Association of Resistin with Insulin Resistance and Factors of Metabolic Syndrome in North Indians

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Abstract *Metabolic syndrome* (MetS) is a cluster of interrelated common clinical disorders. The role of resistin in insulin sensitivity and MetS is controversial till date. So, the aim of the present study was to investigate the relationship of plasma resistin levels with markers of the MetS in Indian subjects. In a case control study, total 528 subjects were selected for the study. 265 (194 male and 71 female) were cases (with MetS) and 263 (164 male and 99 female) were controls (without MetS). Required anthropometric measurements and calculations were carried out accordingly. All the Biochemical estimations were carried out according to standard protocol. Resistin level was measured by the standard protocol (By ELISA i.e. enzyme linked immunosorbent assay) as illustrated in the kit. Insulin level was also measured by the standard protocol as illustrated in the kit and insulin resistance was calculated by the standard procedures. Plasma resistin levels were significantly higher in cases compared with controls (male = 13.05 ± 4.31 vs. 7.04 ± 2.09 ng/ml; $p \leq 0.001$

and female = 13.53 ± 4.14 vs. 7.42 ± 2.30 ng/ml; $p \leq 0.001$). Plasma resistin levels were well correlated with waist circumference, glucose, triglycerides, waist/hip ratio, systolic and diastolic blood pressure, high density lipoprotein, total cholesterol, serum low density lipoprotein, serum very low density lipoprotein, insulin and insulin resistance. Plasma resistin levels were elevated in presence of the MetS and were associated with increased metabolic risk factors.

Keywords Resistin · Metabolic syndrome · Insulin resistance · Triglyceride · Insulin · Waist circumference

Introduction

Resistin is a 12.5 kDa (Kilo Dalton) protein, made up of 114 amino acids, which belongs to the “resistin-like molecule” family [1, 2]. The main function of resistin in

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humans is still unclear. Studies in rodents have suggested resistin as a link between obesity, insulin resistance (IR) and diabetes [3, 4]. In humans, data on the role of this adipokine in insulin sensitivity and obesity are controversial [5]. Studies also suggested that mice injected with recombinant resistin or over expressing resistin had impaired glucose tolerance and insulin action. [6]. In addition, resistin was found to be an in vitro antagonist of insulin in human pre-adipocytes [7]. It was found that human hepatic cells over expressing resistin had impaired glucose uptake and glycogen synthesis. Some studies suggested a close relationship of resistin with inflammatory and fibrinolytic markers and this relationship may mediate the association of resistin with IR and metabolic syndrome (MetS) [8, 9]. Resistin is clearly involved in inflammation but its specific function in that situation remains to be clarified. Because of its link with obesity and inflammation and its potential link with insulin resistance, resistin has been tagged as a potential MetS marker. Supporting this theory, adults with MetS tend to have higher resistin levels than the healthy counterparts. In a study authors have concluded that the resistin levels are not associated with markers of IR and/or central obesity. However, the resistin levels are associated with the total body fat mass and with markers of systemic inflammation in lean healthy subjects [10]. In a study on obese class II, leptin concentration was significantly higher than in obese class I, but adiponectin and resistin were not different [11]. However, the correlation between IR and plasma resistin in adult humans remains controversial, supported by some studies [12] and not by some others [13, 14], therefore, weakening the relation between resistin and MetS. Some authors indicated that increased plasma resistin levels were

associated with increased obesity, visceral fat [1, 15, 16] insulin resistance, and type 2 diabetes [12], while other groups failed to observe such correlations [17, 18]. Furthermore, the contribution of resistin to the MetS is still under investigation [19, 20].

The aim of the present study was thus to investigate the relation of plasma resistin levels with markers of the MetS and biochemical characteristics in a case control study in Indian subjects.

Materials and Methods

Study Design

This is a case control study, conducted in north Indian adult subjects with age between 20 and 40 years. All the subjects were diagnosed according to the NCEP ATP III (National Cholesterol Education Program—Adult Treatment Panel-III) criteria for MetS [21]. We enrolled 528 adult subjects for the study of which 170 were female and 358 were male. All the participants in this study were non-alcoholic as well as non-diabetic and were without any kind of cardiac, respiratory, inflammatory and metabolic diseases. A structured performa was filled to collect the information regarding their behavioral, medical, personal, familial as well as dietary history. The study was approved by the ethical committee of our institute and by the Indian Council of Medical Research (ICMR), New Delhi. Written informed consent was obtained from all the subjects. This study was conducted under the principles of the Declaration of Helsinki.

Table 1 Summary of demographic and biochemical analysis of human volunteers enrolled in the study

Variables	Male (n = 358)		p value	Female (n = 170)		p value
	Controls (n = 164)	Cases (n = 194)		Controls (n = 99)	Cases (n = 71)	
Age (years)	31.76 ± 5.24	32.56 ± 4.58	NS	30.92 ± 5.07	31.74 ± 4.72	NS
Height (cm)	166.14 ± 7.31	167.25 ± 6.86	NS	154.06 ± 6.14	154.15 ± 5.81	NS
Weight (kg)	63.65 ± 10.08	83.38 ± 13.68	0.001	54.06 ± 9.58	68.82 ± 8.02	0.001
BMI (kg/m ²)	22.99 ± 2.93	29.7 ± 3.82	0.001	22.82 ± 4.06	28.93 ± 3.85	0.001
HC (cm)	90.59 ± 7.10	102.43 ± 7.61	0.001	90.56 ± 9.10	96.52 ± 7.94	0.001
WHR	0.92 ± 0.07	1.05 ± 0.06	0.001	0.83 ± 0.08	0.94 ± 0.10	0.001
TC (mg/dl)	152.89 ± 26.97	182.12 ± 34.88	0.001	155.28 ± 45.01	173.83 ± 41.63	0.009
VLDL (mg/dl)	23.00 ± 7.18	35.90 ± 07.95	0.001	21.27 ± 8.19	32.20 ± 5.88	0.001
LDL (mg/dl)	85.52 ± 26.13	108.82 ± 33.82	0.001	85.72 ± 32.16	101.26 ± 32.39	0.002
TC/HDL	3.52 ± 0.83	4.94 ± 1.25	0.001	3.56 ± 1.32	4.43 ± 1.35	0.001
HDL/LDL	0.58 ± 0.25	0.39 ± 0.19	0.02	0.62 ± 0.35	0.44 ± 0.17	0.001
LDL/HDL	1.98 ± 0.0.74	2.95 ± 1.10	0.001	2.22 ± 0.91	2.59 ± 0.97	0.012

Values are presented as mean ± SD and significance was calculated between control versus case $p < 0.05$ = Significant

BMI body mass index, *HOMA-IR* homeostasis model assessment-insulin resistance, *TC* total cholesterol, *HDL-C* high density lipoprotein-cholesterol, *VLDL* very low density lipoprotein, *LDL* low density lipoprotein

Fig. 1 Analysis of parameters of MetS of human volunteers enrolled in the study. Values are presented as mean $\pm$ SD and significance was calculated between controls versus cases. WC waist circumference; TG Triglyceride; SBP Systolic Blood Pressure; DBP Diastolic Blood Pressure; BP blood pressure; HDL-C high density lipoprotein-cholesterol)

Samples were divided into case and control groups. Controls are comprised of 263 adult healthy human samples (of these 263 samples, 164 were male (mean age 31.76 ± 5.24 years, WC 83.68 ± 10.83 cm, WC = waist

circumference) and 99 were female (Mean age 30.92 ± 5.07 years, WC 75.63 ± 12.46 cm) without MetS and case group comprised of 263 age matched healthy human subjects with MetS, (of these 265 cases 194 were male (mean age 32.56 ± 4.58 years; WC 106.45 ± 10.08 cm) and 71 were female (mean age 31.74 ± 4.72 years; WC 91.69 ± 13.51 cm). Furthermore, all samples were collected from Lucknow and nearby areas.

Anthropometric Measurements

All the subjects were evaluated, in addition to waist hip ratio (WHR, a good marker for measuring central/visceral obesity), through the following anthropometric parameters: body mass index (BMI), height (Ht.), weight (Wt.), WC, blood pressure (BP), and pulse rate. BMI was calculated as weight (in kilograms) divided by height (in meters) squared.

Biochemical Measurements

Blood samples for measuring the biochemical parameters were collected in the morning after 12 h of fasting. From

Fig. 2 Shows the concentration of Resistin in **a** controls and cases **b** male and female controls and cases and **c** indicates the fasting plasma insulin (FPI) and homeostasis model assessment (HOMA) index in male and female controls and cases

Fig. 3 Pearson correlation of serum resistin (ng/ml) with **a** waist circumference (cm), **b** systolic blood pressure (mmHg) (SBP), **c** diastolic blood pressure (mmHg) (DBP), **d** fasting plasma glucose (mg/dl), **e** serum triglyceride (mg/dl) (TG), and **f** serum high density lipoprotein in 358 north Indian male volunteers aged between 20 and 40 years

3.0 ml of the blood, serum/plasma was separated. Estimation of Plasma glucose was done by Glucose oxidase per-oxidase (GOD-POD) method (Randox Laboratories Ltd., Antrim, UK) and Serum Lipid profile was done by enzymatic method (Randox Laboratories Ltd., Antrim, UK). Plasma Insulin was estimated by immuno-radiometric assay method (Immunotech Radiova, Prague). Subsequently, IR was calculated by homeostatic model assessment index (HOMA index), using the equation:

$$\text{HOMA index} = \frac{\text{fasting insulin } (\mu\text{U/I}) \times \text{fasting glucose (mmol/l)}}{22.5}$$

Determination of Plasma Resistin Levels

The plasma concentration of resistin was measured with a sandwich ELISA kit (Biovendor Research and Diagnostic Products, CZECH REPUBLIC), according to the manufacturer's instructions. Plasma samples were diluted with 1:3 with dilution buffer. The lowest level of human resistin detectable by the assay was 0.1 ng/ml. The inter-assay variability was 5.1 % and the intra-assay variability was

2.8 %. For this analysis, an aliquot of plasma kept at -20°C was thawed for the first time and processed.

Statistical Analysis

Results are expressed as mean $\pm$ SD (standard deviation). Groups were compared by Student's *t* test. Correlation analysis was used to assess association of circulating resistin level with demographic characteristics and biochemical profiling in control, cases and both (control + cases). A two-tailed ($\alpha = 2$) $p < 0.05$ was considered statistically significant. Furthermore multiple regression analysis was performed to know about the factor of MetS which was significantly associated with the development of MetS.

Result

Physiological and biochemical parameters of control and cases are depicted in Table 1. The mean levels of all five characteristics of MetS (WC, BP, glucose, triglyceride and

Fig. 4 Pearson correlation of serum resistin (ng/ml) with **a** waist circumference (WC) (cm), **b** systolic blood pressure (SBP) (mmHg), **c** diastolic blood pressure (DBP) (mmHg), **d** fasting plasma glucose (mg/dl), **e** serum triglyceride (mg/dl), and **f** serum high density lipoprotein (HDL) in 170 north Indian female volunteers aged between 20 and 40 years

HDL-cholesterol) in cases (with MetS) were found to be significantly higher as compared to control (without MetS) in both the sexes (Fig. 1). Similarly, the serum resistin levels (mean $\pm$ SD) were also significantly higher in cases compared to controls (in case of males 13.05 ± 4.31 vs. 7.04 ± 2.09 ng/ml; $p \leq 0.001$ and in case of females 13.53 ± 4.14 vs. 7.42 ± 2.30 ng/ml, $p \leq 0.001$ (Fig. 2). We observed a significant difference in levels of biochemical parameters of cases compared to controls. We also observed a significant difference in levels of parameters of MetS of cases compared to controls in males as well as females (Fig. 1). Serum resistin levels were not correlated with the age of the cases and controls in both of the sexes. We observed that plasma resistin levels were positively correlated with glucose, triglycerides, waist circumference, waist/hip ratio, systolic and diastolic blood pressure while they were inversely correlated with HDL levels, thus suggesting the correlation of plasma resistin levels with the determinants of the MetS in both of the sexes (Figs. 3, 4).

In male cases a positive correlation of resistin was observed with total cholesterol, very low density lipoprotein (VLDL) and low density lipoprotein (LDL). While in female cases positive correlation of resistin was observed with total cholesterol (TC) and VLDL and it was negatively correlated with LDL. One important observation that HOMA-IR was positively correlated with resistin in both male ($r = 0.484$; $p = 0.001$) and females ($r = 0.439$; $p = 0.001$) (Table 2).

We also performed multiple regression analysis including all the parameters in the statistical model and observed that only triglycerides are significantly correlated to plasma resistin levels (Tables 3, 4).

When subjects were stratified according to the presence of increasing number of determinants of the MetS, plasma resistin levels significantly increase with the increasing number of the determinants of MetS.

Other anthropometric parameters like BMI, HC, WHR were also significantly higher in cases as compared to the controls in both the sexes (In case of Males BMI

Table 2 Pearson correlation (r) of plasma resistin levels with anthropometric and biochemical variables in total samples, (male n = 358, and female n = 170)

Variables	Male Samples (n = 358)		Female Samples (n = 170)	
	Correlation coefficient (r)	p value	Correlation coefficient (r)	p value
BMI (Kg/m ²)	0.506	0.001	0.503	0.001
TC (mg/dl)	0.317	0.001	0.151	0.049
LDL-C (mg/dl)	0.263	0.001	0.102	0.186
VLDL (mg/dl)	0.427	0.001	0.350	0.001
TC/HDL-C ratio	0.368	0.001	0.238	0.002
HOMA-IR	0.484	0.001	0.439	0.001

BMI body mass index, *HOMA-IR* homeostasis model assessment-insulin resistance, *TC* total cholesterol, *HDL-C* high density lipoprotein-cholesterol, *VLDL* very low density lipoprotein, *LDL* low density lipoprotein

22.99 ± 2.93 vs. 29.7 ± 3.82 kg/m²; HC 90.59 ± 7.10 vs. 102.43 ± 7.61 cm; WHR 0.92 ± 0.07 vs. 1.05 ± 0.06 and in case of females BMI 22.82 ± 4.06 vs. 28.93 ± 3.85 kg/m²; HC 90.56 ± 9.10 vs. 96.52 ± 7.94 cm and WHR 0.83 ± 0.08 vs. 0.94 ± 0.10). Fasting plasma insulin and calculated HOMA index was also found significantly high in cases compared to the controls for both the sexes (males FPI (μU/ml) 6.55 ± 1.85 vs. 11.68 ± 3.27; HOMA-IR 1.48 ± 0.53 vs. 3.17 ± 1.26 and females FPI (μU/ml) 6.52 ± 1.73 vs. 13.14 ± 3.40; HOMA-IR 1.47 ± 0.46 vs. 3.44 ± 1.78).

Discussion

This study shows that plasma resistin levels are correlated significantly with the factors of MetS like waist circumference, fasting plasma glucose, triglycerides, HDL-C, systolic and diastolic blood pressure in both male and female subjects. Resistin was also correlated significantly with waist/hip ratio, in male and female subjects. It was negatively associated with HDL-C levels. Resistin was also correlated positively with insulin resistance. Furthermore, plasma resistin levels increase with the number of determinants of the MetS.

Resistin is a protein involved in glucose homeostasis, lipid metabolism and insulin action [22]. Recently, in a study it is observed that resistin levels contributed to the development of obesity and type 2 diabetes mellitus in Egyptian population. The observed data among obese patients demonstrated that serum resistin is positively correlated with BMI, waist/hip ratio, total cholesterol, triglycerides, and LDL cholesterol, while it was negatively correlated with HDL cholesterol [23].

A study carried out by Kim et al. [24] demonstrated that there is an increased susceptibility to IR in patients with Behçet's disease (BD) as compared to healthy controls. They also hypothesized that serum resistin level may be an independent determinant for IR in BD patients.

According to Reilly et al. [25] plasma resistin levels are associated with inflammatory markers in a large, non-diabetic cohort as well as in type 2 diabetes. In spite of these findings, the role of resistin in the MetS is controversial. Some researchers reported that in human plasma resistin

Table 3 Multiple regression analysis for the relationship between resistin and different phenotypic and metabolic variables in male samples

Predictors	Coef.	SE	t Ratio	p value	95 % CI	
					Lower	Upper
Constant	14.940	7.457	2.003	0.046	0.324	29.556
BMI	0.035	0.108	0.329	0.742	−0.176	0.247
SBP	0.003	0.035	0.109	0.912	−0.065	0.072
DBP	−0.012	0.040	0.310	0.756	−0.092	0.067
WHR	−0.014	0.037	0.377	0.706	−0.087	0.059
WC	0.055	0.042	1.311	0.191	−0.027	0.138
GLU	−0.030	0.048	0.626	0.532	−0.125	0.064
TC	−0.007	0.017	0.434	0.664	−0.041	0.026
TG	0.041	0.011	3.722	0.0003	0.019	0.063
HDL-C	−0.057	0.082	0.699	0.485	−0.219	0.103
VLDL	−0.021	0.039	0.555	0.579	−0.099	0.055
LDL	0.024	0.023	1.051	0.294	−0.021	0.071
TC/HDL	−0.141	0.531	0.266	0.790	−1.183	0.899
HDL/LDL	0.420	2.623	0.160	0.872	−4.721	5.563
LDL/HDL	−0.491	0.757	0.649	0.517	−1.977	0.993
HOMA-IR	1.421	1.263	1.125	0.262	−1.054	3.896

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *WHR* waist to hip ratio, *WC* waist circumference, *GLU* glucose, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high density lipoprotein-cholesterol, *VLDL* very low density lipoprotein, *LDL* low density lipoprotein, *HOMA-IR* homeostasis model assessment-insulin resistance, *Coef.* coefficient, *SE* standard error, *95 %CI* 95 % confidence interval

Table 4 Multiple regression analysis for the relationship between resistin and different phenotypic and metabolic variables in female samples

Predictors	Coef.	SE	t ratio	p value	95 % CI	
					Lower	Upper
Constant	−63.979	82.143	0.778	0.439	−229.21	101.26
BMI	0.185	0.1801	1.027	0.309	−0.177	0.547
SBP	0.0934	0.065	1.432	0.158	−0.037	0.224
DBP	−0.026	0.102	0.261	0.785	−0.232	0.179
WHR	86.288	88.261	0.977	0.333	−91.263	263.84
WC	−0.932	0.928	1.004	0.320	−2.799	0.935
GLU	−0.207	0.152	1.363	0.179	−0.514	0.988
TC	0.108	0.185	0.580	0.5640	−0.265	0.481
TG	−0.046	0.036	1.264	0.212	−0.120	0.027
HDL	0.006	0.363	0.017	0.986	−0.724	0.737
VLDL	0.087	0.140	0.619	0.538	−0.196	0.370
LDL	−0.182	0.241	0.756	0.453	−0.668	0.303
TC/HDL	−1.758	7.596	0.231	0.817	−17.300	13.52
HDL/LDL	−1.510	5.059	0.298	0.766	−11.681	8.666
LDL/HDL	4.480	9.849	0.454	0.651	−15.334	24.292
HOMA-IR	5.793	4.793	1.20	0.232	−3.843	15.43

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *WHR* waist to hip ratio, *WC* waist circumference, *GLU* glucose, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high density lipoprotein-cholesterol, *VLDL* very low density lipoprotein, *LDL* low density lipoprotein, *HOMA-IR* homeostasis model assessment-insulin resistance, *Coef.* coefficient, *SE* standard error, *95 %CI* 95 % confidence interval

levels correlate with obesity, insulin resistance, and type 2 diabetes [1, 2, 26], while other authors failed to observe any correlation of plasma resistin levels with either metabolic or lipid markers, and no significant difference was observed in plasma resistin levels in subjects with the MetS compared to controls [17, 27]. Different explanations could account for these discrepancies, including the use of different assay methods, the low number of patients enrolled in the different studies, and the definition used to select patients with the MetS.

In 2011 Malo et al. [28] demonstrated that the plasma resistin concentration is associated with central obesity and other MetS components and is elevated in study subjects with MetS defined by different criteria in this cross-sectional, population-based study. These data clarify the inconsistent link between resistin, obesity, and MetS in the general population, providing further evidence that elevated resistin levels are related to these metabolic disturbances. Consistent with some previous reports in western and Japanese populations, plasma resistin was correlated with IR and low serum HDL cholesterol [29]. We also found that women had higher resistin concentrations than men.

Conclusion

In a case control study in Indian subjects we observed that, cases have significant higher values for the factors of MetS and serum resistin when compared with normal controls.

Serum resistin levels were very strongly correlated with serum triglyceride; a factor of MetS, in Indian males.

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Conflict of interest There is no conflict of interest exists among the authors.

References

1. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, et al. The hormone resistin links obesity to diabetes. *Nature*. 2001;409:307–12.
2. Steppan CM, Lazar MA. Resistin and obesity-associated insulin resistance. *Trends Endocrinol Metab*. 2002;1:18–23.
3. Juan CC, Au LC, Fang VS, Kang SF, Ko YH, Kuo SF, et al. Suppressed gene expression of adipocyte resistin in an insulin-resistant rat model probably by elevated free fatty acids. *Biochem Biophys Res Commun*. 2001;289:1328–33.
4. Le Lay S, Boucher J, Rey A, Castan-Laurell I, Krief S, Ferre P. Decreased resistin expression in mice with different sensitivities to a high-fat diet. *Biochem Biophys Res Commun*. 2001;289:564–7.
5. Ukkola O. Resistin—a mediator of obesity-associated insulin resistance or an innocent bystander? *Eur J Endocrinol*. 2002;147:571–4.
6. Palanivel R, Maida A, Liu Y, Sweeney G. Regulation of insulin signalling, glucose uptake and metabolism in rat skeletal muscle cells upon prolonged exposure to resistin. *Diabetologia*. 2006;1:183–90.
7. Kim KH, Lee K, Moon YS, Sul HS. A cysteine-rich adipose tissue specific secretory factor inhibits adipocyte differentiation. *J Biol Chem*. 2001;14:11252–6.
8. Qi Q, Wang J, Li H, Yu Z, Ye X, Hu FB. Associations of resistin with inflammatory and fibrinolytic markers, insulin resistance,

- and metabolic syndrome in middle-aged and older Chinese. *Eur J Endocrinol*. 2008;159:585–93.
9. Sharma P, Mishra S. Metabolic syndrome: early identification prevents type II diabetes and cardiovascular disease. *Indian J Clin Biochem*. 2007;22(1):1–3.
 10. Won JC, Park CY, Lee WY, Lee ES, Oh SW, Park SW. Association of plasma levels of resistin with subcutaneous fat mass and markers of inflammation but not with metabolic determinants or insulin resistance. *J Korean Med Sci*. 2009;24:695–700.
 11. Sinorita H, Asdie RH, Pramono RB, Purnama LB, Asdie AH. Leptin, Adiponectin and Resistin concentration in obesity class I and II at Sardjito Hospital Yogyakarta. *Acta Med Indones*. 2010;42:74–7.
 12. Wasim H, Al-Daghri NM, Chetty R, McTernan PG, Barnett AH, Kumar S. Relationship of serum adiponectin and resistin to glucose intolerance and fat topography in South-Asians. *Cardiovasc Diabetol*. 2006;2:5–10.
 13. Degawa-Yamauchi M, Bovenkerk JE, Juliar BE, Watson W, Kerr K, Jones R, et al. Serum resistin (FIZZ3) protein is increased in obese humans. *J Clin Endocrinol Metab*. 2003;11:5452–5.
 14. Heilbronn LK, Rood J, Janderoova L, Albu JB, Kelley DE, Ravussin E, et al. Relationship between serum resistin concentrations and insulin resistance in nonobese, obese, and obese diabetic subjects. *J Clin Endocrinol Metab*. 2004;4:1844–8.
 15. Pagano C, Marin O, Calcagno A, Schiappelli P, Pilon C, Milan G, et al. Increased plasma resistin in adults with Prader–Willi syndrome is related to obesity and not to insulin resistance. *J Clin Endocrinol Metab*. 2005;90:4335–40.
 16. Matsuda M, Kawasaki F, Yamada K, Kanda Y, Saito M, Eto M, et al. Impact of adiposity and plasma adipocytokines on diabetic angiopathies in Japanese type 2 diabetic subjects. *Diabet Med*. 2004;21:881–8.
 17. Utzschneider KM, Carr DB, Tong J, Wallace TM, Hull RL, Zraika S, et al. Resistin is not associated with insulin sensitivity or the metabolic syndrome in humans. *Diabetologia*. 2005;48:2330–3.
 18. Filippidis G, Liakopoulos V, Mertens PR, Kiropoulos T, Stakias N, Verikouki C, et al. Resistin serum levels are increased but not correlated with insulin resistance in chronic hemodialysis patients. *Blood Purif*. 2005;23:421–8.
 19. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*. 2002;288:2709–16.
 20. Ninomiya JK, L'Italien G, Criqui MH, Whyte JL, Gamst A, Chen RS. Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. *Circulation*. 2004;109:42–6.
 21. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–97.
 22. Rajala MW, Obici S, Scherer PE, Rossetti L. Adipose-derived resistin and gut-derived resistin-like molecule-beta selectively impair insulin action on glucose production. *J Clin Invest*. 2003;111:225–30.
 23. El-Shal AS, Pasha HF. Association of resistin gene polymorphisms with insulin resistance in Egyptian obese patients. *Gene*. 2013;515:233–8.
 24. Kim S-K, Choe J-Y, Park S-H, Lee SW, Lee GH, Chung WT. Increased Insulin Resistance and Serum Resistin in Korean Patients with Behçet's Disease. *Arch Med Res*. 2010;41(4):269–77.
 25. Reilly MP, Lehrke M, Wolfe ML, Rohatgi A, Lazar MA, Rader DJ. Resistin is an inflammatory marker of atherosclerosis in humans. *Circulation*. 2005;111:932–9.
 26. Azuma K, Katsukawa F, Oguchi S, Murata M, Yamazaki H, Shimada A, et al. Correlation between serum resistin level and adiposity in obese individuals. *Obes Res*. 2003;11:01–997.
 27. Lee JH, Chan JL, Yiannakouris N, Kontogianni M, Estrada E, Seip R, et al. Circulating resistin levels are not associated with obesity or insulin resistance in humans and are not regulated by fasting or leptin administration: cross-sectional and interventional studies in normal, insulin-resistant, and diabetic subjects. *J Clin Endocrinol Metab*. 2003;88:4848–56.
 28. Malo E, Ukkola O, Jokela M, Moilanen L, Kahonen M, Nieminen MS, et al. Resistin is an indicator of the metabolic syndrome according to five different definitions in the Finnish health 2000 survey. *Metab Syndr Relat Disord*. 2011;9:203–11.
 29. Osawa H, Tabara Y, Kawano R, Ohashi J, Ochi M, Onuma H, et al. Plasma resistin, associated with single nucleotide polymorphism –420, is correlated with insulin resistance, lower HDL, and high sensitivity CRP in the Japanese general population. *Diabetes Care*. 2007;30:1501–6.