

# High Serum Resistin Is Associated With an Increase in Adiposity But Not a Worsening of Insulin Resistance in Pima Indians

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Resistin is an adipokine with putative prodiabetogenic properties. Like other hormones secreted by adipose tissue, resistin is being investigated as a possible etiologic link between excessive adiposity and insulin resistance. Although there is growing evidence that circulating levels of this adipokine are proportional to the degree of adiposity, an effect on insulin resistance in humans remains unproven. To evaluate the relations among resistin, obesity, and insulin resistance, we measured fasting serum resistin levels in 113 nondiabetic (75-g oral glucose tolerance test) Pima Indians (ages  $29 \pm 7$  years, body fat  $31 \pm 8\%$ , resistin  $3.7 \pm 1.1$  ng/ml [means  $\pm$  SD]), who were characterized for body composition (assessed by hydrodensitometry or dual-energy X-ray absorptiometry), whole-body insulin sensitivity ( $M$ ; assessed by hyperinsulinemic clamp), basal hepatic glucose output (BHGO) and hepatic glucose output during low-dosage insulin infusion of a hyperinsulinemic clamp (HGO; a measure of hepatic insulin resistance), and acute insulin secretory response (AIR; assessed by 25-g intravenous glucose tolerance test). Follow-up measurements of  $M$ , BHGO, HGO, and AIR were available for 34 subjects who had normal glucose tolerance at baseline and remained nondiabetic at follow-up. The average time to follow-up was  $4.5 \pm 2.7$  years. In cross-sectional analyses, serum resistin levels were positively associated with percent body fat ( $r = 0.37$ ,  $P = 0.0001$ ) and 2-h glucose ( $r = 0.19$ ,  $P = 0.04$ ), respectively. Serum resistin levels were not associated with fasting glucose and insulin levels,  $M$ , BHGO, HGO, or AIR ( $r = 0.17$ ,  $0.12$ ,  $-0.13$ ,  $-0.06$ ,  $-0.03$ , and  $-0.04$ , respectively; all  $P > 0.05$ ). After adjusting for percent body fat, there was no association between serum resistin levels and 2-h glucose ( $r = 0.06$ ,  $P = 0.6$ ). In prospective analyses, high serum resistin levels at baseline were not associated with a decline in  $M$  ( $r = -0.1$ ,  $P > 0.5$ ). Resistin levels were, however, associated with increases in percent body fat, fasting plasma insulin,

and HGO ( $r = 0.34$ ,  $0.36$ , and  $0.37$ ; all  $P < 0.05$ ) after adjusting for sex, age, and time to follow-up. After additional adjustment for the change in percent body fat, there was no association between baseline serum resistin levels and changes in plasma insulin or HGO ( $r = 0.26$  and  $0.23$ ; both  $P > 0.1$ ). We conclude that in Pima Indians, like other human populations, circulating resistin levels are proportional to the degree of adiposity, but not the degree of insulin resistance. We unexpectedly found that high serum resistin levels do predict future increases in percent body fat. Our data suggest that resistin promotes obesity but not obesity-associated insulin resistance in humans. *Diabetes* 53: 1279–1284, 2004

Obesity causes insulin resistance. One mechanism through which the enlarged adipose tissue mass is thought to influence insulin action is via secretion of adipokines, such as tumor necrosis factor- $\alpha$ , leptin, and adiponectin (1–3). Resistin, an adipokine belonging to the recently described resistin-like molecules family of small cysteine-rich secreted proteins (4), has also been suggested as a link between obesity and insulin resistance (5).

Serum resistin is increased in diet-induced obese, *ob/ob*, and *db/db* mice; the insulin sensitizer rosiglitazone has been shown to reduce serum resistin in these mice (5). In normal weight mice, the infusion of recombinant resistin worsened glucose tolerance and anti-resistin antibodies lowered blood glucose (5). Resistin-induced increases in blood glucose in vivo result predominantly from exaggerated hepatic glucose production, with no effects being observed in the rest of the body (6). However, resistin has been shown to inhibit glucose uptake in 3T3-L1 adipocytes (5) and L6 muscle cells (7).

The role of resistin in the pathophysiology of obesity and insulin resistance in humans is controversial. Resistin mRNA and protein expression were initially reported to be low in isolated subcutaneous and omental adipocytes (8–10) and resistin mRNA did not correlate with BMI (8). However, McTernan et al. (11) documented significantly greater resistin protein levels in subcutaneous adipose tissue homogenates from obese subjects compared with that from lean subjects. Resistin is expressed in preadipocytes in addition to adipocytes, which may contribute to the elevation of resistin content in adipose tissue of obese humans (11,12). Resistin mRNA is also found in human

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AIR, acute insulin secretory response; BHGO, basal hepatic glucose output; EMBS, estimated metabolic body size; HGO, hepatic glucose output; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; WBC, white blood cell count.

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TABLE 1  
Physical and metabolic characteristics of the study populations in the cross-sectional and prospective analyses

	Baseline population	Prospective analysis	
		Baseline	Follow-up
<i>n</i>	113	34	34
Age (years)	29 ± 7 (18–47)	28 ± 7	32 ± 7
Body weight (kg)	91 ± 19 (50–148)	89 ± 21	96 ± 23*
Body fat (%)	31 ± 8 (14–47)	28 ± 7	30 ± 5†
Fasting plasma glucose (mg/dl)	86 ± 10 (60–116)	82 ± 7	88 ± 7*
2-h plasma glucose (mg/dl)	118 ± 33 (51–198)	98 ± 25	125 ± 28*
Fasting plasma insulin (μU/ml)	41 ± 18 (11–108)	35 ± 17	40 ± 17‡
2-h plasma insulin (μU/ml)	194 ± 170 (17–1,101)	111 ± 95	205 ± 180†
<i>M</i> (mg · kg EMBS <sup>-1</sup> · min <sup>-1</sup> )	2.68 ± 1.13 (1.41–8.2)	3.15 ± 1.65	2.7 ± 1.06‡
AIR (μU/ml)	263 ± 171 (57–867)	278 ± 185	288 ± 237
BSGO (mg · kgEMBS <sup>-1</sup> · min <sup>-1</sup> )	1.90 ± 0.28 (0.91–2.67)	1.94 ± 0.29	1.92 ± 0.3
HGO (mg · kgEMBS <sup>-1</sup> · min <sup>-1</sup> )	0.29 ± 0.31 (0–1.33)	0.38 ± 0.38	0.40 ± 0.37
Resistin (ng/ml)	3.67 ± 1.1 (1.56–7.45)	3.4 ± 1	—

Data are means ± SD or means ± SD (range). \**P* < 0.001; †*P* < 0.01; ‡*P* < 0.05 for baseline vs. follow-up variables (except for age) in the prospective analysis (paired *t* test).

monocytes (8,9), and differentiation of monocytes into macrophages *in vitro* increases resistin mRNA (13).

Resistin protein is detectable in human serum, and its circulating levels were found to be elevated in proportion to the degree of obesity (14,15). However, in a study by Degawa-Yamauchi et al. (14), serum resistin adjusted for BMI was not a significant predictor of insulin resistance measured by the homeostasis model assessment score.

To better evaluate a possible role of resistin in the development of insulin resistance, we examined the association of serum resistin levels, adiposity, and a more direct measure of insulin action (the hyperinsulinemic-euglycemic glucose clamp) in the Pima Indians of Arizona, a population with marked obesity and insulin resistance and one of the highest reported prevalence rates of type 2 diabetes in the world (16). Our aims were to examine 1) whether high serum resistin levels were cross-sectionally associated with adiposity, whole-body, or hepatic insulin sensitivity; and 2) whether high serum resistin levels at baseline were associated with a subsequent decline in whole-body or hepatic insulin sensitivity.

## RESEARCH DESIGN AND METHODS

The study subjects were participants in a longitudinal study of the pathogenesis of type 2 diabetes initiated in 1982 (17). All participants were Pima (or closely related Tohono O'odham) Indians from the Gila River Indian Community near Phoenix, Arizona. Subjects were invited at approximately annual intervals for repeat 75-g oral glucose tolerance tests (OGTTs) and an assessment of insulin sensitivity and insulin secretion. All subjects were aged 18–50 years, nondiabetic (having normal glucose tolerance [NGT] or impaired glucose tolerance [IGT]) at baseline according to the OGTT (World Health Organization 1985 criteria) (18), nonsmokers at the time of the study, and, except for obesity, healthy according to a physical examination and routine laboratory tests. No subject had clinical or laboratory signs of acute or chronic infection or was taking any medication at the time of the study. The protocol was approved by the Tribal Council of the Gila River Indian Community and by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases. All subjects provided written informed consent before participation.

Cross-sectional analyses were carried out in 113 nondiabetic (80 NGT/33 IGT) Pima Indians (42 female and 71 male), who had been characterized for serum resistin levels, white blood cell count (WBC), body composition, fasting and 2-h plasma glucose and insulin levels, basal hepatic glucose output (BHGO), whole-body insulin sensitivity (*M*), hepatic insulin sensitivity (hepatic glucose output [HGO]), and acute insulin secretory response (AIR) (Table 1). Plasma adiponectin levels were available in 83 subjects (26 female and 57 male).

Prospective analyses were performed in 34 subjects who had NGT at baseline, were nondiabetic at follow-up, and had baseline serum resistin levels and follow-up assessment of body composition, fasting and 2-h plasma glucose and insulin levels, *M*, BHGO, HGO, and AIR. Prospective analyses were restricted to individuals with NGT because these analyses are intended to identify etiologic risk factors of disease in healthy individuals.

All subjects were admitted for 8–10 days to the National Institutes of Health Clinical Research Unit in Phoenix, Arizona, where they were fed a weight-maintaining diet (50, 30, and 20% of daily calories provided as carbohydrate, fat, and protein, respectively) and abstained from strenuous exercise. Body composition was estimated by underwater weighing, with simultaneous determination of residual lung volume by helium dilution (19) or by total body dual-energy X-ray absorptiometry (Lunar Radiation, Madison, WI) with calculations of percent body fat, fat mass, and fat-free mass performed as previously described (20). Waist and thigh circumferences were measured at the umbilicus in the supine position, the gluteal fold was measured in the standing position, and the waist-to-thigh ratio was calculated as an index of body fat distribution.

At least 3 days after admission and after a 12-h overnight fast, subjects underwent a 2-h 75-g OGTT (17). Plasma glucose levels were determined by the glucose oxidase method (Beckman Instruments, Fullerton, CA) and plasma insulin levels by an automated immunoassay (Access; Beckman). Fasting serum resistin levels were determined by enzyme-linked immunosorbent assay (BioVender Laboratory Medicine, Brno, Czech Republic) with an intra-assay variation of 4.3% and an interassay variation of 7.2% at a standard level of 6.2 and 6.6 ng/ml resistin, respectively. All samples were run in duplicate in a single assay. Total WBC was evaluated on admission. WBC was measured in the local laboratory by an automated cell counter. Reliability coefficients, based on blind replicated control data, were 0.96–1.00.

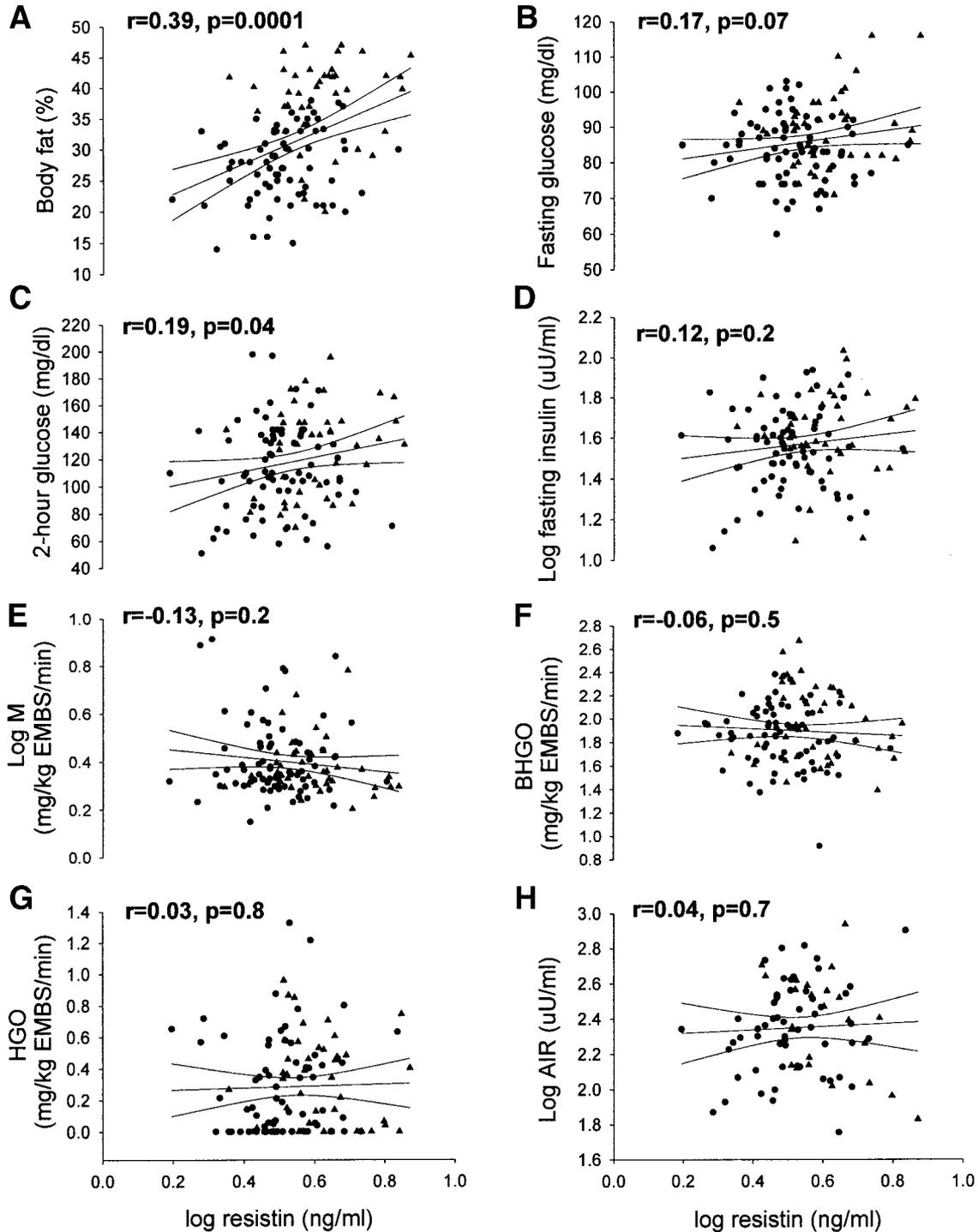
Insulin action was assessed by hyperinsulinemic-euglycemic glucose clamp, as previously described (21). In brief, after an overnight fast, a primed continuous intravenous insulin infusion was administered for 100 min at a constant rate of 290 pmol (40 mU) · m<sup>2</sup> body surface area<sup>-1</sup> · min<sup>-1</sup>. This infusion achieved steady-state plasma insulin levels of 172 ± 32 μU/ml (means ± SD). The rate of total insulin-stimulated glucose disposal was calculated for the last 40 min of the insulin infusion (*M*). The rate of endogenous glucose output was calculated before insulin infusion (calculated from Steele's equation using a primed [30 μCi], continuous [0.3 μCi per min] 3-<sup>3</sup>H-glucose infusion) and during the last 40 min of insulin infusion (HGO). *M* was also corrected for the rate of HGO (21), adjusted for the steady-state plasma glucose and insulin levels, and normalized to the estimated metabolic body size (EMBS; fat-free mass + 17.7 kg), as previously described (21).

AIR was measured in response to a 25-g intravenous glucose tolerance test and calculated as the average incremental plasma insulin level from the 3rd to the 5th min after the glucose bolus (21).

**Statistical analyses.** Statistical analyses were performed using software of the SAS Institute (Cary, NC). Results are given as means ± SD. Fasting serum resistin, insulin levels, WBC, AIR, and *M* were logarithmically transformed to approximate a normal distribution.

In the cross-sectional analyses, the relation between serum resistin levels

## Cross-sectional analyses



**FIG. 1.** Correlation between fasting serum resistin levels and percent body fat, fasting and 2-h glucose, fasting insulin, whole-body (*M*) and hepatic (BHGO and HGO) insulin sensitivity, and AIR in 42 male (●) and 71 female (▲) nondiabetic Pima Indians.

and selected anthropometric and metabolic variables was examined by calculation of Pearson's correlation coefficient. No attempt was made to correct the significance of these correlations to account for multiple comparisons (22). Partial correlations were used to examine the relation between serum resistin levels and fasting and 2-h glucose and insulin levels, adiponectin levels, *M*, BHGO, HGO, and AIR after adjustment for percent body fat. A stepwise linear regression model was used to examine determinants of serum resistin levels.

In the prospective analyses, the predictive effect of serum resistin levels at baseline on change (follow-up adjusted for baseline) in percent body fat, fasting and 2-h glucose and insulin levels, *M*, BHGO, HGO, and AIR were evaluated using multiple linear regression models. Models were adjusted for sex, age at follow-up, and time to follow-up and, in the case of metabolic variables, also for change in body fat. Differences between anthropometric and metabolic characteristics at baseline and follow-up were assessed by paired *t* tests.

TABLE 2

Correlation between serum resistin levels at baseline and changes (from baseline) in metabolic variables in prospective analyses

	Unadjusted log baseline resistin	Adjusted for change in percent body fat
Δ Percent body fat	0.34*	—
Δ Weight	0.24	—
Δ Fasting plasma glucose	0.18	0.10
Δ 2-h plasma glucose	-0.12	-0.21
Δ Fasting plasma insulin	0.36*	0.26
Δ 2-h plasma insulin	0.10	0.08
Δ Log <i>M</i>	-0.10	0.02
Δ Log AIR (μU/ml)	-0.06	-0.06
Δ BSGO	-0.28	-0.19
Δ HGO	0.37*	0.23

Changes are expressed as follow-up variable adjusted for baseline and adjusted for sex, age at follow-up, time of follow-up, and change in body fat. Data given for  $n = 34$ . \* $P < 0.05$ .

## RESULTS

The anthropometric and metabolic characteristics for the subjects included in the cross-sectional and prospective analyses are summarized in Table 1.

**Cross-sectional analyses.** Serum resistin levels were higher in female compared with male subjects ( $4.3 \pm 1.2$  vs.  $3.3 \pm 0.9$  ng/ml, respectively;  $P = 0.0001$ ) before and after adjustment for percent body fat ( $P = 0.01$ ). There was no difference in serum resistin levels between subjects with NGT and IGT ( $3.6 \pm 1.1$  vs.  $3.8 \pm 1.2$  ng/ml, respectively;  $P = 0.9$ ).

Serum resistin levels were positively associated with weight ( $r = 0.19$ ,  $P < 0.05$ ), percent body fat ( $r = 0.39$ ,  $P = 0.0001$ ) (Fig. 1), BMI ( $r = 0.26$ ,  $P = 0.005$ ), and 2-h glucose ( $r = 0.19$ ,  $P = 0.04$ ) (Fig. 1). Serum resistin levels were not associated with waist-to-thigh ratio, fasting glucose, fasting and 2-h insulin levels, *M*, BHGO, HGO, or AIR ( $r = -0.03$ ,  $0.17$ ,  $0.12$ ,  $0.06$ ,  $-0.13$ ,  $-0.06$ ,  $-0.03$ , and  $-0.04$ , respectively; all  $P > 0.05$ ). Serum resistin levels were also not associated with WBC before ( $r = 0.09$ ,  $P = 0.4$ ) or after ( $r = 0.01$ ,  $P = 0.9$ ) adjustment for percent fat. There was no association between serum resistin levels and 2-h glucose ( $r = 0.06$ ,  $P = 0.6$ ) after adjustment for percent body fat. The relation between serum resistin levels and percent body fat did not differ between male and female subjects ( $P = 0.4$ ).

In a stepwise multiple regression analysis including age, sex, percent body fat, and all metabolic variables (fasting and 2-h glucose levels, insulin levels, *M*, BHGO, HGO, and AIR), percent body fat ( $P = 0.0008$ ) was the only independent determinant of serum resistin, explaining 13% of the variance.

In 83 individuals in whom plasma adiponectin levels were also available, there was a positive association between plasma adiponectin levels and serum resistin levels after adjustment for percent body fat ( $r = 0.26$ ,  $P = 0.02$ ).

**Prospective analyses.** Higher serum resistin levels at baseline were not associated with a worsening of *M* (Tables 2 and 3). They were associated with an increase in percent body fat (Tables 2 and 3; Fig. 2A), fasting plasma insulin, and HGO ( $r = 0.34$ ,  $0.36$ , and  $0.37$ , respectively; all

TABLE 3

Multivariate associations between serum resistin levels at baseline and change in percent body fat and insulin sensitivity (*M*) adjusted for sex, age at follow-up and time of follow-up.

	Estimate	Standard error	<i>P</i>
Body fat at follow-up (%)			
Intercept	10.1	4.2	0.02
Age at follow-up (years)	-0.04	0.09	0.6
Sex	1.72	1.55	0.3
Body fat at baseline (%)	0.51	0.09	0.0001
Time of follow-up (years)	0.000008	0.00007	0.9
Serum resistin (ng/ml)	10.0	5.1	0.04
<i>M</i> at follow-up (mg · kg EMBS <sup>-1</sup> · min <sup>-1</sup> )			
Intercept	0.70	0.19	0.001
Age at follow-up (years)	-0.004	0.002	0.1
Sex	0.08	0.006	0.02
Body fat at baseline (%)	-0.01	0.02	0.0001
Body fat at follow-up (%)	0.001	0.004	0.8
<i>M</i> at baseline (mg · kg EMBS <sup>-1</sup> · min <sup>-1</sup> )	0.04	0.01	0.007
Time of follow-up (years)	0.000001	0.00002	0.6
Serum resistin (ng/ml)	0.03	0.2	0.9

$P < 0.05$ ) after adjustment for sex, age, and time to follow-up. Serum resistin levels at baseline were not associated with an increase in weight ( $r = 0.25$ ,  $P = 0.2$ ) (Fig. 2B). After additional adjustment for the change in percent body fat, there was no association between baseline serum resistin levels and change of plasma insulin and HGO ( $r = 0.26$  and  $0.23$ ; both  $P > 0.1$ ) (Table 2).

## DISCUSSION

In the present study, we sought to describe the relation between serum resistin levels and obesity and insulin resistance in Pima Indians, a population with marked obesity and insulin resistance and one of the highest reported prevalence rates of type 2 diabetes in the world (16). We found that high serum resistin levels were cross-sectionally associated with adiposity, but not with whole-body or hepatic insulin resistance. Prospectively, there was no relation between baseline resistin and changes in insulin resistance, but there was a surprising association between high serum resistin and increased adiposity.

Our cross-sectional analyses confirmed that in nondiabetic individuals, serum resistin levels are not associated with whole-body insulin resistance, which was assessed by a more direct measure of insulin action than any other previously published (9,12,14,23,24). Infusion of recombinant resistin into rats rapidly induced hepatic insulin resistance without a change in peripheral insulin resistance, suggesting that the observed increases in blood glucose may have resulted entirely from actions of resistin on the liver (6). Here we showed that in Pima Indians, serum resistin levels are not associated with hepatic insulin resistance. Low plasma adiponectin has been shown to predict the decrease in insulin sensitivity and type 2 diabetes in Pima Indians (25,26). The positive relation between circulating adiponectin and resistin levels further disproves the hypothesis of a role of resistin in the development of insulin resistance. Thus, our data add

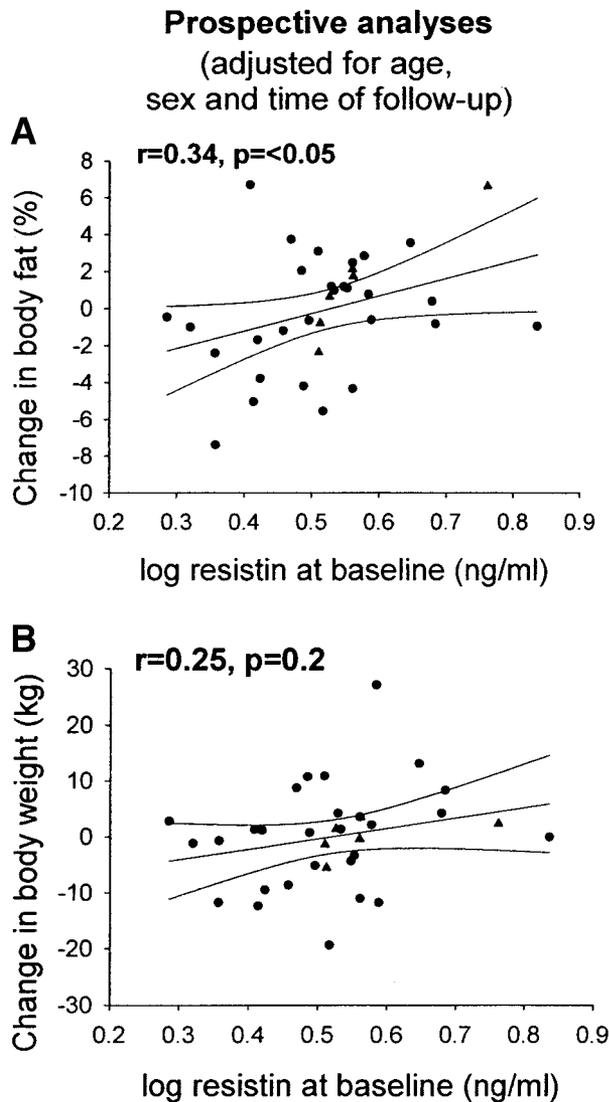


FIG. 2. Correlation between the logarithm of fasting serum resistin levels (log resistin) at baseline and changes in percent body fat (A) and body weight (B) adjusted for sex, age at follow-up, and time to follow-up in 28 male (●) and 6 female (▲) Pima Indians with NGT at baseline.

to a growing body of evidence indicating that in humans, unlike in rodents, there is no direct relation between circulating levels of resistin and insulin action in peripheral tissues (9,12,14,23,24).

Human studies looking at the association between resistin and obesity are controversial. Whereas two studies reported no association between resistin expression in adipocytes and body weight (8,12), one study has documented significantly greater resistin protein levels in subcutaneous adipose tissue homogenates from obese subjects in comparison with lean subjects (11). In serum, resistin levels were greater in obese subjects than in lean subjects (14) and positively correlated with adiposity (15). In the present study, we showed that higher serum resistin levels were associated with adiposity. Moreover, we have added the novel finding that high serum resistin levels may be associated with future increases in adiposity.

Although some studies in rodents suggest that resistin may promote lipogenesis or be a marker of the lipogenic

state (27), the explanation for our observation of an effect of resistin on future adiposity is not immediately apparent, especially because resistin has also been shown to inhibit differentiation of 3T3-L1 and rodent preadipocytes to adipocytes (27). Furthermore, given the strong relation between changes in adiposity and worsening of insulin resistance, it is quite surprising that resistin was selectively associated with a change in percent body fat, but not with  $M$  in this study. Whether resistin has paracrine and/or endocrine properties remains an open question (28), although the results of a recent study seems to negate the former possibility (29). Although a predominantly paracrine role might explain the weakness of the correlations between circulating resistin and some of the metabolic variables, it would not explain why we found an association with changes in percent body fat, but not body weight (i.e., tissue remodeling). Therefore, we believe that the true nature of our observation remains largely unexplained and that caution should be exercised in drawing definitive conclusions until independent confirmation of this initial finding is obtained in a larger group of Pima Indians or in other populations. If our observation is replicated, it will be important also to understand how circulating resistin changes in response to changes in body composition, an aspect not addressed in our study.

We conclude that higher serum resistin levels predict future increases in percent body fat, but not changes in insulin resistance in Pima Indians. Our data suggest that resistin promotes development of obesity, but does not seem to play a role in the development of insulin resistance in humans.

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