficult and may be due to the fact that resistin appears to be derived from different sources in humans and rodents. Reports point to the adipocyte as the sole source of resistin in mice (1, 7), whereas investigations in humans suggest that very little resistin is expressed in adipocytes, but rather, monocytes and macrophages produce large quantities of resistin (8, 9). A lack of homology between the human and mouse resistin genes might also suggest a divergence in function (10). Although resistin appears to be involved in rodent metabolism, the data in humans are less clear. Rather, resistin may be an inflammatory marker in humans, because macrophages are known inflammatory modulators.

In support of a possible inflammatory role in humans, recombinant resistin activates human endothelial cells, as measured by increased expression of endothelin-1 and various adhesion molecules and chemokines, while simultaneously increasing CD40 ligand signaling by down-regulating tumor necrosis factor receptor-associated factor-3 (11). These findings suggest a possible mechanistic link between resistin and cardiovascular disease via proinflammatory pathways.

We have recently demonstrated that resistin mRNA and protein are present in atherosclerotic lesions in the aorta of apoE-deficient mice. In addition, we found elevated serum levels of resistin in apoE-deficient mice compared with wild-type controls, and in patients with premature coronary artery disease compared with individuals with angiographically normal coronary arteries (12).

The purpose of this study was to assess cross-sectional relationships of plasma resistin levels with prevalent coronary heart disease (CHD) in participants in the third examination of the Strong Heart Study (SHS)—the largest study

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Abbreviations: BMI, Body mass index; CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAI-1, plasminogen activator inhibitor 1; QUICKI, Quantitative Insulin Sensitivity Check Index; SHS, Strong Heart Study.

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of CHD in American Indians. previously (13). In brief, the SHS recruited 4549 volunteers of American Indian heritage from three geographic areas (Arizona, North and South Dakota, and Oklahoma) (13). Volunteers were invited to a study examination on three occasions (SH1: 1988–1992; SH2: 1993–1995; SH3: 1997–1999) and remained under continued surveillance for development of vascular disease. Data for this study are taken from the third examination (SH3). By the time of SH3 there had been 835 deaths (18.4% of participants). The response rate for the third examination was 86.1% of surviving participants.

Subjects and Methods

Clinical examination

The examination consisted of a personal interview and physical examination. Fasting blood specimens were obtained for measurement of lipids (total cholesterol and triglycerides; very low-density lipoprotein, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol; and very low-density lipoprotein triglycerides), insulin, plasma creatinine, plasma fibrinogen, and glycosylated hemoglobin. A 75-g oral glucose tolerance test (13, 14), assays (15–20), and anthropometric measures including estimation of body composition by bioimpedance (14) were performed as previously described. Quantitative Insulin Sensitivity Check Index (QUICKI) was calculated [QUICKI = 1/(log[fasting insulin] + log[fasting glucose]) in microunits per milliliter and milligrams per deciliter, respectively] as a measure of insulin sensitivity (21). Albuminuria was defined by the ratio of urinary albumin (milligrams per milliliter) to creatinine (grams per milliliter). Microalbuminuria was defined as a ratio of albumin to creatinine between 30 and 299 mg/g and macroalbuminuria by a ratio of 300 mg/g or greater in a morning urine specimen.

Plasma resistin levels were measured using a commercially available ELISA kit (BioVendor, Brno, Czech Republic) (sensitivity 0.2 ng/ml; intraassay coefficient of variation 2.8–3.4%). This is a sandwich-type assay using a rabbit polyclonal antihuman resistin antibody that detects homodimeric resistin. All samples were assayed in duplicate, and the mean of these two measures was used for analysis.

Definition of terms and case control selection

Diabetes and hypertension. Participants were classified as having type 2 diabetes where they were taking insulin or oral antidiabetic medication or if they met 1998 American Diabetes Association criteria for fasting (≥126 mg/dl) glucose (22). Participants were considered hypertensive if they were taking antihypertension medication or if they had a systolic blood pressure greater than 140 mm Hg or a diastolic blood pressure greater than 90 mm Hg.

CHD. The process used to ascertain fatal and nonfatal CHD events has been described previously (14, 23). Medical records for each identified CHD event were reviewed using a standard protocol.

Selection of cases and controls. The source population from which cases and controls are drawn are SHS participants who were examined at the third Strong Heart examination (SH3) and in whom adequate samples were available as well as baseline biochemistry including fasting insulin and glucose. A total of 2299 Strong Heart Participants met these criteria (72% of all participants taking part in SH3). Cases were defined as SH3 participants who had previously suffered from myocardial infarction. A total of 114 SH3 participants with previous myocardial infarction were identified, of whom 100 (47 females, 53 males) were randomly selected with approximately equal numbers from each of the three study sites (33 Arizona, 33 Oklahoma, 34 South and North Dakota). Controls were defined as SH3 participants with no record of cardiovascular disease, including all categories of CHD and stroke. Controls were randomly selected after matching for sex and study site.

Analysis. Continuous variables were analyzed using general linear models with log transformation of skewed variables (fasting insulin, plasminogen activator inhibitor 1 (PAI-1), C-reactive protein, albumin to creatinine ratio). The relation of variables at the SH3 examination to myocardial infarction was examined by conditional logistic regression using SAS statistical software (SAS Institute, Cary, NC).

Results

Baseline characteristics of the study population are summarized in Table 1. Cases were, on average, 2 yr older than controls, of similar BMI, but more likely to have diabetes, hypertension, and renal impairment (creatinine >1.5 mg/dl). Cases had significantly lower levels of high-density li-

TABLE 1. Baseline measures in those with and without CHD

	Control	Case	*P*
N	100	100	
No. of females	47	47	
Center (Arizona/Oklahoma/North and South Dakota)	33/33/34	33/33/34	
Age (yr)	62.4 ± 7.0	64.6 ± 7.9	0.04
BMI (kg/m^2)	30.7 ± 6.3	30 ± 5.4	0.85
Diabetes (%)	41	67	<0.0001
Hypertension (%)	48	67	0.007
Smoking [no/ex/current (%)]	34/36/29	32/40/28	0.86
Cholesterol (mg/dl)	190 ± 35	191 ± 40	0.91
Triglycerides (mg/dl)	116 (85–178)	141 (86–212)	0.15
LDL cholesterol (mg/dl)	119 ± 31	117 ± 34	0.62
HDL cholesterol (mg/dl)	43 ± 14	39 ± 12	0.04
Renal impairment (creatinine >1.5 mg/dl)	0	13	0.0002
Urine ACR [normo/micro/macro (%)]	81/11/8	47/33/19	<0.0001
Fasting glucose (mg/dl)	102 (96–139)	136 (104–202)	0.002[a]
Fasting insulin (μU/ml)	16 (11–26)	21 (14–34)	0.01[a]
Plasma creatinine (mg/dl)	0.8 (0.7–1.0)	0.9 (0.8–1.15)	0.006
Fibrinogen (mg/dl)	353 (300–401)	379 (331–449)	0.02
PAI-1 (ng/ml)	39 (22–67)	38 (20–61)	0.86
Resistin (ng/ml)	2.8 (2.1–4.0) (n = 99)	3.4 (2.5–4.7)	0.003[a]

Data are presented as mean ± SD or median (interquartile range). Case, Participants at the third Strong Heart examination who had previously suffered myocardial infarction.

[a] *P* value by Wilcoxon test.

TABLE 2. Simple correlation of plasma resistin to anthropometric and biochemical variables

	N	r value with resistin	*P*
Age	199	0.21	0.002
BMI	199	0.13	0.07
Fasting glucose	199	0.10	0.18
Two-hour glucose	79	0.08	0.49
Fasting insulin	199	0.21	0.003
QUICKI[a]	199	−0.17	0.02
SBP	199	0.10	0.18
DBP	199	−0.15	0.04
Cholesterol	198	−0.11	0.13
Triglycerides	198	−0.03	0.65
HDL cholesterol	198	−0.09	0.18
LDL cholesterol	198	−0.06	0.39
Urinary albumin to creatinine ratio	190	0.19	0.01
Plasma creatinine	198	0.27	<0.0001
Fibrinogen	190	0.34	<0.0001
Uric acid	197	0.18	0.01
PAI-1	191	−0.08	0.25

Spearman r correlation across all cases and controls. SBP, Systolic blood pressure; DBP, diastolic blood pressure.

[a] QUICKI = (1/log[fasting insulin] + log[fasting glucose] in milliunits per milliliter and milligrams per deciliter, respectively.

poprotein cholesterol and higher fasting glucose and insulin concentrations as well as higher concentrations of fibrinogen (Table 1).

Resistin levels were higher in cases than controls [median (interquartile range): 3.4 (2.5–4.7) *vs.* 2.8 (2.1–4.0) ng/ml, $P = 0.003$] and had univariate correlations with age, fasting insulin, insulin resistance by homeostasis model, albumin to creatinine ratio, and fibrinogen (Table 2).

In multivariate analysis, resistin levels were higher in cases after adjustment for age, sex, and BMI (Table 3, model 1), but this relationship was not significant after inclusion of log albumin to creatinine ratio (Table 3, model 2) or log of plasma creatinine which was also an independent predictor of plasma resistin ($P < 0.0001$). Resistin levels were around 50% higher in those with evidence of diabetic nephropathy [geometric mean resistin (95% confidence interval): nephropathy 4.3 (3.5–5.1) ng/ml; microalbuminuria 2.9 (2.5–3.3) ng/ml; normoalbuminuria 2.9 (2.7–3.2) ng/ml; $P = 0.0013$ for effect of nephropathy status as categorical variable with addition of age, sex, and heart disease status as covariates] as shown in Fig. 1. When added to the variables in model 2, fasting insulin, QUICKI, glucose, or diabetes status were not independent predictors of resistin concentrations. Both plasma creatinine and fibrinogen proved robust predictors of plasma resistin (Table 3, model 3). When considered separately, plasma creatinine was a significant predictor of resistin in cases and controls separately ($P < 0.0001$ and $P = 0.0028$, respectively) in a model including age, sex, and study center as additional covariates.

When participants with nephropathy were excluded, resistin was not associated with previous myocardial infarction [geometric mean (95% confidence intervals for estimate of mean): cases 3.1 (2.8–3.4) ng/ml; controls 2.8 (2.5–3.1) ng/ml; $P = 0.21$ with additional adjustment for study center, age, and sex].

Discussion

Resistin is a novel secretory protein of potential importance to metabolic and vascular disease. Our data share a number of features with previous studies including some in American Indians (24). In human studies, relationships of circulating resistin to measures of insulin sensitivity (24–26), adiposity (24–27), and type 2 diabetes (25, 26) have been inconsistent, and were not apparent in multivariate analysis in the Strong Heart population. In contrast, the actions of resistin to stimulate inflammatory pathways (28–30), activate vascular endothelial cells (11, 31), and stimulate smooth muscle cell proliferation (32), make it an attractive candidate as a marker of, or etiological factor in, vascular disease. In keeping with this hypothesis, we have recently found that patients with premature coronary artery disease have higher plasma resistin levels compared with individuals with angiographically normal coronary arteries (12).

We found that prevalent CHD is associated with higher resistin levels in this population, and that this finding predominantly reflects a novel association of resistin with diabetic nephropathy in American Indians. Our finding is consistent with recent reports of increased resistin concentrations in patients with progressive impairment of renal function (33, 34). Kielstein *et al.* (33) measured the resistin blood concentrations in male patients with IgA glomerulonephritis in various stages of renal disease. In this

TABLE 3. Relation of resistin to renal disease and CHD: multivariate regression

	Multivariate predictors of plasma resistin	β	*P*
Model 1	Age	0.01	0.003
	Sex (female, 0; male, 1)	−0.17	0.02
	BMI		0.25
	Heart disease status (control, 0; case, 1)	0.15	0.04
Model 2	Age	0.01	0.006
	Sex (female, 0; male, 1)	−0.17	0.02
	BMI		0.36
	Heart disease status (control, 0; case, 1)	0.08	0.28
	Log albumin to creatinine ratio	0.06	0.002
Model 3	Age	0.001	0.12
	Sex (female, 0; male, 1)	−0.34	<0.0001
	Log albumin to creatinine ratio	0.04	0.05
	Log plasma creatinine	0.61	<0.0001
	Log fibrinogen	0.39	<0.0001

Association of plasma resistin with demographic variables, ischemic heart disease, and renal disease. Plasma resistin is modeled as the independent variable in comparison to predictor variables in three models.

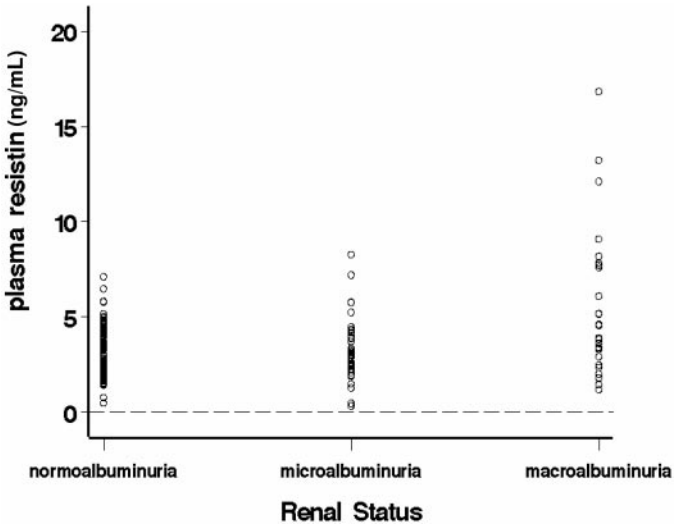

FIG. 1. Plasma resistin levels and renal status.

small population of 30 patients, glomerular filtration rate was the only independent predictor of plasma resistin concentrations (33). The authors proposed that insufficient filtration by the kidney may account for the observed increase in resistin concentration with declining renal function. Interestingly, the highly elevated resistin levels in these patients (up to 100 ng/ml) were not found to be associated with impaired insulin sensitivity. Diez *et al.* (34) recently measured resistin levels in patients with end-stage renal disease undergoing different courses of treatment. Patients undergoing peritoneal dialysis or hemodialysis had significantly higher resistin concentrations compared with controls. Although logistic regression analysis did not reveal a relationship between serum resistin levels and the presence of vascular disease of any type, subgroup analysis demonstrated a significant relationship between resistin levels and previous heart disease [odds ratio 1.80 (1.03–3.15), $P = 0.039$]. However, this study is somewhat limited in that the patients were classified as having vascular disease (cerebral, peripheral, or heart disease) based on the occurrence of clinical events, thus it is possible that the true prevalence of atherosclerotic disease is underestimated.

Diabetic nephropathy has been associated with alteration of a variety of inflammatory markers, and our findings would indicate that resistin is also increased in this condition. Diabetic nephropathy is an important predictor of later cardiovascular disease in this population (35). The presence of macroalbuminuria is associated with a 3.8-fold increase in incidence of cardiovascular disease in men and 5.4-fold increase in women (35). Similarly, fibrinogen has emerged as an independent predictor of incident cardiovascular disease in previous analyses (35). It remains possible then, that that hyperresistinemia contributes to increased vascular risk in the presence of nephropathy. In contrast, however, the lack of relationship of resistin with vascular disease after exclusion of those with nephropathy makes a major etiological role in development of myocardial infarction in this population less likely. A number of other authors have examined the role of resistin in vascular disease in human populations. Reilly *et al.* (36) have recently reported a cross-sectional relationship of resistin with coronary artery calcification in healthy middle aged people. Similarly to this study, plasma resistin levels were associated with markers of inflammation but not insulin resistance in multivariate analysis. Resistin levels were significantly correlated with coronary artery calcification.

Our findings differ then, from previous results in our (12) and other (36) groups. There are a number of potential explanations. All three studies have examined cross-sectional relationships of resistin with disease. Such study designs are influenced by survivor effects and differences in circulating biomarkers may represent changes secondary to rather than causing disease. Because the previous two studies examined an earlier stage of disease [coronary artery calcification (36) or angiographically proven coronary artery disease (12)], whereas we have measured resistin in survivors of myocardial infarction, it is possible that differences in resistin are found only early in the course of disease or that those with the highest resistin levels are dying from their disease and are not represented in our study. It is also possible that differences in resistin levels exist between different ethnic groups. Reilly *et al.* (36) report median resistin levels in a predominantly Caucasian population of 5 ng/ml. Median resistin levels in patients with premature coronary artery disease in Caucasians and African-Americans (using the assay used in this study) were 9 ng/ml, whereas the median value obtained in this study (2.8 in controls) is much lower and similar to a previous study in American Indians (24). These observed differences in serum resistin levels may reflect the impact of genetic or environmental factors on resistin expression. Although differences in etiological factors for atherosclerosis may vary between ethnic groups, one of the critical advantages of studying such risk factors in diverse populations is that the most important etiological factors are likely to be shared. In that light, we conclude that resistin is not raised in survivors of myocardial infarction. However, our study does highlight a potentially important relationship of diabetic renal disease with raised resistin concentrations.

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