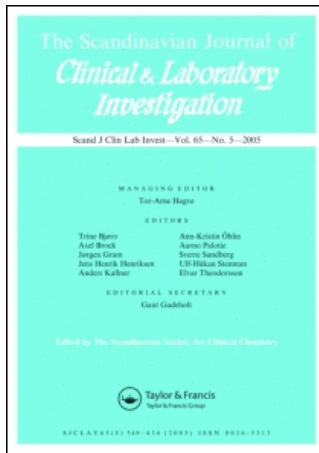


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Associations of resistin with inflammation and insulin resistance in patients with type 2 diabetes mellitus

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ORIGINAL ARTICLE

Associations of resistin with inflammation and insulin resistance in patients with type 2 diabetes mellitus

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Abstract

Objective. Resistin has been linked to obesity, type 2 diabetes, inflammation and atherosclerosis but the results of animal and human studies have been at variance. The purpose of this study was to investigate the potential roles of resistin in patients with type 2 diabetes and to evaluate the correlation between resistin and markers of obesity, inflammation, insulin resistance, metabolic parameters, diabetes control and complications. **Material and methods.** Fasting resistin, leptin, insulin, glucose, HbA1c, full lipid profile, C-reactive protein (CRP) (high sensitivity assay) and complete blood count were determined in 135 patients with type 2 diabetes. Univariate regression and multivariate logistic regression analyses were used to relate resistin with indices of obesity, inflammation, insulin resistance (homeostasis model, HOMA), insulin sensitivity, diabetic control, coronary heart disease (CHD) and degree of microalbuminuria. **Results.** Resistin showed significant ($p < 0.05$) correlations with body mass index (BMI) (Spearman $r = 0.67$), waist circumference ($r = 0.54$), fasting insulin (0.51), insulin sensitivity ($r = -0.29$), HOMA ($r = 0.30$), leptin ($r = 0.39$), CRP ($r = 0.29$), white cell count ($r = 0.25$) and lipid parameters but showed no significant correlation with glucose and HbA1c. Partial correlation analysis, with correction for BMI, abolished the correlation of resistin with insulin sensitivity and HOMA but not with the white cell count. When confounding factors were fixed using multiple logistic regression, resistin was not independently associated with CHD (odds ratio = 1.05, $p = 0.08$) and degree of microalbuminuria (odds ratio = 1.06, $p = 0.24$). **Conclusions.** Resistin showed significant BMI-dependent associations with insulin resistance and factors linked with obesity and inflammation in patients with type 2 diabetes. Resistin may represent a link between obesity and insulin resistance via pro-inflammatory pathways.

Key Words: *Inflammation, insulin resistance, resistin, type 2 diabetes mellitus*

Introduction

Resistin is a 12.5 kDa adipokine that has been proposed to be the link between obesity, insulin resistance and type 2 diabetes mellitus (DM) [1]. Data from animal experiments suggest that resistin plays a significant role in insulin resistance. Serum resistin concentration was found to be significantly increased in obese mice with insulin resistance,

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and the administration of insulin-sensitizing drugs (thiazolidinedione compounds) was found to down-regulate resistin gene expression in obese mice [1,2].

Although these results suggest that resistin may be an important link between obesity and insulin resistance, results in animal models have yielded conflicting results on whether there is an association between resistin, obesity and insulin resistance [1–8]. In humans, some published data on the association between DM and resistin led to the conclusion that resistin was probably not a major determining factor of DM-associated insulin resistance [9]. Therefore the association between resistin, obesity, insulin resistance and type 2 diabetes has remained controversial.

Obesity is prevalent in Kuwait where it is linked to increased morbidity, mortality and a relatively high prevalence of type 2 diabetes and coronary heart disease (CHD) [10]. Like obesity, type 2 DM and CHD are increasingly linked to chronic inflammatory states; markers that could be used to link metabolic and inflammatory signals have become additional tools for defining increased risk. We have shown previously that leptin, another product of adipose tissue, is strongly associated with CHD risk factors and markers of inflammation in patients with DM [11]. Resistin belongs to a family of proteins found in inflammatory zones (FIZZ), called resistin-like molecules [3,12], and in a recent study it is suggested that it could be a marker of inflammation [13]. Therefore, this study was performed to evaluate whether circulating resistin correlates with markers of obesity, inflammation, insulin resistance, metabolic abnormalities, diabetes control and complications in patients with type 2 diabetes.

Material and methods

Patients and clinical features

This clinic-based, cross-sectional study comprised Kuwaiti patients with type 2 diabetes who were attending the diabetic clinic at Mubarak Al Kabir Hospital. All patients were confirmed as having type 2 diabetes if they met the World Health Organization criteria [14]. All patients gave informed voluntary consent to participate in the study according to the protocol approved by the local ethics committee and in accordance with the ethics standards of the Helsinki Declaration. Patients with inter-current illness or clinically evident infections were excluded and none of the patients had overt clinical or laboratory evidence of connective tissue diseases or haemoglobinopathies. Patients were taking oral antidiabetic medications but none was on insulin or insulin-sensitizing drugs (thiazolidinedione compounds) and none of the patients was taking angiotensin II receptor antagonists.

We studied 135 (57 M, 78 F) patients with type 2 diabetes mellitus. The details of these patients have been described in an earlier publication [15] and will be summarized here. The weight, height, waist (WC) and hip circumferences were measured using standard methods and body mass index (BMI) (kg/m^2) and waist-to-hip ratio (WHR) were calculated. Arterial blood pressure was measured twice in the right arm after a 10-min rest period while the patient was in supine position using a mercury sphygmomanometer to record phase I (systolic) and phase V (diastolic) blood pressures; hypertension was defined as mean systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or use of antihypertensive medication [16].

The subjects were interviewed by an Arabic-speaking trained nurse who completed a questionnaire on age, smoking status, duration of diabetes, history of hypertension and/or

antihypertensive medication and symptoms of cardiovascular disease. Patients were classified as those with CHD and those without CHD based on the presence or absence of: resting electrocardiographic (ECG) abnormalities consistent with CHD (ECG was coded using the Minnesota codes [17] and CHD was defined as probable ischaemia (code 1.1–1.2) or possible ischaemia (code 1.3, 4.1–4.4, 5.1–5.3, or 7.1)), a history of myocardial infarction or angina (evaluated by the Rose questionnaire [18] with a positive exercise tolerance test), or angiographically proven coronary artery disease.

Laboratory methods

Each patient's blood was sampled after a 12- to 14-h fast for all analyses. Full blood count (white cell count (WBC), platelet count and haemoglobin concentration) was determined using the Gen S Coulter counter (Beckman-Coulter, Fullerton, Calif., USA).

Fasting plasma resistin was measured using an enzyme-linked immunoassay (ELISA) kit (BioVendor, Brno, Czech Republic) with a limit of detection of 0.20 ng/mL. The intra- and interassay coefficients of variation on pooled plasma specimens with a resistin concentration of 24.2 ng/mL were 3.1 % and 4.8 %, respectively. Fasting serum insulin was determined by ELISA (DSL-10-1600 ACTIVE; Diagnostics Systems Laboratories, Tex., USA). Insulin resistance was calculated using the homeostasis model assessment (HOMA) formula using a calculator downloaded from <http://www.dtu.ox.ac.uk/index.html?main-doc=/publications/> [19]. The HOMA calculator also gives estimates of steady-state insulin sensitivity (% S). A HOMA index > 2 was taken to indicate insulin resistance [20]. Plasma leptin concentration was determined with the WAK ELISA kit (Diagnostics Systems Laboratories) as previously described [11]. Concentrations of C-reactive protein (CRP) were determined by a high-sensitivity chemiluminescent assay on the Immulite (DPC, Los Angeles, Calif., USA) as previously described [21].

Fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), apolipoprotein-A1 (Apo-A1), apolipoprotein-B (Apo-B) and creatinine were analysed on an automated analyser (Beckman LX20; Beckman Corporation, Brea, Calif., USA). We calculated the low-density lipoprotein cholesterol (LDL-C) using the Friedewald formula [22]. Serum cystatin C was also measured using the Hitachi 911 analyser (Roche, Basle, Switzerland) as an additional test of renal function, in view of its superiority to serum creatinine estimation in diabetic subjects [23]. The respective intra- and interassay coefficients of variation for each of the assays have been reported previously [11,21].

Glycated haemoglobin (HbA_{1c}) was measured on the Beckman LX20 analyser (Beckman Corporation). Patients were classified as those with HbA_{1c} ≤ 7 %; HbA_{1c} > 7 % ≤ 8 % and those with HbA_{1c} > 8 %. Each patient provided first-of-the-morning urine samples for determination of urine microalbumin concentration, which was measured with the Beckman Array analyser (Beckman Corporation). Urine creatinine was determined with the Beckman Synchron LX20 automated analyser (Beckman Corporation). The intra- and interassay coefficients of variation for urine microalbumin assay have been reported previously [11]. The patients were classified on the basis of mean urine microalbumin: creatinine excretion ratio of three morning urine collections as normo-, micro-, or macroalbuminuric [24].

Statistical methods

SPSS version 12.0 software (SPSS Inc., Chicago, Ill., USA) was used for statistical analyses and $p < 0.05$ was considered statistically significant. Data are presented as mean values

(95 % confidence interval, CI). Spearman's correlation coefficients were used to describe the association between resistin and anthropometric (BMI, WC, WHR), metabolic (fasting glucose, HbA1c, insulin, insulin sensitivity (% S), HOMA, leptin, lipid profile) and inflammatory (CRP and WBC) parameters. A partial correlation coefficient was used to control for the effects of BMI. A comparison of two groups was made using the Mann-Whitney U-test and the Kruskal-Wallis analysis of variance was used to make comparisons between more than two groups. Logistic regression analyses were used to ascertain the associations between resistin and CHD as well as the degree of microalbuminuria. In the logistic regression analyses, we included factors that have been associated with CHD as potential confounding variables such as smoking status, systolic and diastolic blood pressures, leptin, CRP, HOMA and levels of FPG, HbA1c, Apo-A1, Apo-B, TC, HDL-C, TG and urinary albumin creatinine ratio.

Results

General results

The anthropometric and metabolic variables in the patients grouped according to gender are summarized in Table I. There were no significant differences in BMI, WC and resistin between male and female patients but leptin and CRP were significantly higher in the female patients.

Correlations of resistin

The resistin correlations are summarized in Table II. Resistin showed significant correlations ($p < 0.05$) with indices of obesity (BMI, WC, WHR), fasting insulin, HOMA, Apo-B, the urine microalbumin:creatinine ratio and showed a significant negative correlation with insulin sensitivity (% S) and Apo-A1. Resistin also showed significant correlations with obesity-related variables (leptin, CRP) as well as WBC, but the correlations with glucose, HbA1c and the lipid profile were not significant. In patients with a BMI > 30 (29.97 ng/mL (27.86–32.08) the mean (95 % CI) resistin was significantly higher than that in patients with a BMI < 30 (18.41 ng/mL (16.43–20.39) ($p < 0.0001$). Figure 1 shows the correlations between resistin and indices of obesity.

Since resistin showed significant correlations with obesity-related variables, partial correlation analyses were performed after correcting for BMI. After this correction, the only variables that showed significant correlations with resistin were duration of diabetes, insulin, Apo-B and WBC, suggesting that the associations of these variables with resistin are independent of BMI (Table II).

Figure 2 shows the relationship between resistin and the degree of insulin resistance and Figure 3 depicts the trend of resistin in the patients classified according to the American Heart Association recommendations [25] for CRP cut-points of low risk (< 1.0 mg/L), average risk (1.0–3.0 mg/L), and high risk (> 3.0 mg/L).

Resistin and diabetes control

There was no significant correlation between resistin and FPG or HbA1c (Table II) and the trend for resistin in patients with HbA1c ≤ 7 %; HbA1c > 7 % ≤ 8 % and those with HbA1c > 8 % was not statistically significant ($p = 0.48$).

Table I. Anthropometric and metabolic variables in the patients grouped according to gender.

Variable	Males (n=57)	Females (n=78)	<i>p</i>
Age (years)	58.8 (56.6–61.0)	59.0 (57.2–60.7)	NS
Duration of DM (years)	13.5 (11.9–15.1)	11.3 (10.0–12.6)	NS
BMI (kg/m ²)	30.4 (29.3–31.4)	31.8 (30.7–32.8)	NS
Waist (cm)	106.7 (104.0–109.3)	105.2 (102.8–107.6)	NS
Systolic blood pressure (mmHg)	137 (134–141)	140 (138–143)	NS
Diastolic blood pressure (mmHg)	84 (82–85)	84 (83–85)	NS
Total cholesterol (mmol/L)	5.20 (4.98–5.41)	5.40 (5.20–5.60)	NS
Triglycerides (mmol/L)	1.89 (1.64–2.16)	1.94 (1.71–2.16)	NS
HDL-C (mmol/L)	1.14 (1.08–1.21)	1.23 (1.18–1.28)	NS
LDL-C (mmol/L)	3.24 (3.05–3.41)	3.34 (3.18–3.50)	NS
ApoA1 (g/L)	1.25 (1.21–1.31)	1.35 (1.29–1.39)	NS
ApoB (g/L)	1.04 (0.99–1.10)	1.10 (1.05–1.15)	NS
FPG (mmol/L)	9.83 (9.13–10.54)	10.00 (9.43–10.58)	NS
HbA1C (%)	8.19 (7.77–8.62)	8.49 (8.11–8.87)	NS
Insulin (μIU/mL)	18.57 (15.02–22.13)	23.19 (19.19–27.19)	NS
HOMA	9.90 (5.82–13.97)	8.28 (6.11–10.44)	NS
Percent S	53.84 (42.96–64.73)	61.48 (49.02–73.94)	NS
WBC (10 ⁹ /L)	7.34 (6.80–7.88)	7.00 (6.61–7.41)	NS
Leptin (ng/mL)	23.78 (19.07–28.49)	46.30 (41.54–51.07)	<0.0001
CRP (mg/L)	0.50 (0.35–0.64)	1.06 (0.79–1.32)	<0.0001
Resistin (ng/mL)	22.11 (19.57–24.64)	24.71 (22.35–27.07)	NS

Abbreviations: DM=diabetes mellitus; BMI=body-mass index; FPG=Fasting plasma glucose; HOMA=homeostasis model assessment; LDL-C=low density lipoprotein cholesterol; HDL-C=high density lipoprotein cholesterol; Apo A1=apolipoprotein-A1; Apo B=apolipoprotein B; CRP=C-Reactive protein; WBC=white cell count; Percent S=Insulin sensitivity; NS=Not significant ($p>0.05$). Data are expressed as mean values (95 % CI).

Resistin and diabetes complications

Seventy-one patients (31 M, 40 F) were normoalbuminuric; 59 (24 M, 35 F) were microalbuminuric and 5 (2 M, 3 F) were macroalbuminuric. Fifty-three patients (25 M, 28 F) had CHD and 82 patients (32 M, 50 F) did not have CHD. Mean (95 % CI) resistin was not significantly ($p=0.33$) higher in patients with CHD (24.26 ng/mL (20.78–27.75)) compared with patients without CHD (22.46 ng/mL (19.89–25.04)). Patients with normoalbuminuria had significantly ($p=0.027$) lower mean (95 % CI) resistin (21.57 ng/mL (18.51–24.62)) compared with patients with micro- or macroalbuminuria (24.89 ng/mL (22.21–27.57)). The lack of correlation between resistin and serum creatinine and cystatin C (Table II) suggests that the glomerular filtration rate has no effect on circulating resistin.

To assess whether resistin was independently associated with the presence of CHD and the degree of microalbuminuria, we used a multivariate logistic regression analysis including potentially confounding variables (smoking status, systolic and diastolic blood pressures, leptin, CRP, HOMA and levels of FPG, HbA1c, Apo-A1, Apo-B, TC, HDL-C, TG and urinary albumin creatinine ratio). Resistin was not significantly associated with CHD (OR=1.05; 95 % CI=0.98–1.12; $p=0.08$) and the degree of microalbuminuria (OR=1.06; 95 % CI=0.97–1.15; $p=0.24$).

Table II. Correlations of resistin with clinical, anthropometric and metabolic variables in patients with type 2 diabetes mellitus.

Parameter	*Correlation coefficient	p-value	†Partial correlation coefficient	p-value
Age (years)	-0.080	NS	0.008	NS
Duration of DM (years)	0.06	NS	0.19	0.03
Systolic blood pressure (mmHg)	0.04	NS	-0.02	NS
Diastolic blood pressure (mmHg)	0.05	NS	-0.14	NS
BMI (kg/m ²)	0.67	0.000	-	-
Waist (cm)	0.54	0.000	-0.06	NS
Percent S	-0.29	0.007	0.04	NS
HOMA	0.30	0.005	0.12	NS
Insulin (μIU/mL)	0.51	0.000	0.40	0.000
FPG (mmol/L)	-0.01	NS	0.03	NS
HbA1c (%)	0.08	NS	0.15	NS
Total cholesterol (mmol/L)	0.06	NS	0.12	NS
LDL-C (mmol/L)	0.04	NS	0.09	NS
HDL-C (mmol/L)	-0.16	NS	-0.19	0.03
Triglycerides (mmol/L)	0.15	NS	0.16	NS
Apo-A1 (g/L)	-0.19	0.04	-0.23	0.009
Apo-B (g/L)	0.26	0.003	0.18	0.04
Cystatin C (mg/L)	0.05	NS	0.02	NS
Serum creatinine (μmol/L)	0.05	NS	0.02	NS
Urine microalbumin: creatinine ratio (mg/g)	0.22	0.02	0.11	NS
Leptin (ng/mL)	0.39	0.000	0.09	NS
CRP (mg/L)	0.29	0.001	-0.07	NS
WBC (10 ⁹ /L)	0.25	0.004	0.24	0.005

Abbreviations: DM=diabetes mellitus; BMI=body-mass index; FPG=fasting plasma glucose; HOMA=homeostasis model assessment; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; Apo-A=apolipoprotein A1; Apo-B=apolipoprotein B; CRP=C-reactive protein; WBC=white blood cell count; percent S=insulin sensitivity; NS=not significant. *Spearman rank correlation; †after correction for BMI. $p > 0.05$.

Discussion

There have been many conflicting published data since the initial suggestion that resistin may be the link between obesity, insulin resistance and diabetes in rodent models [1-8]. In this cross-sectional study we have shown that resistin is strongly associated with markers of obesity, inflammation and insulin resistance and negatively associated with estimates of insulin sensitivity. Furthermore, the finding that these associations appear to be dependent on BMI (Table II) suggests that there may be a link between circulating resistin and the insulin resistance and low-grade inflammation that accompany obesity.

One of the areas of controversy on the potential role of resistin is the source of human resistin – while in rodents, resistin is predominantly adipocyte derived [1-3], the role of human resistin has been questioned because it is produced largely by macrophages [26]. In agreement with studies showing an association between obesity and leucocytosis [27,28] as

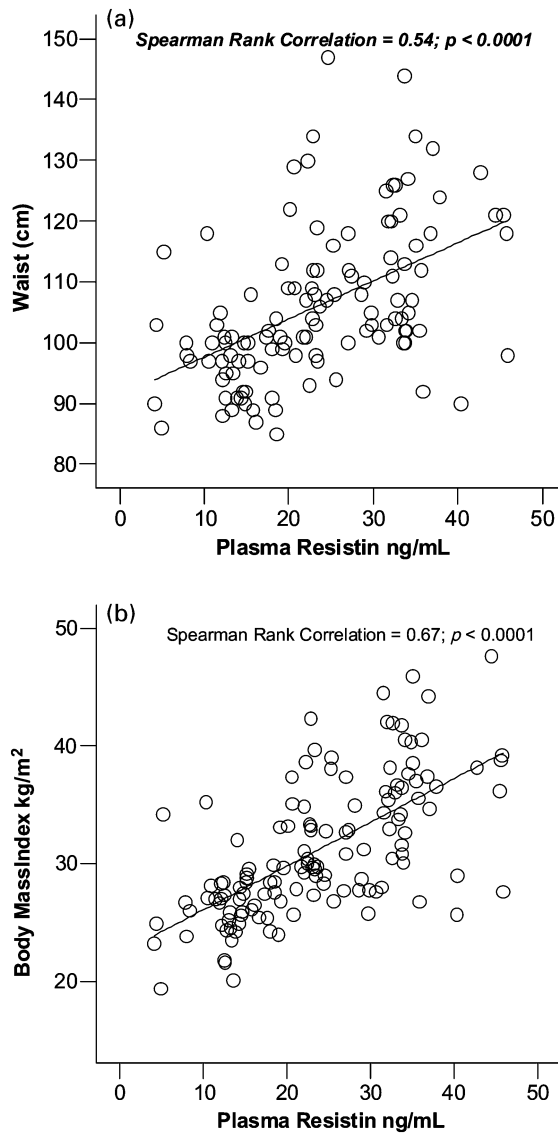


Figure 1. A. B. Scattergrams showing the relationship between plasma resistin and obesity indices. The lines through the scatterplots represent regression-based fit lines indicating the trend of the data.

well as increased resistin expression in mononuclear cells (monocytes, macrophages and lymphocytes) [29], we found a significant association between resistin and WBC. Our data support an extra-adipocyte origin of resistin as shown by the association between resistin and WBC, which appears to be independent of BMI (Table II). Regardless of its source, the potential link between resistin and the degree of adiposity is supported in our study which shows a significant BMI-dependent association of resistin with other obesity-related variables such as leptin and CRP (Table II, Figure 3).

With regard to the association between resistin and insulin resistance (Figure 2), the increased level of resistin with increasing adiposity is probably partly due to an indirect

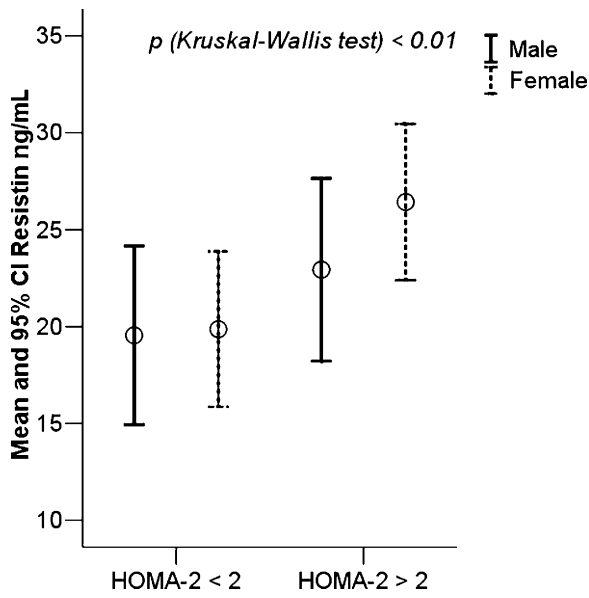


Figure 2. Mean (○) and 95 % confidence interval (CI) of resistin in patients grouped according to degree of insulin resistance (HOMA).

effect of obesity-induced elevation of inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha), which are produced by adipose tissue. Increased pro-inflammatory cytokines can stimulate leptin and resistin production, stimulate CRP production, potentially induce chronic low-grade inflammation and

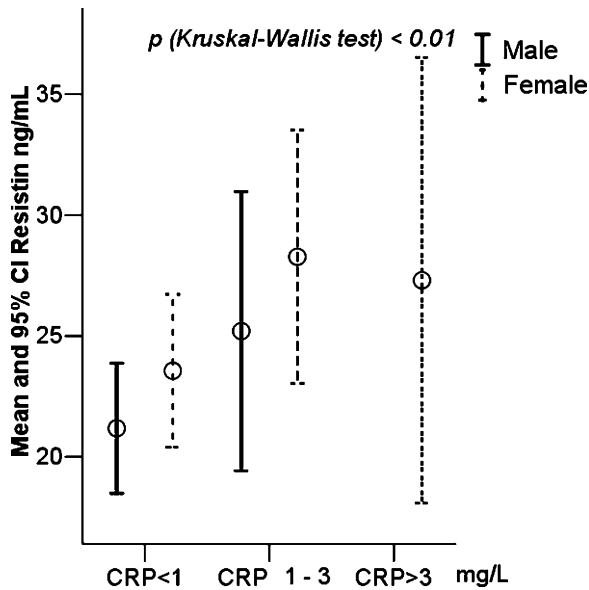


Figure 3. Mean (○) and 95 % confidence interval (CI) of resistin in patients grouped according to the American Heart Association recommendations for C-reactive protein (CRP) cut-points of low risk (<math>< 1.0 \text{ mg/L}</math>), average risk ($1.0\text{--}3.0 \text{ mg/L}$) and high risk ($> 3.0 \text{ mg/L}$). None of the male patients had CRP > 3 mg/L.

contribute to the insulin resistance that develops in obese patients [29–35]. The finding that resistin messenger-RNA expression is increased by these pro-inflammatory cytokines [33,36] provides evidence to support a possible mechanistic link between resistin and inflammation. In this study, we have shown that resistin is associated with the low-grade inflammation and insulin resistance that accompany obesity.

Our results are different from those observed in other populations, as we have not found the association between resistin and renal function or nephropathy and CHD reported elsewhere [9,37–40]. Heilbronn et al. [9] did not find an independent association between insulin sensitivity and resistin and, in a study on Pima Indians, Vozarova et al. [39] concluded that circulating resistin levels are proportional to the degree of adiposity, but not the degree of insulin resistance. Our study suggests that the association of insulin resistance with resistin is dependent on their co-association with obesity. Since we used the same resistin assay, there could be a number of reasons for the differences between these studies and our study. The population studied by Vozarova et al. [39] was much younger than our population, while the resistin level in the study by Heilbronn et al. [9] was much lower than that in the present study despite similarities in the BMI of the two populations. There may be ethnic differences in the resistin gene which could account for differences in resistin concentrations as well as physiological actions. Some studies have shown that genetic variability in the resistin gene may influence insulin sensitivity and the association of a pro-inflammatory state with incident diabetes [41–43].

Our study has some limitations, mostly due to the cross-sectional design. Whilst we have been able to show clearly that resistin and insulin resistance are co-related with obesity, we acknowledge that demonstration of a good correlation or association does not necessarily imply pathophysiological activity since the latter could be dependent on factors such as resistin receptors and/or signalling pathways [44]. Furthermore, the lack of a significant association between resistin and CHD in our cohort is at variance with a recent study [13] that concluded that resistin levels could be predictive of CHD independently of CRP. In our study, resistin increased with increasing degrees of low-grade inflammation (Figure 3) supporting an attractive hypothesis that resistin could be a marker, aetiological factor or predictor of CHD. The failure to find a significant link with CHD in our study might be due to confounding of the CHD risk factors in our cohort, as the patients are managed according to guidelines emphasizing CHD risk reduction [24]. Longitudinal studies are required to confirm whether, like CRP, resistin could be used as a predictor of CHD in patients with type 2 diabetes.

In conclusion, resistin showed a significant BMI-dependent association with insulin resistance and factors linked with obesity in patients with type 2 diabetes. Resistin is also associated with elevated CRP and WBC, suggesting that the relationship between obesity and resistin in relation to insulin resistance may be via the inflammation mechanism. Therefore, the role of resistin in humans may be that of a component of obesity-related inflammation and, although high resistin may contribute to an increased risk of complications in patients with type 2 diabetes, the lack of a significant association after correction for confounding variables suggests that it may not play an independent role.

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Conflicts of interest

None.

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