Relation of Serum Resistin to Glomerular Filtration Rate and Urinary Albumin Excretion Non-Diabetic Chronic Kidney Disease Patients

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Abstract: Background: Accumulating evidence supports that resistin modulates metabolism, promotes endothelial dysfunction and proinflammatory activation, leading to acceleration of subclinical atherosclerosis. So the aim of this study was to explore the relationship between serum resistin and urinary albumin excretion, as albumin-to-creatinine ratio, and to the glomerular filtration rate in non diabetic patients with chronic kidney disease. **Methods:** We investigated the association of plasma resistin with estimated glomerular filtration rate and albuminuria in 40 non diabetic hypertensive adults and 10 controls. Resistin was measured by a solid phase sandwich immunoassay, estimated glomerular filtration rate was estimated from serum creatinine, and albuminuria was expressed as urine albumin/creatinineratio. **Results:** Serum Resistin levels were significantly higher (p< 0.001& t3.418) inpatients (11.270ng/ml ± 3.042) compared to controls (7.042 ng/ml ± 2.387). Resistin was found to be positively correlated with systolic blood pressure (r=. o. 342, *p*=0.01), and albumin-to-creatinine ratio (r=0.321, *p*=0.043) and negatively correlated to the glomerular filtration rate. No significant correlation was found between resistin and BMI or insulin resistance. **Conclusion:** Circulating levels of resistin are statistically significantly higher in chronic kidney disease patients as compared to controls. Resistin is positively correlated with systolic blood pressure, and albumin-to-creatinine ratio and negatively correlated to the glomerular filtration rate. In a multiple linear regression model including factors significantly associated with resistin in univariate analysis, as well as age and gender, only GFR and the SBP were significantly associated with circulating resistin levels.

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Key words: Resistin, hypertension, chronic kidney disease, glomerular filtration rate, albumin creatinine ratio.

1. Introduction

Resistin belongs to a family of cysteine-rich secretory proteins called resistin-like molecules. In rodents, resistin is derived almost exclusively from fat tissue, and its serum levels are elevated in animal models of obesity and insulin resistance[1]. In humans, on the other hand, resistin is highly expressed in monocytes and macrophages; thus, its pathophysiological role may differ between species. *In vitro*, resistinis activated in human endothelial cells, leading to increased expression of adhesion molecules, and induced human aortic muscle cell proliferation [2]. Some clinical and epidemiological studies revealed positive correlations between plasma resistin levels and pro-inflammatory cytokines [3].

Accumulating evidence supports that resistin modulates metabolism, promotes endothelial dysfunction and proinflammatory activation, leading to acceleration of subclinical atherosclerosis[4]. Augmented levels of resistin characterize patients with abdominal obesity, type 2 diabetes mellitus, as well as essential hypertension, suggesting involvement of this protein in multiple vascular disease states[5].

A few clinical studies also showed an inverse correlation between resistin level and eGFR in CKD patients[6]. Albuminuria is an index of renal damage and a marker of diffuse vascular dysfunction. So the aim of this study was to explore the relationship between serum resistin and urinary albumin excretion, expressed as albumin-to-creatinine ratio, and to the glomerular filtration rate in non diabetic patients with chronic kidney disease.

2. Subjects and Methods:

The study is a cross sectional study, it was conducted in Kasr El Eini School of Medicine between January2011 and January 2012.The study included 40 non diabetic chronic kidney disease patients and 10 normal healthy controls. All patients and controls gave an informed consent of the study.

Height was measured by stadiometer and weight measured by electronic balance were used to calculate body mass index (BMI: kilograms /meter squared). Patients with diabetes, impaired glucose tolerance, cardiovascular diseases, strokes or active inflammatory diseases were excluded from the study. Glomerular filtration rate was estimated using the Estimated GFR was calculated by the following formulas: Cockcroft Gaultformula:GFR= [140-Age (years)] x body weight (Kg) x 0.85 (if female) serum creatinine (mg/dl) x 72[7]. Albuminuria was assessed

by urinary albumin creatinine ratio (ACR). Albumin-Creatinine Ratio (ACR) was determined as average of three nonconsecutive morning spot urine by using a quantitative assay (DCA 2000, Bayer Diagnostics, Ireland).

Serum total cholesterol, high density lipoprotein (HDL) cholesterol, glucose, and creatinine were measured by standard enzymatic methods. Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as fasting plasma insulin (microunits per melliliter) × fasting plasma glucose (mellimoles per litre) /22.5.

Resistin concentration was measured by human resistinimmunosorbent assay kit supplied by R&D (Quantikine^R, Minneapolis, MN).

Statistical Analysis: Statistical presentation and analysis of the present study was conducted, using the mean, standard error, student t- test, Chi-square, Linear Correlation Coefficient tests by SPSS V17.

3. Results:

Our results showed statistically significant differences (*P*-value<0.001& t: 4.222) between patients compared to controls as regards BMI (mean ± SD was 29.233± 4.721 kg/m^{2}in patients & 22.470± 3.590 kg/m^{2}in controls). Systolic Blood Pressure (SBP) was significantly higher (*P*-value 0.00) in patients (148.000 ± 18.285mmHg) compared to controls (114.200± 6.179). Diastolic Blood Pressure (DSP) was significantly higher (P-value <0.001& t: 4.724) inpatients (87.750 ± 8.239 mmHg compared to controls (75.000 ± 4.082 mmHg) -Cholesterol levels were significantly higher in patients compared to controls (mean ± SD was 217.800± 27.149 mg/dl in patients vs123.200± 11.603 in controls) *P*-value 0.001& t: 3.418). Triglyceride levels were significantly higher in patients compared to controls (mean ± SD was 224.475± 31.277in patients&79.500 ± 22.907 mg/mlin controls) (*P*-value <0.001& t: 13.720). Low-density lipoprotein (LDL) levels were significantly higher in patients compared to controls (mean ± SD was 140.325± 22.326in patients&90.800 ± 7.871mg/ml in controls) *P*-value <0.001& t: 6.86.

High-density lipoprotein (HDL) levels were significantly higher in patients compared to controls (mean ± SD was 69.100mg± 23.333in patients &50.100 ± 6.244 in controls) *P*-value 0.015& t: 6.863.Glomerular Filtration Rate (GFR) levels were significantly higher in controls compared to patients (mean ± SD was 21.333ml/min± 9.402 inpatients&105.000ml/min± 12.247 in controls) *P*-value<0.001& t: 23.671). Albumin-Creatinine Ratio (ACR) was significantly higher in patients compared to controls (mean ± SD was 191.475 µg/mg ± 102.424 in patients& 15.900 µg/mg ± 9.689 in controls) P-value 0.000& t: 5.373.Homeostasis model assessment of insulin resistance (HOMA-IR) levels were significantly higher in patients compared to controls (mean ± SD was 1.436± 0.567in patients vs. 0.809± 0.206 in controls) T-test (*P*-value 0.001& t: 3.418). HOMA IR was significantly higher in patients (mean±SD1.436±0.567) than control (0.809±0.206). The characteristics of the study participants are summarized in table (1).

Table (1): Clinical and laboratory data of patients and controls

	Patients	Controls	*P*-value
Number	40	10	
Gender (female/male)	16/24	4/6	1.000
Age (years)	53.475 ± 7.828	50.600 ± 5.275	0.278
BMI (kg/m^2)	29.233 ± 4.721	22.470 ± 3.590	<0.001*
SBP (mmHg)	148.000 ± 18.285	114.200 ± 6.179	<0.001*
DSP (mmHg)	87.750 ± 8.239	75.000 ± 4.082	<0.001*
LDL (mg/dl)	140.325 ± 22.326	90.800 ± 7.871	<0.001*
Cholesterol (mg/dl)	217.800 ± 27.149	123.200 ± 11.603	<0.001*
Triglyceride (mg/dl)	224.475 ± 31.277	79.500 ±22.907	<0.001*
Glucose (mg/dl)	98 ± 17	90 ± 12	0.072
Insulin (mIU/L)	5.658 ± 2.033	4.909 ± 0.621	0.053
GFR (ml/min/1.73cm^2)	21.333 ± 9.402	105.000 ± 12.247	<0.001*
ACR (µg/mg)	191.475 ± 102.424	15.900 ± 9.689	<0.001*
HOMA-IR	1.436±0.567	0.809±0.206	<0.001*
Resistin (ng/ml)	11.270 ± 3.042	7.042 ± 2.387	<0.001*

Serum Resistin levels were significantly higher (*P*-value 0.001 & t: 3.418) in patients compared to controls (11.270ng/ml ± 3.042 in patients vs. 7.042 ng/ml ± 2.387 in controls) (Fig. 1).

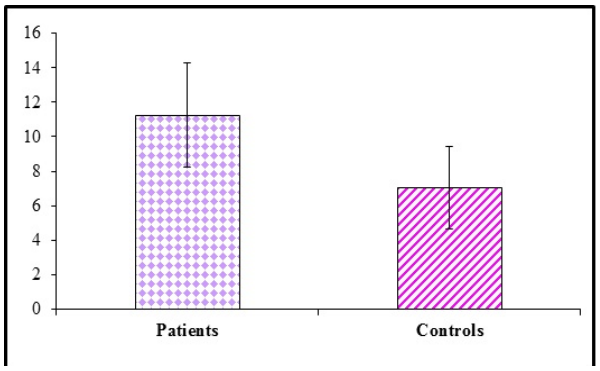

Figure 1: Serum Resistin in Patients & Controls

Resistin was found to be negatively correlated to the glomerular filtration rate (r=- 0.283, *p*=0.046) (Fig 2) and positively correlated to systolic blood pressure (r=. o. 342, *p*=0.01) (Fig. 3), and albumin-to-creatinine ratio (r=0.321, *p*=0.043) (Fig. 4). No significant correlation was found between resistin and BMI or insulin resistance (Table 2).

Table 2: Correlation between Serum Resistin and different parameters

	S. Resistin	
	r	*P*-value
Age	-0.025	0.878
BMI	-0.088	0.589
GFR	-0.283	0.046*
Insulin	0.073	0.654
Glucose	0.017	0.919
HOMA	0.081	0.620
DBP	0.192	0.236
SBP	0.342	0.031*
ACR	0.321	0.043*
LDL	0.150	0.354
HDL	0.018	0.912
Trigl	0.060	0.715
Chole.	-0.046	0.777

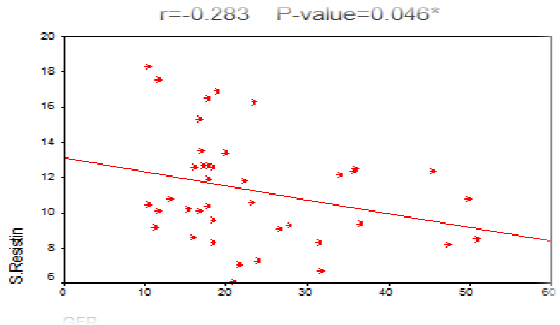

Figure 2: Correlation between Serum Resistin& Glomerular Filtration Rate (GFR)

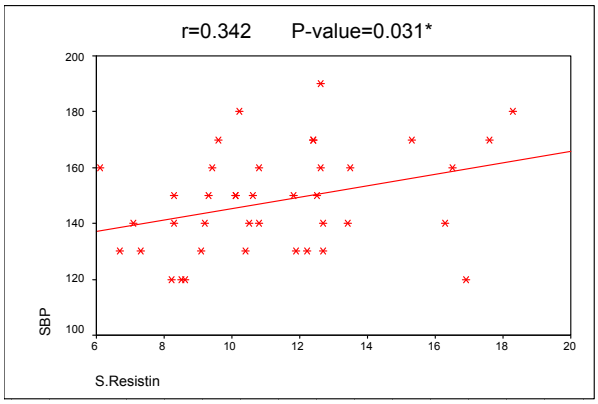

Figure 3: Correlation between Serum Resistin & Systolic Blood Pressure

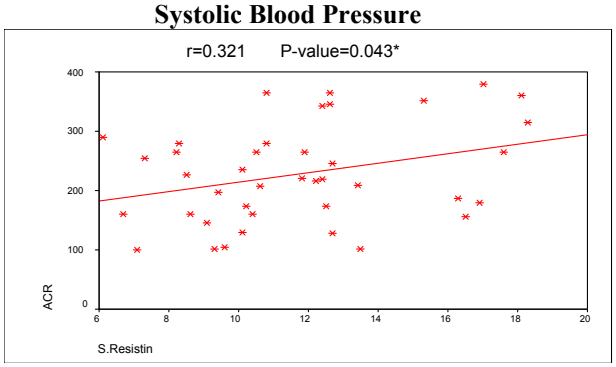

Figure 4: Correlation between Serum Resistin & Albumin-Creatinine Ratio (ACR)

In a multiple linear regression model (Table 3) including factors significantly associated with resistin in univariate analysis, as well as age and gender, only GFR and the SBP were significantly associated with circulating resistin levels.

Table 3: Stepwise Multiple Regression Analysis for Independent Determinants of Resistin Concentrations in Non-diabetic Patients with chronic kidney disease

	Unstandardized Coefficients		Standardized Coefficients	T-test	
	B	Std. Error	Beta	t	*P*-value
(Constant)	2.552	4.476		0.570	0.572
SBP	0.056	0.028	0.339	2.425	0.040*
ACR	0.001	0.005	0.035	0.215	0.831
GFR	0.008	0.053	0.024	3.146	0.035*

4. Discussion:

Our results show that serum levels of resistin are statistically significantly higher in chronic kidney disease patients as compared to controls. Resistin was found to be positively correlated with systolic blood pressure, and albumin-to-creatinine ratio and negatively correlated to the glomerular filtration rate. No significant correlation was found between resistin and BMI or insulin resistance. In a multiple linear regression model including factors significantly associated with resistin in univariate analysis, as well as age and gender and, only GFR and the SBP were significantly associated with circulating resistin levels.

Our study confirms previous studies, which showed that resistin was inversely correlated with eGFR[6, 8, 9]. Resistin is a 12.5-kd protein and should be free filterable, at least theoretically. Polypeptides that have molecular weights comparable to those of resistin are thought to be freely filtered at the normal glomerulus, subjects with advanced renal impairment might have serum resistin accumulations due to reduced renal clearance;that is renal dysfunction might cause elevated serum resistin levels[8, 10].

Previous studies however reported that resistin levels were significantly raised even in subjects with CKD stage 2 (eGFR of 60-89mL/min/1.73m^2), in which polypeptides would be filtered almost normally. Another study by *Kielstein et al.* [9] on patients with immunoglobulin A glomerulonephritis, serum resistin levels were also significantly higher in subjects with mild renal dysfunction who had a mean GFR of 76mL/min/1.73m^2 than in those who had a mean GFR of 114mL/min/1.73m^2. *Dimitriadis K et al.* reported that circulating plasma resistin levels, like other adipokines such as leptin and adiponectin are markedly elevated in patients with renal function impairment[11]. These results suggest that resistin may play a role in the pathogenesis of chronic kidney disease. From another point of view, due to that the kidneys play an important role in the catabolism of small polypeptides such as resistin, a blunt in functional renal parenchyma could augment resistin concentrations[12].

Insulin resistance (IR) is highly prevalent in diabetic and nondiabetic patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) and is an established risk factor for the development of cardiovascular disease and all-cause mortality in this population[13]. Recent studies indicate that many of the metabolic derangements that accompany kidney disease contribute to the development of insulin resistance through different pathways, such as chronic inflammation, metabolic acidosis, vitamin D deficiency, oxidative stress, and decreased clearance of adipocytokines. Accordingly, the assessment of insulin sensitivity in CKD patients requires consideration of these complex factors [14].

Previous studies showed that the effects of resistin are mediated via insulin resistance or inflammation[6, 9]. Resistin directly stimulates the expression of pro inflammatory cytokines as tumour necrosis factorα and interleukin 6 in human peripheral blood mononuclear cells [12].

In our study resistin was not found to be correlated with HOMA-IR . Although resistin seems to be strongly associated with insulin resistance in mice models, several studies have questioned the hypothesis that resistin is a significant determinant of insulin resistance in humans [15].

Janke*et al.* found low levels of resistin expression in subcutaneous adipocytes and no correlation with insulin resistance[16]. Similarly, Heilbronn *et al.* found that serum resistin concentrations did not differ among non-obese, obese and obese diabetic subjects, nor were they significantly correlated with glucose metabolism during a hyperinsulinemic glucose clamp across the groups[17]. When comparing three different immunoassays for resistin, Pfutzner*et al.* found no correlation between fasting plasma levels of resistin and any of the measured parameters of insulin resistance or with blood lipids in patients with type II diabetes mellitus [18]. *Kielstein JT et al*studied resistin in patients with IgA glomerulonephritis and did not support the notion that resistin may be of importance in the pathophysiological process of insulin resistance syndrome present in patients with renal disease[9].

This study proved a positive correlation to Albunin/creatinie ratio an index of diffuse vascular dysfunction. Increased ACR in hypertensive subjects can be considered a consequence of preglomerularmicrovasculopathy or might be a result of eGFRdecline. Resistin may augment the expression of endothelin, adhesion molecules, matrixmetalloproteinases, promoting systemic vascular dysfunction and affecting unfavorably albuminuria levels. Taking this notion further, ACR might be an expression of exposure of kidney structures to both elevations in BP and resistin-mediated vascular compromise [19]. Hypertensives with microalbuminuria exhibited significantly higher resistin levels further supporting the association of resistin with urinary albumin excretion in this setting. Our results also showed that resistin is positively correlated with systolic blood pressure, which confirms the effect of resistin and hemodynamic load on ACR.

Regarding resitin levels and coronary heart disease in patients with decreased kidney function Baldasseroni*et al.* showed that the rise of resistin plasma levels described in patients affected by chronic heart failure is mediated mainly by the level of kidney function [20]. Further studies are needed to evaluate the role of resistin as a marker in the cardiorenal syndrome.

5. Conclusion

Circulating resistin is statistically significantly higher in chronic kidney disease patients as compared to controls. Resistin was found to be positively correlated with systolic blood pressure and albumin-to-creatinine ratio and negatively correlated to the glomerular filtration rate. In a multiple linear regression model including factors significantly associated with resistin in univariate analysis, as well as age and gender and, only GFR and the SBP were significantly associated with circulating resistin levels.

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