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Association of Resistin with Components of Metabolic Syndrome in Our Local Population

Mozaffer Rahim Hingorjo, Muhammad Noman Rashid, Naila Parveen, Lubna Riaz, Riaz Ahmed Shahid, Zainab Hasan

ABSTRACT

Objective: To investigate the association of resistin with components of metabolic syndrome (MetS) in our local population.

Study design & setting: Case-control study, Medical OPD; Lyari General Hospital Karachi (from 15th July 2020 till 15th December 2020).

Methodology: A total of 164 subjects (83 cases & 81 controls) between the age ranges of 35-65 years were selected. Subjects with metabolic syndrome were included in concordance with International Diabetes Federation criteria. Serum resistin levels in both cases and controls were compared. SPSS 20 was used for statistical analysis. Eighty-three patients with metabolic syndrome were enrolled and compared with 81 healthy unmatched controls. Obesity indices, blood pressure, lipid profile, fasting blood sugar, insulin resistance and serum resistin levels were evaluated. Predictive values of resistin for MetS were analyzed using odds ratios.

Results: Significantly elevated levels of resistin were found in subjects with metabolic syndrome compared to healthy controls (8.23±4.43 vs 6.82±3.64 ng/mL, $p<0.05$). The odds ratio (95% confidence interval) for metabolic syndrome in subjects having higher resistin were: males:2.62[1.11–6.19], females: 2.81[1.05–7.49], all $P_{trend}<0.05$.For individual components of metabolic syndrome, we found the odds ratio to be greatest for hypertension, fasting blood sugar, and insulin resistance; 2.64, 4.83, 2.85, respectively, all $P_{trend}<0.05$.

Conclusion: The present study suggests significant association of resistin with components of metabolic syndrome such as hypertension, fasting blood sugar, and insulin resistance. Compared to healthy controls, subjects with MetS had significantly higher resistin levels. Further research is required to incorporate this biomarker in clinical setting.

KEYWORDS: Diabetes Mellitus; Metabolic syndrome; Resistin

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INTRODUCTION

Metabolic syndrome is defined as a cluster of metabolic risk factors such as high blood pressure, impaired fasting blood glucose levels, increased insulin resistance, high triglyceride levels, decreased healthy cholesterol levels, and increased waist circumference. Moreover, it is a collection of metabolic irregularities that confer upon the individual a high risk of dying due to cardiovascular disease.[1]

According to some experts, increased intra-abdominal fat accumulation or high waist line plays a dominant role in metabolic syndrome in comparison with the other risk factors. Epidemiological studies have shown that Asian people are at a greater risk of developing type 2 diabetes and early cardiovascular events compared to Europeans, therefore a lower cutoff values have been set for the classification of body mass index and waist circumference for Asians by World Health Organization. Several studies have demonstrated that obesity being a chronic inflammatory disorder forms a link between insulin resistance and MetS. With the rise in incidence of obesity, the risk of acquiring MetS and dying of heart disease increases manifold.

Adipokines released from the adipose tissue may provide the missing link for the development of MetS. Identifying these biomarkers may enable early detection and intervention of cardiovascular disease (CVD) and its complications.[2]

Resistin is a small protein molecule secreted by the macrophages and adipose tissues. It promotes inflammation by inducing various proinflammatory makers such as tumor necrosis factor alpa and interleukins. Anectodal evidences have suggested that resistin is not only associated with the development of obesity and diabetes, but it does have a profound impact in the emergence of cardiovascular diseases, hypertension and atherosclerosis[3].

Resistin, produced by macrophages in humans, has been observed to inhibit the peripheral actions of insulin, increasing insulin resistance. Many adipokines work towards maintenance of energy balance. However, human resistin and recently identified resistin like molecules (RELM) are found to act as antagonist to insulin, contributing to insulin resistance and MetS.[4]

Resistin is considered as an important adipocytokine which lowers the insulin sensitivity and increases insulin resistance and inflammation leading to type 2 diabetes. Obesity, a comorbid in diabetes causes a dysfunction in adipose tissue, leading to disruption of adipocytokine release[5].

A similar study conducted by Yousaf et al, studied the effect of visceral obesity on insulin resistance and observed that thiazolidinediones increased insulin sensitivity while decreasing resistin levels. Moreover, he concluded that increased serum resistin levels indicated insulin resistance and impending increased blood sugar levels[6]. Animal studies have shown that thiazolidinediones, drugs given to reduce insulin resistance in type 2 diabetes, reduce resistin levels[7].

Increased incidence of cardiovascular diseases among the South Asians as a consequence of central obesity has been hypothesized by various epidemiological researches. Central obesity is a primary risk factor for metabolic syndrome which alters the relationship between adipokines and metabolic syndrome and leading to metabolic and cardiovascular disorders. Visceral obesity poses a major risk to adipose tissue dysfunction which further leads to the development of other risk factors of Metabolic syndrome such as hypertension, impaired insulin sensitivity, atherogenesis, and dyslipidemia. Moreover, obesity is the key source of resistin secretion by the adipose tissue which plays an important role in the pathogenesis of insulin resistance. Several antidiabetic drugs have been proposed that decrease the serum resistin levels and improve the lipid profile to restore insulin sensitivity to normal in insulin resistant humans[8,9,10].

With the rise in incidence of obesity in our local population, the risk of acquiring metabolic syndrome and dying of heart disease increases manifold. Adipokines released from the adipose tissue may provide the missing link for the development of metabolic syndrome. Identifying these biomarkers may enable early detection and intervention of cardiovascular disease (CVD) and its complications. In this study, we explored the association of adipokine resistin with components of Metabolic syndrome in our local population.

METHODOLOGY

This case-control study was conducted at Lyari General Hospital and a total of 164 subjects (83 cases & 81 controls), both males (46) & females (34) were selected from 15th July 2020 till 15th December 2020. Eighty three participants, aged 35-65 years, with Metabolic syndrome were selected from Medical OPD of Lyari General Hospital. Metabolic syndrome was diagnosed based upon criteria proposed by new International Diabetes Federation (IDF) [11]. This requires absolute presence of central obesity plus increase in any two of the following: triglycerides, cholesterol, blood pressure, fasting blood sugar.[11]

Exclusion criteria included those with active infection, end stage systemic disease, malignancy, pregnancy and lactation.

Healthy controls included subjects between ages of 35-65 years, both genders (males (46) & females (34) with no history of metabolic syndrome and were taken from the general population (n = 81). Written informed consent was taken from the subjects and approval was given by the Research Ethics committee of Shaheed Mohtarma Benazir Bhutto Medical College, Lyari (ERC)/2020-21/0301). Sample size was calculated using the open epi sample size calculator; CI-95%, Power: 80%, OR: 2.2[12], N=164.

All subjects were evaluated for the components of metabolic syndrome. Waist circumference measured to the nearest 0.1cm was taken at the midpoint between iliac crest and lower border of rib cage. Blood pressure was measured by mercury sphygmomanometer in the sitting position and a mean of three measurements was recorded. Fasting venous blood samples were collected to measure glucose, glycated hemoglobin, lipid profile, insulin, and resistin levels.

ELISA kits were used to measure the insulin and resistin levels with a sensitivity to detect lowest concentration at 1.76 µIU/mL for insulin and 0.03 ng/mL for resistin. Insulin resistance was measured by Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). The 75th percentile for resistin in healthy controls was taken as the cutoff points above which the levels were considered as high.

Data was analyzed using SPSS version 20. Descriptive statistics were presented as mean ± standard deviation (SD). Shapiro-Wilk test was done to test for normality of distribution. Student t-test was used to compare means. Chi-square test was applied to analyze the strength of association. Statistical significance was considered at $p<0.05$.

RESULTS:

Of the total 164 participants (83 cases and 81 controls), 90(54.8%) were males and 74(45.1%) were females. The

mean age was 50.15±9.36 years (range 35–65 years). We observed significant difference in all anthropometric measurements and biochemical parameters between subjects with metabolic syndrome and healthy controls (Table 1). Compared to healthy controls, subjects with metabolic syndrome had significantly higher resistin levels ($p<0.05$).

The 75th percentile for resistin in control subjects was taken as the cutoff point above which the levels were considered as high. The cutoff level (ng/mL) in males and females were 7.30 and 7.27, respectively. Univariate regression analysis showed that subjects having higher resistin levels were more than twice as likely to develop metabolic syndrome (Table 2).

Table 3 shows OR between individual components of MetS and the adipokine studied. As the number of components of MetS increased, the odds of having the disease also increased. Subjects with higher levels of resistin were more likely to have central obesity and higher levels of blood pressure, fasting blood glucose and dyslipidemia.

Table 1: Descriptive Measures of Study Population

	Controls (n = 81)	MetS (n = 83)	P
Age (y)	49.12±2.52	52.35±3.30	0.06
Anthropometric Indices of Obesity			
Body Mass Index (kg/m^2)	24.97±4.16	28.60±4.34	<0.001
Waist Circumference (cm)	84.63±2.17	92.81±4.36	<0.001
Hip Circumference (cm)	100.31±8.20	105.49±10.01	0.004
Percent Body Fat (%)	30.11±5.24	34.81±4.80	<0.001
Clinical Examination			
Systolic BP (mmHg)	127.85±15.29	144.18±20.60	<0.001
Diastolic BP (mmHg)	80.02±9.37	84.77±10.75	0.003
Biochemical			
HDL-Cholesterol (mg/dL)	43.65±4.12	42.61±4.64	0.131
Triglyceride (mg/dL)	137.99±58.48	159.06±61.67	0.026
Fasting Blood Glucose (mg/dL)	100.34±5.12	150.36±5.69	0.002
HbA1c (%)	4.35±1.02	7.35±1.71	<0.001
Insulin (µIU/mL)	5.54±6.02	9.99±9.47	<0.001
HOMA	1.74±2.12	3.67±3.46	<0.001
Resistin (ng/mL)	6.82±3.64	8.23±4.43	0.02

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; HOMA, homeostasis model assessment of insulin resistance.
Note: Unpaired student's t test was used to compare means between control group and MetS group. Values expressed as mean±SD, significance level taken as $p<0.05$

Table 2: Odds Ratio Between Resistin Levels and Metabolic Syndrome

	Males (44)			Females(40)		
	OR	[95% CI]	p	OR	[95% CI]	p
Resistin	2.62	[1.11–6.19]	0.027	2.81	[1.05–7.49]	0.038

Abbreviations: OR, odds ratio; CI, confidence interval.
Note: Significance level taken as $p<0.05$

Table 3: Odds Ratio Between Resistin & Risk factors of Metabolic Syndrome

	OR	[95% CI]	p
Hypertension	2.64	[1.11–6.28]	0.027
WC	1.68	[0.72–3.92]	0.021
Triglyceride	2.08	[0.81–5.32]	0.022
HDL-C	1.89	[0.74–4.79]	0.180
FBS	4.83	[1.72–13.53]	0.002
HOMA-IR	2.85	[1.17–6.89]	0.0 20

Abbreviations: WC, waist circumference; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment of insulin resistance; OR, odds ratio; CI, confidence interval.
Note: Significance level taken as $p<0.05$

DISCUSSION:

In the present study, significant association was found between resistin and components of metabolic syndrome such as central obesity, hypertension, hyperglycemia, increased insulin resistance and impaired lipid profile. Abdominal obesity is a growing epidemic worldwide and has a strong relationship with insulin resistance and Metabolic syndrome.[12]

Results of our study showed significant difference in all anthropometric measurements and biochemical parameters between subjects with Metabolic syndrome and healthy controls. Also significantly increased levels of resistin were found in patients with Metabolic syndrome compared to healthy controls (8.23±4.43 vs 6.82±3.64 ng/mL, $p<0.05$).This was in concordance with the systemic review and meta-analysis conducted by Su KZ et al who found a significant relationship (P=0.003) between circulating resistin levels and insulin resistance in patients with type 2 diabetes mellitus and obesity[13]. A similar study was conducted by Zahary MN et al in Malaysia. His results showed serum resistin levels to be significantly higher in subjects with metabolic syndrome (11.22 ± 6.34 ng/ml; P = 0.002) compared to non-MetS subjects. After investigating, the significant relationship of resistin with metabolic syndrome criteria, he indicated that resistin can be used as a potential biomarker for the diagnosis of metabolic syndrome [14].

For individual components of MetS in cases (83), we found the odds ratio for hypertension, fasting blood sugar, and insulin resistance as 2.64, 4.83, 2.85, respectively, all Ptrend<0.05.

In our study, significant association of resistin was found with hypertension (P=0.02). This was consistent with the study conducted by Mostafa zadeh et al. He reviewed the effect of resistin and its contribution in the initiation and progression of metabolic syndrome and included both consistent and inconsistent studies regarding relationship of resistin with fasting blood glucose, triglycerides, high density lipoprotein and central obesity. Data obtained from recent experimental and clinical studies revealed significantly higher levels of resistin (12±4vs6.8±3.6) in hypertensive individuals when compared with normotensive individuals (P<.01).

Several mechanisms by which resistin affects blood pressure have been proposed which include its vasoconstriction

property, proliferation of smooth muscle cells and upregulation of angiotensinogen expression in the liver and thus activating the renin-angiotensin system (RAS) Activation of RAS leads to the elevation of blood pressure.[15,16,17]. The vasoconstrictor property of resistin has also been supported by Niaz S et al study. He reported that resistin is released from white blood cells and plays an important role in inflammation leading to endothelial dysfunction, inhibiting the release of vasodilator NO from endothelium, while promoting the release of vasoconstrictor endothelin-1[18].

Our study results showed significant association between resistin and triglycerides (OR: 2.08; CI (95%) [0.81–5.32]; P=0.022). This was in favor with the study conducted by Niu et al.[19]

His study results suggested that increased serum resistin contributes to a higher risk of dyslipidemia (P<.05). Anthropometric measurements including waist circumference was associated with resistin levels in this study (OR: 1.68 [0.72–3.92]; CI (95%); P=0.02).

Study conducted by Farah revealed a significant relationship (P<0.01) between resistin and anthropometric parameters (waist circumference, hip circumference, waist-hip ratio and body mass index) in young obese adults[20].Wijetunge also found a significant association between resistin and waist circumference (P<0.05).Immunohistochemistry of adipose tissue showed increased expression of resistin in adipocytes of subcutaneous adipose tissue compared to visceral adipose tissue (P<.05).[21].

Inconsistent studies by Asgary S, Chen CC & Kielstein JT mentioned in the systematic review by Mostafazadeh et al, observed that serum levels of resistin were not correlated with waist circumference and body mass index15.

Increased association of resistin with impaired fasting blood sugar (OR:4.83[1.72–13.53];P=0.002)and insulin resistance (OR:2.85[1.17–6.89];P=0.020) was found in our study which was in concordance with the study conducted by Bilgetekin et al & Wijetunge et al (P<0.001). In their study, they identified resistin as an important biomarker linked to central obesity and insulin resistance in subjects with impaired fasting blood glucose levels[21,22].

In our study, odds ratio between resistin levels and metabolic syndrome was found to higher in women compared to men. The odds ratio (95% confidence interval) for MetS in subjects having higher resistin were females: 2.81[1.05–7.49] compared to males: 2.62[1.11–6.19], all Ptrend<0.05. This was consistent with the study conducted by Qi et al. His data suggested that subjects in higher resistin quartiles were more likely to be women with metabolic syndrome[23](P<.001).

Marcelino-Rodríguez et al showed insignificant association (OR: 0.76-3.83) between resistin and HDL-C[24]. This was in relation to our study which showed non-significant association of resistin with high density lipoprotein cholesterol (0R: 0.74–4.79; P=0.180).

There were some limitations to our study. Results from a case control design having small sample size may not be applicable to the whole population due to high prevalence of MetS in Pakistan. Second, the cutoff value of WC, the primary criteria for diagnosing MetS, has not been defined for our population that may have affected the results. However, the highly significant relationship observed in our study between resistin and MetS cannot be totally ignored. Finally, investigating genetic factors may further explain variations in adipokine levels.

CONCLUSION

It is concluded that that there is a strong association of resistin with waist circumference, increased blood pressure, elevated fasting blood sugar levels and impaired lipid profile. Thus, resistin can be used as a biomarker for the diagnosis of metabolic syndrome in clinical settings. Future recommendations for additional research are needed to recognize the receptors used by resistin in order detecting the signaling pathways. This will help in clarifying the role of resistin in the pathogenesis of MetS.

Authors Contribution:
Mozaffer Rahim Hingorjo: Revising it critically for important intellectual content.
Muhammad Noman Rashid: Conceived, designed and writeup.
Naila Parveen: Drafting the article and compilation of results
Lubna Riaz: Data collection and Literature search.
Riaz Ahmed Shahid: Designed and editing
Zainab Hasan: Data entry SPSS & Statistical analysis

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