Circulating Levels of Resistin and Risk of Type 2 Diabetes in Men and Women: Results From Two Prospective Cohorts

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OBJECTIVE — The purpose of this study was to investigate the role of circulating resistin levels in the development of type 2 diabetes using two prospective cohorts of well-characterized men and women.

RESEARCH DESIGN AND METHODS — We conducted two prospective case-control studies nested in the Women's Health Study (WHS) and Physicians' Health Study II (PHS II). In the WHS, during a median of 10-years of follow-up, 359 postmenopausal women, who were apparently healthy at baseline and later developed type 2 diabetes, were prospectively matched with 359 healthy control subjects. In the PHS II, with 8 years of total follow-up, 170 men, who were apparently healthy at baseline and later developed type 2 diabetes, were matched with 170 healthy control subjects. Control subjects were matched by age, race, and time of blood draw.

RESULTS — Resistin levels at baseline were significantly higher in women than in men ($P = 0.003$) and in case patients than in control subjects for both women ($P < 0.001$) and men ($P = 0.07$). After adjustment for matching factors, physical activity, alcohol intake, smoking, and family history of diabetes, the relative risk of type 2 diabetes comparing the highest to the lowest quartile of resistin in women was 2.22 ([95% CI 1.32–3.73]; $P_{trend} = 0.002$). This association was attenuated after further adjustment for BMI (1.51 [0.86–2.65]; $P_{trend} = 0.20$) or C-reactive protein (1.18 [0.68–2.07]; $P_{trend} = 0.60$). A similar but weaker pattern was observed in men.

CONCLUSIONS — Elevated levels of circulating resistin were significantly related to increased risk of type 2 diabetes, which appears to be partially accounted for by adiposity and the inflammatory process.

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Resistin (also known as adipocyte-secreted factor), an adipocyte-derived hormone, may serve as a critical molecular link between obesity and insulin resistance (1–3). Obese and diabetic mice exhibit high levels of resistin. In murine models, functional reductions in resistin protein (e.g., anti-resistin antibodies, resistin gene knockouts) have been demonstrated to improve insulin sensitivity as well as to decrease blood glucose (2–4), free fatty acid (2), and triglyceride levels (2). A reduction in the amount of functional resistin also increases adipocyte differentiation and adipose mass (2), which can be reversed upon administration of recombinant resistin (4).

In humans, however, the contribution of resistin to the pathogenesis of type 2 diabetes remains elusive. Plasma resistin levels have been observed to be higher in diabetic individuals than in apparently healthy individuals (5–7). In addition, thiazolidinedione therapy lowered plasma resistin levels in clinical trials (8,9). However, the primary source of resistin in rodents is adipocytes, whereas the major source in humans has been shown to be macrophages (10,11), suggesting species-specific physiological effects. To this end, prospective data are needed in well-defined populations to examine the association of circulating levels of resistin with the incident diagnosis of type 2 diabetes.

Therefore, we conducted two case-control studies nested within two large, prospective cohorts, the Women's Health Study (WHS) and the Physicians' Health Study II (PHS II), to investigate the associations of plasma resistin levels with type 2 diabetes risk in men and women. We also explored the potential role of BMI and inflammatory markers on the association between resistin and type 2 diabetes.

RESEARCH DESIGN AND METHODS

— The WHS is a randomized, double-blind, placebo-controlled, 2 × 2 factorial trial of low-dose aspirin and vitamin E for the primary prevention of cardiovascular disease and cancer. The original study consisted of 39,876 U.S. female health professionals aged ≥45 years (mean age 53.9 years at baseline) who were free of diabetes, cancer (except nonmelanoma skin cancer), and cardiovascular disease at baseline (12,13). Of the original 39,876 participants, baseline blood samples were obtained from 28,345 participants (71%). We restricted our population to 6,574 postmenopausal women who were not using hormone replacement therapy at the time of blood

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collection. Women who had developed incident diabetes during a median follow-up of 10 years (by February 2005) were matched in a 1:1 ratio to control subjects by age (within 1 year), duration of follow-up (within 1 month), race, and fasting status at time of blood draw (72% provided fasting blood samples, defined as ≥10 h since the last meal). On the basis of these eligibility criteria, a total of 359 case patients and 359 control subjects were included in our analyses from the WHS.

The PHS II is a randomized, double-blind, placebo-controlled 2 × 2 × 2 × 2 factorial trial of vitamin E, vitamin C, β-carotene, and multivitamins in the prevention of cardiovascular disease and cancer in 14,641 U.S. male physicians aged ≥55 years who were free of cancer and cardiovascular disease at baseline (14). Baseline blood samples were obtained from 11,130 (76%) of the 14,641 PHS II participants. For each incident case occurring during 8 years of follow-up, one appropriate control subject was selected at random from men who provided baseline blood samples at the time of diagnosis in the case patient. In total, 170 case patients were matched with 170 control subjects by age (within 1 year), race, duration of follow-up (within 1 month), and time of blood draw.

Written informed consent was obtained from all participants in both the WHS and PHS II. Both studies were conducted according to the ethics guidelines of Brigham and Women's Hospital, Harvard Medical School, and the UCLA institutional review board.

Ascertainment of diabetes

Details regarding ascertainment of incident type 2 diabetes in our cohorts have been reported previously (15). After excluding those with diabetes at baseline, all participants were asked annually whether and when they had a diagnosis of diabetes since baseline. With use of the diagnostic criteria of the American Diabetes Association, (16), all self-reported cases of type 2 diabetes were confirmed by a supplemental questionnaire. In populations of health professionals such as the WHS and PHS II, self-reported diagnosis of diabetes yields high validity in identifying true cases. As confirmation, a small validation study was conducted, in which self-reported diabetes in the WHS was validated against physician-led telephone interviews, supplementary questionnaires, and medical record reviews, all yielding positive predictive values >91% (17).

Laboratory procedures

Blood samples were centrifuged and stored in liquid nitrogen freezers. Matched case-control pairs were handled identically and assayed in random order in the same analytical run in each cohort. Laboratory personnel were blinded to case-control status during all assays. A1C was measured using a Food and Drug Administration– and U.S. National Glycohemoglobin Standardization Program–approved immunoassay (Hitachi 911; Roche Diagnostics), as described previously (18). Plasma levels of resistin were measured by ELISA (ALPCO Diagnostics, Windham, NH). The assay has a sensitivity of 0.2 ng/ml and day-to-day variabilities of the assay at concentrations of 8.95 and 13.08 ng/ml are 8.9 and 7.4%, respectively. Tumor necrosis factor-α receptor II (TNF-RII) was also measured by ELISA (R&D Systems). The day-to-day variabilities of the assay at concentrations of 89.9, 197.0, and 444.0 pg/ml are 5.1, 3.5, and 3.6%, respectively. As described previously (19), C-reactive protein (CRP) (performed in the WHS only) was assayed using validated methods at a certified laboratory; the average intra-assay coefficient of variation for CRP was 7.8% and the inter-assay coefficients of variations were 2.5 and 5.1%.

Statistical analysis

Biomarker values were log-transformed in all analyses to enhance compliance with normality assumptions. Baseline characteristics between case patients and matched control subjects were compared using McNemar's χ^2 test for categorical variables and a paired *t* test for continuous variables. Age- and/or BMI-adjusted partial correlation coefficients were estimated to evaluate associations between plasma resistin levels and traditional metabolic risk factors among control subjects. We reported regression estimates after multiple imputation of missing values using the ICE and MIM procedures in STATA 10.0. Variables with the largest number of missing variables were BMI ($n = 12$) and multivitamin use ($n = 11$).

To assess the resistin–type 2 diabetes association, we analyzed the WHS and PHS II data sets separately using conditional logistic regression with robust variance estimators. The levels of resistin were categorized into quartiles based on their distributions among control subjects. Conditional logistic regression was applied to estimate the odds ratio (OR) and 95% CI for type 2 diabetes risk in each quartile using the lowest quartile as the referent category. Because risk set sampling was used for our matched case-control pairs, the ORs yielded unbiased estimates of the relative risk (RR), specifically, the rate ratio. Tests of linear trends across increasing quartiles of resistin levels were conducted by assigning the median values within quartiles treated as a continuous variable. We also estimated the RR per 1 SD increase in log-transformed resistin levels, assuming a linear relationship. The following models were prespecified in this analysis. The basic model (model 1) was adjusted for matching factors (age, ethnicity, and fasting status at time of blood draw). The full model (model 2) was further adjusted for established type 2 diabetes risk factors of smoking (current or former/never), alcohol use (<3 drinks/month, 1–6 drinks/week, or ≥1 drink/day), physical activity (<1, 1–3, or ≥4 times/week), and family history of diabetes in a first-degree relative (yes/no). In model 3, we additionally adjusted for BMI (continuous) in the full model to assess the impact of BMI on the resistin–type 2 diabetes association. In model 4, we further adjusted the full model for CRP, but because CRP was not available in the PHS II data set, we adjusted the full model for TNF-RII in the PHS II data set as a surrogate marker for CRP; the Pearson's correlation between TNF-RII and CRP was $r = 0.28$ in the WHS data set, consistent with findings in other populations. Model 5 was the same as model 4 with the addition of BMI as a covariate.

Because there was insufficient statistical evidence to suggest that the resistin–type 2 diabetes association differed by sex, we subsequently performed subgroup analyses in the pooled data set to examine potential effect modification by levels of prespecified risk factors: sex (male or female), BMI (normal/underweight, overweight, or obese), age (<60 or ≥60 years), family history of diabetes in a first-degree relative (yes/no), physical activity (<1, 1–3, or ≥4 times/week), alcohol intake (<3 drinks/month, 1–6 drinks/week, or ≥1 drink/day), smoking status (nonsmoker, former smoker, or current smoker), A1C (less than median or more than or equal to median), and TNF-RII (less than median or more than or equal to median). The statistical significance of these interactions was tested by using a

Table 1—*Baseline characteristics of case patients and control subjects*

	Women			Men		
	Case patients	Control subjects	*P*	Case patients	Control subjects	*P*
n	358	358		170	170	
Demographics						
Age (years)	60.4 ± 6.0	60.3 ± 6.1	(Matched)	63.6 ± 7.5	63.4 ± 7.5	(Matched)
Race (% Caucasian)	92.3	92.9	(Matched)	86.9	85.0	(Matched)
BMI (kg/m^2)	31.0 ± 6.1	26.0 ± 5.0	<0.001	28.7 ± 3.9	25.6 ± 3.5	<0.001
Lifestyle factors						
Alcohol consumption (≥1 drink/day)	5.2	11.2	0.001	28.8	26.1	0.72
Current smoking (%)	14.7	13.5	0.74	5.9	1.3	0.01
Strenuous physical activity (% ≥4 times/week)	9.2	10.9	0.26	9.2	11.8	0.38
Current multivitamin use (%)	23.3	25.3	0.52	28.1	25.5	0.90
Medical history						
Family history of diabetes (%)	48.3	24.1	<0.001	36.6	19.0	0.01
Biological markers*						
Resistin (ng/ml)	13.0 ± 1.9	10.8 ± 1.7	<0.001	10.9 ± 2.0	9.6 ± 1.8	0.07
TNF-IIR (pg/ml)	2,811 ± 1.3	2,671 ± 1.3	0.009	2,300 ± 1.3	2,229 ± 1.2	0.19
A1C (%)	5.7 ± 1.2	5.1 ± 1.1	<0.001	6.1 ± 1.2	5.2 ± 1.1	<0.001

Data are means ± SD unless indicated otherwise. Paired *t* test was used to calculate *P* values of continuous variables between case patients and control subjects; for categorical variables, McNemar's test was used to test for differences between case patients and control subjects. *Geometric means are displayed.

Wald test (for variables with two levels) or a χ^2 test for homogeneity (for variables with more than two levels) of the pooled estimates of the interaction terms.

We performed additional sensitivity analyses to assess the robustness of our estimates. First, we conducted a series of analyses to address the concern that underdiagnosed type 2 diabetes may have biased our findings. In one analysis we excluded diabetes case patients (and their matched control subjects) in whom diabetes was diagnosed within the first 3 years of follow-up (154 women and 148 men excluded). In another analysis we excluded case patients who had elevated risks of developing type 2 diabetes at baseline (defined by A1C >6.5% and BMI >30 kg/m^2 at baseline) (462 women and 172 men excluded). Second, we evaluated the influence of adjusting for A1C in our estimates. Third, because CRP was only measured in the WHS, we assessed the influence of adjusting for another inflammatory marker (alone and with BMI), TNF-RII, which was measured in both data sets. Last, we assessed the influence of using a different measure of adiposity by adjusting for waist circumference (instead of BMI); however, waist circumference was only measured in the WHS and was collected 72 months after baseline. Thus, we adjusted for waist circumference in the WHS, adjusted for BMI in the PHS II, and pooled the estimates. All analyses were conducted using Stata 10.0 (StataCorp, College Station, TX).

RESULTS — Compared with control subjects, patients with incident cases of type 2 diabetes had a greater proportion of traditional risk factors at baseline (Table 1). In both men and postmenopausal women, case patients had higher values than control subjects for BMI, proportion with a family history of diabetes, TNF-RII (and CRP, but only measured in women), A1C, and resistin levels. Interestingly, resistin levels were significantly higher in women than in men (geometric mean 11.89 ± 1.81 vs. 10.27 ± 1.87 ng/ml, respectively; $P = 0.003$).

Correlation coefficients between resistin levels and several metabolic measures are displayed in Table 2. BMI was poorly correlated with plasma resistin in men ($r = 0.08$, $P = 0.30$) and moderately correlated in women ($r = 0.26$, $P < 0.001$). The strongest correlations were between resistin and inflammatory markers (TNF-RII and/or CRP), which remained positive even after adjustment for age and BMI (TNF-RII in PHS II: $r = 0.29$, $P < 0.001$; TNF-RII in WHS: $r = 0.28$, $P < 0.001$; and CRP in WHS: $r = 0.19$, $P < 0.001$).

In women, the risk of developing type 2 diabetes among participants categorized in the highest quartile of plasma resistin was significantly higher than that of participants in the lowest quartile (RR 2.35 [95% CI 1.50–3.69]; $P_{trend} < 0.001$) after controlling only for matching factors (Table 3). This association was similar after additional controls for traditional diabetes risk factors were added (2.22 [1.32–3.73], $P_{trend} = 0.002$). However, further adjustment for BMI dramatically attenuated the association (1.51 [0.86–2.65], $P_{trend} = 0.20$). The additional adjustment for inflammatory markers led to an even greater attenuation of the association.

In men, after controlling only for matching factors, there was a trend toward a positive association between resistin levels and type 2 diabetes risk (RR 1.53 [95% CI 0.82–2.85], $P_{trend} = 0.09$, comparing the highest with the lowest quartiles), although it was not statistically significant (Table 3). This nonsignificant association was virtually unchanged after additional adjustment for traditional diabetes risk factors and further attenuated with the additional adjustment for BMI.

Differences in RRs between men and women were not statistically significant in any of the models we examined; thus, we pooled the estimates from both men and women to increase statistical precision in the RR estimates. Our subgroup analyses revealed no substantial evidence for the presence of significant heterogeneity among the prespecified type 2 diabetes risk factor variables that we examined for potential effect modification of the RRs (see supplemental Table A1, available in an online appendix at http://cdx.doi.org/10.2337/dc08-1625).

The sensitivity analyses assessing the influence of underdiagnosed cases showed overall trends that were similar to our main results (see supplemental Table

Table 2—*Partial correlation coefficients of plasma resistin levels with baseline metabolic parameters among men and women control subjects adjusted for age and/or BMI*

	Correlation coefficients			
	Age-adjusted		Age- and BMI-adjusted	
Metabolic factors	*r*	*P*	*r*	*P*
Men (n = 170)				
BMI	0.08	0.30	—	—
TNF-RII	0.29	<0.001	0.29	<0.001
A1C	0.11	0.15	0.10	0.20
Systolic blood pressure	−0.05	0.52	−0.07	0.37
Diastolic blood pressure	−0.06	0.42	−0.06	0.45
BMI	0.26	<0.001	—	—
Women (n = 358)				
Waist circumference	0.20	<0.001	0.02	0.66
TNF-RII	0.33	<0.001	0.28	<0.001
CRP	0.28	<0.001	0.19	<0.001
A1C	0.09	0.11	0.07	0.22
Cholesterol	0.08	0.12	0.04	0.50
HDL cholesterol	−0.13	0.02	−0.05	0.32
LDL cholesterol	0.10	0.07	0.06	0.24
Triglycerides	0.13	0.01	0.07	0.17
Systolic blood pressure	0.13	0.02	0.04	0.41
Diastolic blood pressure	0.10	0.07	0.02	0.70

A2 in an online appendix). Adjusting for A1C strengthened the association between resistin and type 2 diabetes, although some of the estimates were unstable because of the small sample size. Adjusting for TNF-RII in both data sets attenuated the association between resistin and type 2 diabetes but not to the extent observed when CRP was used instead of TNF-RII in the WHS; nonetheless, the linear trend remained significant (P < 0.01). Further adjustment for BMI with TNF-RII did not alter estimates substantially. Furthermore, adjusting for waist circumference (in the WHS) instead of BMI also did not alter the estimates substantially.

CONCLUSIONS — In these two prospective nested case-control studies of middle-aged men and postmenopausal women, elevated baseline levels of resistin were associated with an increased risk of type 2 diabetes, which was attenuated by adjustment for BMI and/or inflammatory markers. Also, there was no significant modification by sex, BMI categories, age, family history of diabetes, physical activity, alcohol consumption, or cigarette smoking status at baseline. The present analysis differed from previous studies, which were predominantly cross-sectional, because it was prospective with several years of follow-up, was adjusted for multiple covariates, and had a relatively large sample size.

In a large, prospectively ascertained cohort, Heidemann et al. (20) used a similar design in 2,274 female nurses and found results nearly identical to ours: a strong association between resistin and risk of diabetes that was attenuated after further adjustment for BMI. Despite the consistency of these findings, further investigation is needed to reveal the mechanisms underlying the interrelationship among adiposity, resistin, and type 2 diabetes.

Our data are consistent with the positive correlation between BMI and resistin levels reported previously (5,6). Despite a nonsignificant linear correlation among men, there was some evidence of a positive correlation between resistin levels and BMI among the overweight and obese control subjects (r^2 = 0.11, P = 0.04). However, findings from previous studies have not been entirely consistent either, as numerous studies showed no significant correlations (7,21) between adiposity and resistin levels. These null findings could be due to the method with which adiposity was measured. In our sensitivity analyses, adjusting for waist circumference (albeit, measured 72 months after baseline)

Table 3—*RR estimates for developing type 2 diabetes by circulating levels of resistin in men and women, separately*

Variable	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}	Continuous (per 1 SD increase)*
Women (case patients/control subjects)	56/90	87/88	88/91	127/89		
Basic model†	1.00	1.63 (1.03–2.58)	1.60 (1.01–2.52)	2.35 (1.50–3.69)	<0.001	1.37 (1.17–1.59)
Full model‡	1.00	1.38 (0.84–2.27)	1.40 (0.84–2.35)	2.22 (1.32–3.73)	0.002	1.36 (1.14–1.61)
Full model + BMI	1.00	1.43 (0.85–2.40)	1.36 (0.81–2.30)	1.51 (0.86–2.65)	0.20	1.17 (0.98–1.39)
Full model + CRP§	1.00	1.12 (0.64–1.95)	1.03 (0.60–1.76)	1.18 (0.68–2.07)	0.60	1.10 (0.92–1.32)
Full model + BMI + CRP§	1.00	1.24 (0.72–2.16)	1.13 (0.66–1.95)	1.13 (0.63–2.01)	0.85	1.07 (0.89–1.28)
Men (case patients/control subjects)	54/59	26/45	38/28	52/38		
Basic model†	1.00	0.76 (0.39–1.51)	1.01 (0.54–1.87)	1.53 (0.82–2.85)	0.09	1.21 (0.98–1.48)
Full model‡	1.00	0.73 (0.34–1.53)	1.10 (0.57–2.12)	1.51 (0.75–3.02)	0.13	1.23 (0.99–1.53)
Full model + BMI	1.00	0.53 (0.23–1.22)	0.80 (0.35–1.86)	1.19 (0.54–2.62)	0.38	1.19 (0.91–1.56)
Full model + TNF-RII§	1.00	0.71 (0.33–1.51)	1.06 (0.54–2.06)	1.42 (0.68–2.98)	0.18	1.22 (0.97–1.53)
Full model + BMI + TNF-RII§	1.00	0.56 (0.24–1.32)	0.93 (0.38–2.28)	1.39 (0.56–3.46)	0.26	1.26 (0.94–1.71)

Data are RR (95% CI). *RR per 1 SD increase in log-transformed values of resistin. †Basic model adjusted for matching factors (i.e., age, ethnicity, and fasting status at time of blood draw). ‡Full model adjusted for matching factors and diabetes risk factors (i.e., alcohol intake, exercise, cigarette smoking status, and family history of diabetes). §As an inflammatory marker, TNF-RII was adjusted in the PHS II because the CRP measure was not available.

instead of baseline BMI in the WHS did not change the estimates substantially.

Cell-culture experiments on isolated monocytes demonstrated that resistin regulates proinflammatory cytokine secretion through the nuclear factor-κB pathway (22), a master controller of the proinflammatory process. Also, the highest levels of resistin mRNA (10) and protein (23) were found in human mononuclear cells (e.g., macrophages), a major source of proinflammatory markers. Macrophage infiltration into adipose tissue is a major feature of obesity (24). Furthermore, our findings that adjusting for inflammatory biomarkers attenuated the magnitude of association between plasma resistin levels and type 2 diabetes support the notion that the role of resistin in the development of type 2 diabetes is mediated through the inflammatory pathway. However, specific regulation and effectors of resistin as well as different effects between plasma and tissue-level resistin remain to be clarified.

Several limitations need to be considered when interpreting our findings. First, positive associations that were of borderline statistical significance may have been due to insufficient sample size. However, we did observe similar trends for the positive associations of resistin with risk of type 2 diabetes in both men and women. End point misclassification may be a concern because the study populations were not screened for glucose intolerance, and the diagnosis was self-reported. However, all participants in this study were health professionals, who have been shown to have more robust and valid self-reported diagnostic information and a relatively high screening rate (25). Moreover, our sensitivity analyses showed consistent trends for the relation of resistin and type 2 diabetes even after the exclusion of all cases occurring in the first 3 years of follow-up or exclusion of participants with high BMI and A1C levels at baseline.

In summary, our prospective study of two well-characterized cohorts of men and women indicate that elevated levels of circulating resistin were significantly related to an increased risk of type 2 diabetes and that the potential effects of resistin on diabetes risk were attenuated after adjustment for adiposity and inflammation.

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