



Association between serum resistin, adiposity measures and inflammatory makers in women without cardiovascular diseases

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ABSTRACT

Aims: The convergence of obesity and inflammation in the pathogenesis of cardiovascular diseases (CVD) has been recognized over the past decade. Resistin has emerged as a novel secreted protein with links to both insulin resistance and inflammation. We aimed to investigate the relationship between changes in serum resistin levels with metabolic parameters, including obesity and inflammatory markers in women free of CVD.

Methods and results: A total of 200 apparently healthy women were consecutively recruited from the Out-patients Clinics at King Abdulaziz university Hospital in Jeddah, Saudi Arabia. They were classified into 4 groups based on quartile for serum resistin. Anthropometric variables were measured in all study subjects. Fasting blood samples were collected for measurement of lipid profile, blood glucose and inflammatory markers. Study subjects within the upper quartile (Q4) had significantly higher body height ($p < 0.0001$), waist and hip circumferences ($p < 0.05$) and inflammatory markers ($p < 0.0001$) values than those in the lower quartile (Q1). Significant correlations were found between circulating resistin levels and systolic blood pressure, some anthropometric measures as well as inflammatory markers.

Conclusion: Serum resistin levels were found to be increased in overweight and obese women. Resistin was also independently associated with hs-CRP in women free of CVD, suggesting that resistin may be related to low-grade inflammation among obese subjects in the absence of overt CVD.

1. Introduction

Despite advances in our understanding of the major modifiable risk factors for cardiovascular diseases (CVD), these diseases remain the leading causes of morbidity and mortality worldwide (Murray and Lopez, 2013). The increase in the prevalence of obesity, particularly elevated abdominal adiposity, with its subsequent effects on cardio-metabolic risk factors (e.g. hypertension, dyslipidemia, insulin resistance) has emerged as a critical obstacle to effective CVD prevention (Lavie et al., 2009). As part of the ongoing efforts for preventing CVD a concerted effort has been made to identify novel biomarkers of obesity-related risk to improve CVD risk prediction and help better understand the pathophysiology of this disease process.

Resistin has received much attention in recent years as an emerging biomarker involved in pathways of adiposity, insulin resistance and inflammation (Steppan et al., 2001; Reilly et al., 2005). Resistin is mainly secreted by inflammatory cells in humans and associated with the presence of atherosclerosis (Reilly et al., 2005; Verma et al., 2003). Prospective data on the association between resistin levels and

cardiovascular disease (CVD) events are increasing with conflicting results (Ohmori et al., 2005; Luo et al., 2012).

However, the relationship between resistin and inflammation or atherosclerosis in human diseases remains largely unexplored. Controversies persist whether the association between circulating resistin levels and CVD events is independent of metabolic disease or inflammatory markers. The evaluation of serum levels of adipokines may be used as a prognostic marker in screening, diagnosing and predicting atherosclerosis.

In this study, we aimed to investigate the relationship between changes in serum resistin levels with metabolic parameters, including obesity and inflammatory markers in women free of CVD.

2. Methods

This cross-sectional study comprised 200 apparently healthy women free of CVD (40–60 years, mean age 50.4 ± 0.4 years). The study participants, who were referred for routine physical check-ups, were consecutively enrolled from the out-patients clinics at King Abdulaziz

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Table 1
Demographics and clinical characteristics of the study population (N = 200) stratified by serum resistin quartiles.

	Q1 (4.18 ± 0.2 ng/ml)	Q2 (6.88 ± 0.1 ng/ml)	Q3 (10.0 ± 0.2 ng/ml)	Q4 (18.3 ± 0.7 ng/ml)	P
Age (year)	51.0 ± 0.7	49.6 ± 0.7	50.3 ± 0.8	50.6 ± 0.8	NS
SBP (mmHg)	131.6 ± 2.4	135.4 ± 2.7	136.1 ± 2.2	141.7 ± 3.1	NS
DBP (mmHg)	87.6 ± 0.8	88.2 ± 0.7	87.6 ± 0.7	88.1 ± 0.8	NS
Body weight (Kg)	76.9 ± 1.4	76.9 ± 1.4	75.9 ± 1.6	75.9 ± 1.3	NS
Body height (cm)	160.9 ± 1.0	158.8 ± 0.8	163.6 ± 0.8	163.3 ± 0.9†	< 0.0001
BMI (Kg/m (Lavie et al., 2009))	29.8 ± 0.6	30.7 ± 0.7	28.4 ± 0.6	28.7 ± 0.6	NS
WC (cm)	104.8 ± 1.5	106.1 ± 1.2	110.3 ± 1.5	109.8 ± 1.1#*	< 0.05
HC (cm)	63.7 ± 0.6	62.2 ± 0.8	65.6 ± 0.7	64.0 ± 0.7	< 0.05
WHR	1.66 ± 0.0	1.73 ± 0.0	1.69 ± 0.0	1.72 ± 0.0	NS
FBG (mmol/L)	5.48 ± 0.1	5.52 ± 0.1	5.57 ± 0.1	5.56 ± 0.1	NS
TC (mmol/L)	3.60 ± 0.1	3.62 ± 0.1	3.65 ± 0.1	3.91 ± 0.1	NS
TG (mmol/L)	0.77 ± 0.1	0.79 ± 0.0	0.56 ± 0.1	0.73 ± 0.1	NS
LDL (mmol/L)	1.08 ± 0.1	1.06 ± 0.1	1.18 ± 0.1	1.28 ± 0.1	NS
HDL (mmol/L)	0.67 ± 0.1	0.83 ± 0.1	0.78 ± 0.1	0.79 ± 0.1	NS
AIP (TG/HDL-C)	1.45 ± 0.1	1.34 ± 0.1	1.59 ± 0.3	1.18 ± 0.1	NS
ESR (mm/hr)	5.46 ± 0.5	6.12 ± 0.7	31.2 ± 1.2	29.9 ± 1.2†	< 0.0001
hs-CRP (mg/L)	0.48 ± 0.0	0.62 ± 0.0	1.19 ± 0.1	1.22 ± 0.1†	< 0.0001

Data are presented as mean ± SEM. Continuous variables were compared ANOVA test or Kruskal Wallis test for non-normally distributed data. AIP: atherogenic index of plasma, BMI: body mass index. ESR: erythrocytes sedimentation rate, DBP: diastolic blood pressure, FBG: fasting blood sugar, HC: hip circumference, HDL: High density lipoprotein, hs-CRP: high sensitivity-C reactive protein, LDL: low density lipoprotein, NS: not significant, SBP: systolic blood pressure, TC: Total cholesterol, TG: Triglycerides, VLDL: very low density lipoprotein. WC: waist circumference, WHR: waist hip ratio. Significant difference is indicated by *p < 0.05, #p < 0.01 and †p < 0.0001 versus Q4 group.

University Hospital (KAUH), Jeddah, Saudi Arabia. They were classified into 4 groups based on resistin quartiles. The study was approved by the ethics committee of KAUH and informed consent was obtained from all subjects.

Patients affected by diabetes mellitus, hypertension, or familial hyperlipidemia were excluded from the study, as were subjects with thyroid disease, liver or renal failure, acute or chronic inflammatory disorders, malignancy, and the use of lipid-lowering drugs, cardiovascular medication (statin, aspirin, angiotensin-converting enzyme inhibitors or angiotensin receptor blocker) and corticosteroids or other immunosuppressive agents.

All patients were asked about their lifestyle and medical history and underwent a physical examination, a series of laboratory tests, and body measurements. Blood pressure was measured using an appropriate mercury sphygmomanometer. Blood pressure was measured twice with 15-minute interval and the mean of the two readings was recorded.

Body weight of each participant was measured to the nearest 100 g using a calibrated portable scale (TANITA ultimate scale 2000 scales, Tanita Corporation, Tokyo, Japan). Measurements were done with the participant in minimal clothing without shoes. Height was measured to the nearest centimetre using a calibrated measuring rod (Seca 217 Mobile Stadiometer, UK) while the participant was in full standing position. Body mass index (BMI) was calculated as weight in kilograms divided by the height in meters squared. BMI was categorized as normal weight if BMI was ≤ 24.9 kg/m (Lavie et al., 2009), overweight if BMI between 25.0 kg/m (Lavie et al., 2009) and 29.9 kg/m² and obesity if BMI ≥ 30.0 kg/m². Waist and hip circumferences were measured using a standard flexible tape measure. Waist was measured at the narrowest point between the costal margin and iliac crest. Hip was measured at the widest diameter over greater trochanters. Waist-to hip ratio (WHR) was calculated by dividing WC by HC. Central obesity was defined by WC > 88 cm and by WHR ≥ 0.8 in women (Vassilakopoulos et al., 2004; World Health Organization. Waist Circumference and Waist-Hip Ratio, 2008).

After the subjects underwent a 12-hour fasting, blood samples were collected for the determination of serum fasting lipid profile, fasting blood glucose (FBG), high-sensitivity C-reactive protein (hs-CRP), Erythrocytes sedimentation rate (ESR) and resistin levels. Blood samples were centrifuged immediately at 3000 × g for 10 min at 4 °C; the supernatant was aliquoted and stored at −80 °C until being assayed.

Total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and FBG levels were measured in the serum according to automated enzymatic procedures (Ortho-Clinical Diagnostics, Johnson & Johnson Co., USA). Atherogenic index of plasma (AIP) was calculated as a marker of CVD by dividing TG/HDL-C (Nwagha et al., 2010). Serum hs-CRP was measured by immunoturbimetry (Roche Diagnostics GmbH, Mannheim, Germany). ESR test was measured using an autoanalyzer (MIXRATE X20, Vital Diagnostics – ELI Tech Group, Australia).

Serum resistin was measured in duplicate by using a commercially available enzyme-linked immunosorbent assay (ELISA) kit following the manufacturer's protocol (Bio Vender, Brno, Czech Republic).

Numeric data are presented as mean ± SEM and categorical data are expressed as number (percentage). Data were tested for normal distribution using the Kolmogorov–Smirnov test. Variables with normal distribution were compared by one-way ANOVA and by Kruskal-Wallis test for nonparametric variables. Chi-square test was used for categorical variables comparison. Correlations were assessed by using Pearson and Spearman's coefficient tests for parametric and nonparametric variables respectively. Multiple stepwise regression analysis was performed with serum resistin as the dependent variable, by entering the independent variable with p value up to 0.1. The threshold for significance was a p value < 0.05. The statistical analysis was performed with SPSS (version 21.0, Chicago, USA).

3. Results

Clinical characteristics of the study subjects across quartiles of resistin levels are displayed in Table 1. The mean value of serum resistin was 9.84 ± 0.5 ng/ml. Study subjects within the upper quartile (Q4) had significantly higher mean values of body height (p < 0.0001), waist and hip circumferences (p < 0.05) and inflammatory markers (p < 0.0001) than those in the lower quartile (Q1). However, there was no significant difference across the quartiles in terms of blood pressure reading and estimated biochemical parameters (p > 0.05).

The whole population is considered with abdominal obesity according to the cutoff values of WHR (100%) and WC (96%). In addition, 41% were overweight and 41% were obese by categorization with BMI classes. Fig. 1 shows that there was a graded nonsignificant increase in median resistin levels across the three BMI classes.

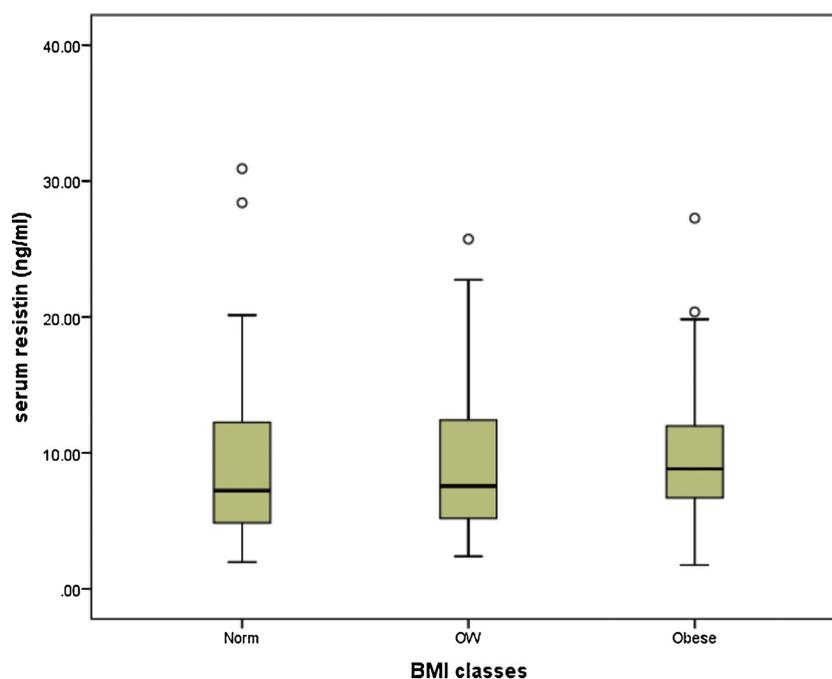


Fig. 1. Serum resistin levels in the study subjects (N = 200) categorized by BMI classes. The box contains the values between the 25th and 75th percentiles and the horizontal line is the median. The error bars stretch the 10th to 90th percentiles.

Table 2

Correlation between serum resistin and all estimated parameters among the study population (N = 200).

	r	p
SBP (mmHg)	0.179	< 0.05
Body height (cm)	0.262	< 0.0001
BMI (Kg/m (Lavie et al., 2009))	-0.175	< 0.05
WC (cm)	0.255	< 0.0001
HC (cm)	0.139	< 0.05
WHR	0.154	< 0.05
ESR (mm/hr)	0.498	< 0.0001
hs-CRP (mg/L)	0.869	< 0.0001

BMI: body mass index. ESR: erythrocytes sedimentation rate, HC: hip circumference, hs-CRP: high sensitivity-C reactive protein, SBP: systolic blood pressure, WC: waist circumference, WHR: waist hip ratio.

Significant correlations were found between circulating resistin levels and SBP, some anthropometric measures as well as inflammatory markers (Table 2).

In multivariate analysis, 3% of the variability in serum resistin could be explained by only hs-CRP ($\beta = -0.228$, $p = 0.004$, 95% CI: -3.432 to -0.651), after adjustment for other confounding factors.

4. Discussion

Obesity is thought to be associated with the activation of innate immune pathways and chronic inflammation (Wang and Inflammation, 2010). Adipocytokines are known to play various roles in the development of atherosclerosis (Reilly et al., 2005). Therefore, we investigated whether resistin is associated with metabolic parameters, including obesity and inflammatory markers in women free of CVD and thus is a potential marker of cardiovascular risk.

In this study we reported significantly higher mean values of body height, WC, HC, ESR and hs-CRP among study individuals within the upper quartile (Q4) vs. those in the lower quartile (Q1) of serum resistin (Table 1). Previous studies have shown that resistin is not only a link between obesity and insulin resistance, but also possesses the ability to participate in the development of atherosclerosis (Reilly et al., 2005).

This is in discordance with other data from published cross-sectional that reported conflicting results (Ohmori et al., 2005; Luo et al., 2012). This might be attributed to a number of reasons like limited statistical power, co-variables adjustment and/or non-standardization of clinical outcomes.

Of interest was the observation that resistin levels were slightly higher among overweight and obese women than their lean counterparts (Fig. 1). This observed difference in serum resistin levels may reflect the impact of genetic or environmental factors on resistin expression (Menzaghi and Trischitta, 2010; Azuma et al., 2003). It is also possible that differences in resistin levels exist between different ethnic groups (Vozaroya de Courten et al., 2004). In addition, some genetic variants (single nucleotide polymorphisms) in the resistin gene have been associated with a risk of diabetes type 2 in Caucasians, especially in case of obesity (Ma et al., 2002).

Moreover, serum resistin levels were positively correlated with body height, WC, HC, WHR, SBP, ESR and hs-CRP as well as inversely correlated with BMI (Table 2). Similar observations were made in several previous studies (Azuma et al., 2003; Degawa-Yamauchi et al., 2003; Vilarrasa et al., 2005), but not by others (Koebnick et al., 2006). Recent studies suggest that the central distribution of fat, which is a source of pro-inflammatory adipokines, has a more important role in the determination of cardiovascular risk (Wang and Nakayama, 2010; Rashid, 2013). Nevertheless, the associations with adiposity measures in the present study were not significant after multi-variable adjustment. It is worth noting that human resistin is more predominantly expressed in macrophages than adipocytes (Patel et al., 2003). This may explain why reports of the relationship of plasma resistin levels to obesity in humans have been conflicting (Lee and Kim, 2018).

Hyperlipidemia is one of the most prevalent of CVD risk factors in obesity, especially in abdominal obesity (Pietrzewicz et al., 2008). However, we found no significant correlation between resistin with lipid profile, supporting results of other studies (Mohammadzadeh et al., 2008). By contrast, serum resistin levels were found to be correlated with TG, LDL-C and CRP in Chinese males (Zhu et al., 2012). Resistin has been shown to have pleiotropic functions in metabolism with roles in inflammation (Aquilante et al., 2008), endothelial dysfunction (Ntaios et al., 2018) and cholesterol metabolism (Melone et al.,

2012).

Our observation of no relationship between serum resistin and FBG is consistent with others (Reilly et al., 2005; Ohmori et al., 2005), but other investigators showed the opposite results (Luo et al., 2012; Zhang et al., 2003). In diabetic patients, resistin was suggested to impair β -cell secretory function, resulting in the increase of blood glucose (Zhang et al., 2003).

After adjustment for potential confounding factors, only hs-CRP was independently related to serum resistin concentrations. Similarly to this study, serum resistin levels were associated with markers of inflammation (Kopff and Jegier, 2005; Chen et al., 2009; de Luis et al., 2010)

Evidence shows that resistin levels might play an important role in the development of inflammatory mechanisms and promote the progression of atherosclerotic disease (Rashid, 2013). The expression of resistin in human monocytes has been shown to be induced by treatment with proinflammatory cytokines (Bokarewa et al., 2005). Furthermore, resistin has been shown to up-regulate the expression of adhesion molecules in human endothelial cells (Kawanami et al., 2004). The relationship of resistin to classic mediators of inflammation, such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) appears more consistent (Reilly et al., 2005; Bokarewa et al., 2005). Notably, inflammatory markers, such as IL-6, TNF- α and CRP have been independently associated with CVD events in older adults (Cesari et al., 2003; Rodondi et al., 2010).

In accordance with some reports (Vilarrasa et al., 2005), we have not revealed any changes in blood resistin concentrations with aging, although a decrease of blood resistin concentration with age was reported by other studies (Koebnick et al., 2006). Although our study population were exclusively females, it has been proposed that a gender-specific effect of resistin might depend on different adipose tissue depots which are responsible for its production in male or female (Luo et al., 2012; Chen et al., 2009). Thus, our study was designed for female subjects to avoid the impact of sex-related differences in the location of the adipose tissue, the number of fat cells, and fat cell size.

This study has several limitations. This is a cross-sectional study and causal inferences cannot be drawn. Also, the generalizability of our findings across ethnic groups is unknown. However, more data are needed to assess the association between genetic variants of the resistin gene and the inflammation.

In conclusion, serum resistin levels were found to be increased in overweight and obese women. Resistin was also independently associated with hs-CRP in women free of CVD, suggesting that resistin may be related to low-grade inflammation among obese subjects in the absence of overt CVD. The potential causality of resistin in the manifestation of CVD, as well as the mechanisms linking resistin to inflammation, needs to be explored in large longitudinal prospective studies.

Disclosure statement

The authors have nothing to disclose.

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