Serum Resistin Levels Are Associated with Adiposity and Insulin Sensitivity in Obese Hispanic Subjects

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Abstract

Background and Aims: Resistin is involved in the development of obesity and insulin resistance (IR) in mice and may play a similar role in humans through mechanisms that remain unresolved. The objective of this study was to characterize the relationship between resistin levels in obese subjects with and without IR among Hispanic subjects.

Material and Methods: A cross-sectional study was performed on 117 nondiabetic Hispanic subjects of both genders that were allocated into three study groups: A control group ($n=47$) of otherwise healthy individuals in metabolic balance, a group with obesity (OB) ($n=36$), and a group with obesity and IR (OB-IR) ($n=34$). Anthropometric and clinical characterization was carried out, and resistin levels were determined by enzyme-linked immunosorbent assay (ELISA).

Results: We found that resistin levels were higher in OB and OB-IR groups when compared to the control group (1331.79 ± 142.15 pg/mL, 1266.28 ± 165.97 pg/mL vs. 959.21 ± 171.43 pg/mL; $P < 0.05$), an effect that was not confounded by age (control, 34.04 ± 10.00 years; OB, 37.30 ± 10.78 years; and OB-IR, 35.67 ± 10.15 years). In addition, we observed a significant correlation ($P < 0.001$) between resistin levels and higher adiposity and insulin sensitivity (IS) in our cohort.

Conclusions: Our results suggest that higher resistin levels are associated with higher adiposity and lower IS among obese Hispanic subjects.

Introduction

OBESITY IS A GROWING GLOBAL epidemic. It is associated with the development of insulin resistance (IR), dyslipidemia, and type 2 diabetes mellitus (T2DM).¹ There is evidence that a variety of hormones, cytokines, growth factors, and bioactive compounds, such as adipokines, that participate in controlling insulin sensitivity (IS) and energy homeostasis are associated with the pathophysiology of obesity.^{2–4}

Resistin, a cysteine-rich adipokine induced during adipogenesis, is proposed as a link between obesity and T2DM and may modulate numerous steps in the insulin-signaling pathway leading to IR.^{5–7} *In vitro* studies in 3T3-L1 adipocytes showed that neutralization of resistin with resistin antiserum led to enhanced insulin-stimulated glucose uptake

and decreased IR.¹ Studies in high-fat diet-induced obese mice showed increased levels of circulating resistin while immunoneutralization of circulating resistin in these animals improved IS.¹ Similar increases in resistin levels were observed in genetic models of obesity, such as the *ob/ob* mouse.⁸

Studies of the pathophysiological role of resistin in human subjects are not as clear. For example, there are reports showing that adipose tissue from obese diabetic subjects has high levels of resistin mRNA expression.^{9–11} Other studies have shown higher serum resistin levels in obese subjects when compared with lean subjects,^{12–14} effects that correlated with changes in body mass index (BMI) and visceral fat area.^{14–17} A more recent study of nondiabetic, obese, Caucasian Italian subjects and adult first-degree relatives

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showed that serum resistin levels were highly heritable, supporting the contention that this adipokine may play a pathogenic role in IR-related abnormalities.¹⁸ However, a study of middle-aged women and healthy young subjects failed to observe any correlation of serum¹⁸ or plasma levels of resistin with markers of adiposity.¹⁹ In addition, studies have reported that in obese female subjects resistin levels correlated with waist circumference (WC) and fat mass but not with BMI.²⁰ These studies suggest that potential confounding variables, such as the presence of ethnic variability, may be distorting the true relationship between resistin, obesity, and IR, thus underscoring the need to further evaluate the relationship between resistin levels and IR in ethnically uniform populations. We evaluated the levels of circulating resistin in obese subjects with and without IR from a cohort of Hispanic subjects from the city of Puebla, Mexico. Our results show that high serum resistin levels are associated with adiposity and low IS in obese Hispanic subjects.

Materials and Methods

Subjects and setting

This was a cross-sectional study of randomly enrolled individuals from the urban and rural communities affiliated with the Family Medical Unit No. 2 (UMF-2) of the Instituto Mexicano del Seguro Social (IMSS) who resided in the city of Puebla, Mexico. The study was approved by IMSS Scientific Research and Ethics Committee. All participants provided written informed consent before study participation and were interviewed for a complete clinical history and anthropometric-biochemical assessment. Subjects were excluded if they did not sign informed consent, did not conclude the clinical history or blood sampling, had chronic proinflammatory diseases (arthritis, rhinitis, or trauma), had endocrine diseases (hyperthyroidism or hypothyroidism), had a previous diagnosis of T2DM, or were women who were pregnant or breastfeeding.

We selected a cohort of 117 subjects (84 females and 33 male) between the ages of 21 and 60 years and without a diagnosis of prediabetes. The subjects were classified into three study groups: (1) Control and otherwise healthy group of subjects that were not overweight or obese (BMI < 25 kg/m²), WC < 80 cm females and < 90 cm males, fasting glucose < 100 mg/dL, glucose 2-hr postload < 140 mg/dL, insulin < 11 μ U/mL, and without IR [homeostatic model assessment of insulin resistance (HOMA-IR) < 2.5]²¹; (2) the obese group (OB) was comprised of subjects with a BMI $\geq$ 30 kg/m² and HOMA-IR < 2.5; (3) the obese and insulin-resistant group (OB-IR) was composed of subjects with BMI $\geq$ 30 kg/m² and HOMA-IR $\geq$ 2.5.

Anthropometric measurements

The height, weight, and percentage body fat (%BF) were determined using an electronic digital scale (Tanita Body Composition Analyzer, Model TBF-215, Tokyo, Japan). WC was established around the waist (using a fiberglass tape with SECA mark) in a position parallel to the floor at the midpoint between the lower edge of the last rib and the edge of the iliac crest, at the end of expiration. BMI was calculated as weight (kg)/height (m²). The waist-to-hip ratio (WHR) was calculated as WC (cm)/hip circumference (HC) (cm).

Biochemical measurements

Blood was obtained from all participants following a 12-hr overnight fast by venipuncture. The determination of fasting glucose, total cholesterol (TC), triacylglycerol (TAG), high-density lipoprotein cholesterol (HDL-C), and a 2-hr glucose postload of 75 grams of glucose were performed according to conventional laboratory protocols. Because the Castelli Cardiovascular Index (CVI) has been used by others to characterize the risk of developing cardiovascular disease in humans,²² we calculated CVI in our cohort using the formula: TC/HDL-C.²³ The levels of plasma glucose and lipid profile were determined using the Synchron CX5 Analyzer System from Beckman Coulter (Fullerton, CA). Insulin levels were determined by chemiluminescence immunoassay (Luminometer Beckman Coulter Access System).

IR in our cohort was classified by a HOMA-IR $\geq$ 2.5, as previously reported for a Mexican population.²⁴ IS was determined using quantitative insulin-sensitivity check index (QUICKI), where low IS was defined by a QUICKI < 0.357.²⁵ Determination of β -cell function was performed using homeostatic model assessment of β -cell function (HOMA- β).²¹

Measurement of serum resistin levels

Resistin levels were measured in blood serum samples by enzyme-linked immunosorbent assay (ELISA) for human resistin (PeproTech, Rocky Hill, NJ). In the present investigation, the inter- and intraassay coefficients of variation were 3.5% and 7.3%, respectively.

Statistical analyses

Data were analyzed with SPSS for Windows version 19.0 (SPSS, Chicago, IL). The results were expressed as the means $\pm$ standard deviation unless otherwise stated. The Kolmogorov-Smirnov test was used to determine the normality of the data distribution. Continuous variables with normality and equal variances were analyzed using one-way analysis of variance (ANOVA). When data were not normally distributed but equal variances were observed, a Kruskal-Wallis test was used. Nonparametric continuous variables were analyzed using the Mann-Whitney U-test. A Spearman correlation test was used for variables, and multivariable linear regression analysis adjusted for age and gender was performed to determine the relation between serum resistin levels and other parameters. Differences between groups were considered significant at $P < 0.05$.

Results

Anthropometric measures, lipid profile, glucose metabolism, and measures of IR of the 117 study subjects are presented in Table 1. OB and OB-IR groups were significantly different from the control group for all the variables considered. Interestingly, the OB-IR group showed no significant differences in the anthropometric measures compared to OB group, except in the %BF where OB-IR had increased adiposity. In addition, we observed increased cardiovascular risk (CVI) that was accompanied with higher insulin levels and a reduced IS compared to OB group (Table 1). Serum levels of resistin were determined. The OB-IR and OB groups had higher levels of resistin than the control

TABLE 1. CHARACTERISTICS OF THE STUDY SUBJECTS IN TARGET POPULATIONS

	Control (n=47)	OB (n=36)	OB-IR (n=34)
Gender (F/M)	36/11	28/8	20/14
Age (years) ^b	34.04 ± 10.00	37.30 ± 10.78	35.67 ± 10.15
Anthropometry			
Weight (kg/m ²) ^b	56.44 ± 7.18	83.71 ± 10.86*	89.52 ± 13.39**
Height (cm) ^b	1.57 ± 0.07	1.58 ± 0.07	1.62 ± 0.10
BMI (kg/m ²) ^b	22.72 ± 1.62	33.30 ± 2.53*	33.94 ± 3.61**
WC (cm) ^b	79.33 ± 5.70	105.46 ± 9.56*	105.81 ± 9.00**
HC (cm) ^b	92.95 ± 4.67	113.19 ± 8.04*	113.39 ± 9.27**
WHR ^b	0.85 ± 0.04	0.93 ± 0.06*	0.93 ± 0.82**
%BF ^b	25.63 ± 8.31	34.61 ± 7.49*	38.61 ± 6.33** [†]
Lipid profile			
TAG (mg/dL) ^a	86.21 ± 31.72	150.36 ± 98.31*	218.58 ± 117.39** [†]
TC (mg/dL) ^b	164.85 ± 24.41	195.63 ± 43.72*	195.50 ± 36.66**
HDL-C (mg/dL) ^b	48.37 ± 11.32	43.57 ± 13.03*	36.68 ± 9.76** [†]
LDL-C (mg/dL) ^b	99.23 ± 21.25	121.98 ± 36.68*	115.10 ± 32.97**
VLDL-C (mg/dL) ^b	17.24 ± 6.34	30.07 ± 19.66*	43.71 ± 23.47** [†]
TAG/HDL-C ^a	1.96 ± 1.09	4.07 ± 4.11*	6.58 ± 4.42** [†]
CVI ^a	3.59 ± 1.08	4.82 ± 1.55*	5.57 ± 1.42** [†]
Glucose metabolism			
Fasting glucose (mg/dL) ^b	87.42 ± 6.02	88.13 ± 6.01*	92.11 ± 4.21** [†]
Glucose 2-hr postload (mg/dL) ^b	96.80 ± 16.95	101.63 ± 16.48*	108.97 ± 17.27** [†]
Fasting insulin (μU/mL) ^a	4.91 ± 1.87	7.25 ± 2.04*	19.27 ± 8.62** [†]
Insulin resistance index			
HOMA-IR ^a	1.07 ± 0.44	1.58 ± 0.48*	4.35 ± 1.85** [†]
HOMA-β ^a	74.54 ± 29.21	113.48 ± 68.18*	248.62 ± 135.91** [†]
QUICKI ^b	0.38 ± 0.028	0.35 ± 0.018*	0.31 ± 0.014** [†]
Resistin (pg/mL) ^b	959.21 ± 171.43	1266.28 ± 165.97*	1331.79 ± 142.15**

Results are expressed as mean ± standard deviation (SD).

^a*P* < 0.05 Mann-Whitney U-test.

^b*P* < 0.05 one-way Kruskal-Wallis test.

**P* < 0.05 between control and OB.

***P* < 0.05 between control and OB-IR.

[†]*P* < 0.05 between group OB and group OB-IR.

OB, obese group; OB-IR, obese and insulin-resistant group; F, female; M, male; BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist-to-hip circumference ratio; %BF, percentage body fat; TAG, triacylglycerides; TC, total cholesterol; HDL-C, cholesterol combined with high-density lipoprotein; LDL-C, cholesterol combined with low-density lipoprotein; VLDL-C, cholesterol combined with very-low-density lipoprotein; CVI, cardiovascular disease index; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β-cell function; QUICKI, index to check the quantitative insulin sensitivity.

group (1331.79 ± 142.15 pg/mL, 1266.28 ± 165.97 pg/mL vs. 959.21 ± 171.43 pg/mL; *P* < 0.05; Table 1). No gender differences were noted in serum resistin levels within each study group (Fig. 1).

To determine whether increases in serum resistin levels correlated with increases in adiposity (measured by %BF), IS (measured by QUICKI), correlation analysis using these variables was performed in the overall group. This analysis showed a significant positive relationship (*P* < 0.001) between adiposity (rho = 0.44) (Fig. 2A) and a negative relationship with IS (rho = -0.50) (Fig. 2B). In the overall group, multivariate linear regression analysis showed a significant association between resistin levels with adiposity (β = 0.23, *P* = 0.015) and IS (β = -0.38, *P* = 0.001), which were independent determinants of resistin levels with an *R*² of 0.304.

Discussion

We characterized the relationship between serum resistin levels and IS in obese Hispanic subjects with and without IR. We provide evidence that OB-IR and OB subjects showed higher levels of resistin than otherwise healthy controls, and that these higher levels of resistin are associated with high

adiposity and low IS in our study cohort. Our results support and expand previous reports showing higher serum resistin levels in obese subjects compared to lean subjects.^{7,9,10,12–15,26,27}

Of importance for the field, our results show an association of high resistin levels among obese subjects that did not have either T2DM or prediabetes. In addition and to the best of our knowledge, there are no other reports on resistin levels among obese Hispanic subjects.

Our study contrasts with that of others that failed to show an association between serum resistin levels and obesity^{11,28,29}; inconsistencies that we propose could be explained by differences in ethnicity as well as the target population studied. In addition, the cellular and physiological roles of resistin are not clearly established, and new roles continue to emerge.^{30–32} Resistin was first proposed to contribute to IR and was recognized as an important adipokine.^{3,19} Others have more recently shown that resistin can regulate lipid metabolism and preadipocyte differentiation.³⁰ Resistin can also function as a proinflammatory molecule *in vitro* as well as *in vivo*³³ and can modulate several molecular pathways involved in inflammatory responses, such as increasing the production of the proinflammatory cytokines, interleukin-8 (IL-8) and monocyte chemoattractant protein-1 (MCP-1) via

FIG. 1. Serum resistin levels by study groups and gender. OB, obese group; OB-IR, obese and insulin-resistant group.

activation of nuclear factor- κ B (NF- κ B).³⁴ Consistent with this proposal, macrophages and circulating leukocytes are recognized as important sources of resistin production in humans as well.¹⁰ Indeed resistin has been localized to the azurophilic granules within neutrophils, thus implicating

activated neutrophils as an important source of circulating resistin.³⁵ Consequently, because obesity is considered by some as a subacute inflammatory state that is also characteristic of IR, it is tempting to speculate that disordered inflammatory status and neutrophil activation may likewise contribute to differences in circulating resistin levels. Finally, genetic variance may contribute to circulating resistin levels as well. Several studies have reported an association of single-nucleotide polymorphisms of the resistin *RETN* gene with resistin levels in humans.^{36,37} Our present study, in an ethnically uniform obese population, took into account age as an important confounder.

In a cross-sectional study of nondiabetic Pima Indians, high serum resistin levels were associated with obesity and adiposity. Prospective analyses of this group showed that resistin levels predicted future increases in adiposity and suggest that resistin promotes future development of obesity.¹⁶ In our study population, we found a relationship between resistin levels and adiposity as determined by %BF. Results in our obese Hispanic cohort and the Pima Indians contrast with other reports that showed the absence of any relationship between adiposity and resistin levels,^{15,19,20,28} thus further supporting the contention of ethnic variability as a confounder when determining resistin levels. Moreover, there is controversy regarding the relationship between resistin levels and IR. Evidence exists supporting the absence of any correlation of resistin with IR,^{16,20,28,29,38,39} whereas others have shown a relationship.^{2,11,14,19,40,41} In our study, we did not observe any significant relationship between IR as determined by HOMA-IR and resistin levels. It is important to note that our OB-IR group differed from the OB group with regard to their adiposity, thus providing a possible explanation for the absence of a relationship with HOMA-IR in these groups.

FIG. 2. Correlation analyses of the overall study group. There are significant correlations between serum resistin levels with percentage body fat (%BF) (A) and quantitative insulin-sensitivity check index (QUICKI) (B). (▲) Control group; (●) obese (OB) group; (◆) obese insulin-resistant (OB-IR) group.

It has been reported that resistin levels rise in response to supraphysiological doses of insulin in obese subjects.¹⁵ Consequently, resistin expression may be acutely regulated by insulin,¹¹ and this suggests that subjects with higher fasting serum insulin will have higher levels of resistin. Consistent with these observations, we showed that in our cohort serum resistin levels were higher in subjects with obesity and obesity with IR than control subjects. However, we did not observe an association between resistin and insulin levels among our population.

There are reports showing that age^{15,42} and gender^{17,19,28,43} are factors that can influence resistin levels. In our cohort, age was not a factor because we observed no significant differences in age among our three groups. In addition, analyses of resistin levels by gender showed no significant differences between resistin levels in men compared to women, results that are consistent with observations from other groups.^{19,27} However, others have reported that resistin levels are significantly higher in females when compared with males,^{17,19,28,43} a discrepancy that may be due to the fact that our study was not balanced with respect to gender distribution. Therefore, it is possible that due to the low number of male subjects studied, our analyses did not have the power to detect differences in resistin levels with respect to gender and as such this result must be taken with caution.

Although our data would support the contention for a functional role of resistin in obesity, we acknowledge that cross-sectional studies such as ours cannot elucidate mechanisms or determine the direction of causality, and therefore prospective studies are clearly warranted in other populations and other ethnic groups to further clarify the role of resistin in obesity and IS. Additional limitations of our cross-sectional study include the age selection criteria we employed and the recruitment of only Hispanic subjects. Our study was powered for resistin levels, and as such all other relationships must be considered exploratory in nature. Future studies must account for genetic variance of the *RETN* gene and measures of proinflammatory markers such as TNF- α and IL-6 because these have been shown to directly stimulate the expression of resistin³⁴ and may be important confounders that must be clarified. Nonetheless, because Hispanics are disproportionately affected by obesity and its complications, our results provide valuable information on the relationship between resistin and obesity among a uniform group of Hispanic subjects.

Conclusion

Our results support the hypothesis that higher resistin levels are associated with higher adiposity and low IS among obese Hispanic subjects through complex mechanisms. Further detailed studies in other well-characterized groups are needed to understand these mechanisms and conclusively address the role of resistin in obesity.

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Author Disclosure Statement

No competing financial interests exist.

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