Association of serum resistin level with albuminuria and estimated glomerular filtration rate in type 2 diabetes mellitus

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Background
Diabetes is a meta bolic disorder characterized by hyperglycemia, resulting from defects in insulin secretion, insulin action, or both. Resistin is described as a potential factor in obesity-mediated insulin resistance and type 2 diabetes mellitus.

Aim
To evaluate the relationship of resistin levels with estimated glomerular filtration rate (eGFR) and albuminuria in type 2 diabetic patients and to elucidate the role of resistin as an early biomarker for early detection of diabetic kidney disease.

Patients and methods
The study included 70 patients with type 2 diabetes mellitus, as well as 18 healthy participants as a control group who were age and sex matched with the patients. Serum resistin levels were assessed using an ELISA kit measured in ng/ml, albumin/creatinine ratio (ACR), eGFR by MDRD formula, and glycated hemoglobin (HbA1C).

Results
There was a significant positive correlation between serum resistin level and both HbA1C and ACR but a significant negative correlation with eGFR.

Conclusion
There was a significant increased level of HbA1C, resistin, and ACR (mg/g), whereas there was decreased level of eGFR in the patient group compared with the control group ($P < 0.001$).

Keywords:
albuminuria, glomerular filtration rate, kidney diseases, resistin

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Introduction

Chronic kidney disease (CKD) is defined as kidney damage [with or without decreased glomerular filtration rate (GFR)] or decreased GFR only less than 60 ml/min/1.73 m^2 for more than or equal to 3 months [1].

Kidney damage is characterized by pathological abnormalities or markers of damage, including abnormalities in kidney function, and urine tests [2].

In patients with type 2 diabetes, CKD is a leading cause of end-stage renal disease, cardiovascular disease, and premature death [3].

Obesity, hypertension, dyslipidemia, hyperglycemia, and many features of type 2 diabetes, all being symptoms in insulin resistance, are considered risk factors for CKD and end-stage renal disease [4].

An important pathogenic factor in a diabetic is the chronic low-grade inflammatory condition [5].

Adipokines (cytokines secreted by adipose tissue) have been linked to both low-grade inflammation and insulin resistance [6].

In cardiovascular diseases and atherogenesis, resistin – a 12.5-kDa cysteine-rich protein that in humans is primarily secreted by the macrophages embedded in the adipose tissue – has been implicated [7].

The important role of resistin in physiological and pathophysiologic is unclear [8].

There was an association of increased resistin levels in obesity, insulin resistance, metabolic syndrome, type 2 diabetes, and increased cardiovascular risk [9].

There was a negative correlation between serum resistin levels and kidney function [estimated glomerular filtration rate (eGFR)]. Relation has been described not only in type 2 diabetes but also in the general population [10].

Plasma resistin levels have been associated with CKD progression. Moreover, increased circulating resistin

level, with its inflammatory, metabolic, and vascular abnormalities, is associated with the pathogenesis of CKD [11].

Aim

We aimed to explore the possible interrelationship of resistin levels with albuminuria and eGFR in type 2 diabetic patients and to elucidate the role of resistin as an early biomarker for early detection of diabetic kidney disease and CKD progression.

Patients and methods

A case–control study was performed between May 2017 and May 2018 that included 70 patients with type 2 diabetes mellitus (DM) (group 1) from the Luxor International Hospital and 18 healthy volunteers as a control group (group 2) who were age and sex matched with the patients.

The participants signed an informed consent form. The study was approved by the ethical committee (IRB) of Assiut Faculty of Medicine, Assiut University, with reference number 17101072.

Inclusion criteria

Type 2 diabetic patients either on insulin or oral hypoglycemic drugs, with or without albuminuria [albumin/creatinine ratio (ACR)], and kidney impairment detected by kidney function tests (urea and creatinine) were included.

Exclusion criteria

The following were the exclusion criteria:

(1) Patients who smoked.
(2) Patients with cardiovascular diseases such as valvular, hypertensive, or ischemic heart disease.
(3) Obese patients with BMI more than or equal to 30.
(4) Dyslipidemia.
(5) Patients with eGFR less than 30 ml/min/1.73 m^2 (stages 4 and 5 CKD by MDRD equation).
(6) Patients with hepatic disease.
(7) Patients with other clinically significant concurrent systemic diseases, such as infection, collagen disease, SLE, or respiratory failure.
(8) Other kidney disease.

Methodology

All the participating patients were subjected to full history, including age, sex, smoking habit, duration of diabetes, and medications used for DM.

Full clinical examination included BMI (calculated by weight in kg/height in m^2), blood pressure, and systematic examination.

Laboratory investigations

These included complete blood count, random blood sugar, C-reactive protein, erythrocyte sedimentation rate, glycated hemoglobin (HbA1C), blood urea, serum creatinine, urine analysis, lipid profile, liver function tests, and assessment of eGFR by using MDRD equation to eGFR from serum creatinine, age, sex, and race. eGFR is expressed in ml/min/1.73 m^2. Serum creatinine is expressed in mg/dl [3].

Albuminuria was assessed by urinary ACR, measured by mg albumin/g creatinine (microalbuminuria when > 30–300 and macroalbuminuria when > 300 mg/g). Serum resistin levels were assessed using a commercially available ELISA kit Elabscience (sandwich-ELISA technique, catalog number E-ELH1213), measured by ng/ml (normal range, 4–12 ng/ml).

(1) Abdominal ultrasonography was done to determine the state of both kidneys, and ECG was done as well.

Ethical considerations

The study has been approved by the faculty's ethics committee before enrollment of the participants in the study.

The data of the patients have been collected from their files to be enrolled in the study after approval by from the ethical committee of the Faculty of Medicine in Assiut University.

Statistical analysis

Per-protocol population was analyzed, and descriptive values were expressed as mean ± SD or *n* (%). Independent Student *t* test was used for comparison between normally distributed data. In the two groups, Mann–Whitney test was used for comparison when data were not normally distributed and χ^2 test to compare proportions between both groups. *P* value was considered significant when less than 0.05 by SPSS, version 24 (IBM, Armonk, New York, USA).

Results

Table 1 shows the demographic data of the patient and control groups. There was no significant difference ($P > 0.05$) between patient and control groups regarding age, sex, and BMI. Table 2 shows

Table 1 Demographic data in patients and control groups

Items	Patient group (*n*=70)	Control group (*n*=18)	*P*
Age (years)	49.44±9.73	45.26±3.56	0.385 NS
Sex [n (%)]			
Male	33 (47.14)	7 (36.0)	0.372 NS
Female	37 (52.85)	11 (64.0)	0.265 NS
BMI	28.89±0.47	27.84±0.43	0.446 NS
WC	103.90±1.04	98.09±1.03	

WC, waist circumference.

Table 2 Kidney functions, glycated hemoglobin, serum resistin level, albumin/creatinine ratio, and estimated glomerular filtration rate in patient compared with control groups

Items	Patients group (*n*=70)	Control group (*n*=18)	*P*
Urea (mg/dl)	32.02±9.60	29.46±8.21	0.382 NS
Creatinine (mg/dl)	1.15±0.34	1.01±0.21	0.218 NS
HBA1C %	9.78±2.62	5.94±0.61	<0.001**
Resistin (ng/ml)	7.82±0.29	6.03±0.17	<0.001**
ACR (mg/g)	33.68±3.23	25.59±2.84	<0.03*
eGFR	62.35±14.12	97.26±7.94	<0.03*

ACR, albumin/creatinine ratio; eGFR, estimated glomerular filtration rate; HbA1C, glycated hemoglobin.

kidney functions in patient and control groups. There was no significant difference ($P > 0.05$) between patient and control groups regarding urea and creatinine. Regarding HbA1C, there was a significant difference ($P < 0.001$) between patient and control groups, with higher level in patient group than control group. Regarding resistin, there was a significant difference ($P < 0.001$) between patient and control groups, with higher level in the patient group than the control group. Regarding ACR, there was a significant difference ($P < 0.05$) between patient and control groups, with higher levels in the patient group. Regarding eGFR, there was a significant difference ($P < 0.05$) between patient and control groups, with lower level in the patient group than control group. Table 3 shows a relation between level of resistin and levels of albuminuria in the patient group. There was a moderate significant positive correlation difference ($P < 0.001$) between patients without microalbuminuria and those with microalbuminuria, with higher level of resistin in patients with microalbuminuria than patients without microalbuminuria. Table 4 shows relation between level of resistin and eGFR in the patient group (negative correlation). There was a highly significant difference ($P < 0.000$), with higher levels of resistin when eGFR was within the range of 30–59 ml/min than other categories (eGFR 60–90). Moreover, there was a moderate significant difference ($P < 0.001$) between eGFR and HbA1C, with higher mean value of HbA1C in eGFR = 30–59.

Discussion

In the present study, regarding HbA1C, there was a moderate significant difference ($P < 0.001$) between patient and control groups, with higher mean value in the patient group than the control group. This is in agreement with that found by Subramanyam *et al.* [16], who reported that HbA1C values increased with decreasing eGFR, indicating that poor glycemic control correlated with increasing incidence of renal damage. This is supported by the statistics, which also reveal HbA1C levels increase with increasing serum creatinine levels.

In the present study, resistin is higher in DM than non-DM, with moderate significance difference. This agrees with Antuna-Puente *et al.*[13] who reported resistin, which is expressed by monocytes and macrophages in humans as a peptide, is associated with insulin resistance. Moreover, serum resistin decreased insulin-stimulated glucose. Serum resistin levels are increased in patients with DM [14].

There was a negative correlation between resistin and renal function, in terms of eGFR.

The present study is in agreement with the previous research studies, which reported that circulating serum resistin levels were increased in patients with renal function impairment [15].

The study of Subramanyam *et al.*[16] is also one of the first few studies to compare the important biochemical parameters between different stages of CKD. HbA1C, eGFR, and serum creatinine are compared in stages 3, 4, and 5 of CKD. A study done by Kundu *et al.*[17,18] found that there was a negative correlation between HbA1C and eGFR and a positive correlation between HbA1C and serum creatinine.

Our study showed that was a moderate significant difference between HbA1C and eGFR. This agrees with Yokoyama *et al.* [17]. A retrospective cohort study done by Lee and colleagues involving 1992 participants showed that there was higher baseline HbA1C with annual decline in eGFR. In fact, high baseline value of HbA1C was found to be a predictor of GFR decline in patients with DM.

These results were in agreement with our study.

In present study, there was a negative correlation between resistin and eGFR. This is in agreement with Mahmoud *et al.* [19], who reported that there was a highly significant difference of serum resistin between patients with CKD and control groups. A significant positive correlation between resistin and creatinine, a

Table 3 Correlation between level of resistin and levels of microalbuminuria in the patient group

Microalbuminuria in patient group	Without microalbuminuria (*n*=38)	With microalbuminuria (*n*=32)	*P*
Resistin level (ng/ml)	6.03±2.03	8.82±1.89	<0.001**

Table 4 Relation between serum level of resistin and estimated glomerular filtration rate and glycated hemoglobin in the patient group

eGFR (ml/min)	eGFR 30–59 (*n*=25)	eGFR 60–89 (*n*=43)	eGFR ≥90 (*n*=2)	*P*
Resistin level (ng/ml)	7.89±2.05	7.03±1.57	6.42±1.22	<0.000***
HbA1C (%)	9.97±2.06	8.26±3.50	7.22±1.98	<0.001**

eGFR, estimated glomerular filtration rate; HbA1C, glycated hemoglobin.

negative correlation between resistin and eGFR were shown, suggesting that resistin concentration depends on renal function and is correlated with the severity of the renal disease.

Kielstein *et al.*[20] reported that there was a significant increase in various adipokines, including resistin, in patients with CKD. Moreover, regulation of these adipokines *in vivo* strongly depends on renal function [21].

Regulation of the systemic levels of resistin is associated with renal function [22].

However, Risch *et al.*[23] failed to find a relation between GFR and serum resistin at GFR more than 60 ml/min/1.73 m^2, suggesting that resistin level in mild impaired and normal renal function is influenced by factors other than GFR.

In the present study, there was a positive correlation between ACR and resistin ($P < 0.000$). This agrees with Menzaghi *et al.* [24], who reported there was a moderately significant relation between resistin and ACR and an inverse association between resistin and eGFR.

Among the studies dispute resistin and GRF Dimitriadis *et al.*, [25] were documented that raised resistin levels in CKD were associated with decreased GFR and inflammation, but not with insulin resistance.

Conclusion

There was a significant positive correlation between serum resistin and albuminuria, blood urea, serum creatinine, and CKD progression in type 2 DM and significant negative correlation with eGFR, so serum resistin level can be used as an early biomarker for early detection of diabetic kidney disease in type 2 DM.

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Conflicts of interest
There are no conflicts of interest.

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