Relation of plasma resistin to obesity and insulin resistance in type 2 diabetic Egyptian patients

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Abstract— Resistin is an adipocyte-secreted hormone proposed to link obesity with type 2 diabetes mellitus. Data from the literature regarding the physiological role of circulating resistin are unclear or conflicting. Therefore, the present study was undertaken to investigate the relationship between circulating resistin levels, obesity, and insulin resistance markers in Egyptian patients with type 2 diabetes. The study included 43 type 2 diabetic patients and 41 age-matched healthy controls. Plasma resistin was found to be significantly higher in diabetic lean and obese patients, compared to their controls ($p < 0.01$) with males have higher levels than females. In addition, Insulin resistance markers assessed by homeostasis model as well as total cholesterol, triglycerides, low density lipoprotein cholesterol (LDL-C), fasting blood glucose, and glycated hemoglobin levels, were also higher among diabetic patients than in the controls. Pearson's analysis revealed positive correlations between plasma resistin and weight, body mass index (BMI), lean body mass (LBM), insulin, homeostasis model assessment-β cell index (HOMA-β), homeostasis model assessment-insulin resistance (HOMA-IR), total cholesterol, and LDL-C. On the other hand, a negative correlation between resistin and homeostasis model assessment-hepatic insulin sensitivity (HOMA-HIS) as well as high density lipoprotein cholesterol (HDL-C) was also observed. These results suggests that circulating resistin is unlikely to play a direct role on the development of type 2 diabetes rather than be associated with obesity and insulin resistance, both of which could, indirectly, contribute to the pathogenesis of type 2 diabetes mellitus in Egyptian patients.

Index Terms— resistin, type 2 diabetes, insulin resistance, obesity and Egyptian.

INTRODUCTION

Obesity is known to be a major risk factor for the development of insulin resistance- a central player in the pathogenesis of type 2 diabetes mellitus. A strong correlation has been reported between insulin resistance and central obesity in type 2 diabetic patients [1]. Although the mechanism remains unclear, it has been appreciated that adipose tissue represents a potential pathophysiological link between obesity and type 2 diabetes mellitus and vascular diseases [2]. Adipose tissue was initially regarded as a passive energy reservoir, however, its role in modulating energy metabolism via secreting a number of circulating adipocytokines has been extensively appreciated over the past decade [3]. One of these adipocytokines is resistin secreted primarily by adipocytes in rodents while expressed by many other tissues, particularly macrophages, in humans [4].

In fact, the role of resistin in the pathogenesis of diabetes mellitus and its relation to obesity and insulin resistance remains to be further elucidated [5]. In addition, data collected from literature relating resistin, obesity, and insulin resistance are still controversial. For example, increased resistin level in association with obesity and insulin resistance in type 2 diabetes has been reported by several authors [6], [7] whereas others failed to detect significant alteration in resistin levels under such conditions [8], [9]. Moreover, other researchers have correlated circulating resistin levels with adiposity, although not detected such correlation with the degree of insulin resistance [10]. In addition, Burnett et al (2006) have suggested that differences in resistin expression among different populations are due to genetic or environmental factors [11]. Taken altogether, these findings indicate that the role of resistin in the pathogenesis of diabetes is still to be further elucidated. Therefore, the present study was undertaken to investigate the relationship between serum resistin, insulin resistance, and obesity markers in type 2 Egyptian diabetics.

SUBJECTS AND METHODS

Patients

The present study included 84 adult subjects (40-60 years) of both sexes classified as diabetic patients (20 lean and 23 obese subjects) that were selected according to the criteria published by the American Diabetes Association and healthy non-diabetic subjects (21 lean and 20 obese subjects) that were age and gender matched to the diabetic patients. Blood samples were recruited from outpatients presenting at clinics of Ain-Shams University Hospitals, Cairo, Egypt. A written informed consent was taken from all participants and the study was approved by Ain Shams Medical Research Ethics Committee. Subjects were considered lean if their body mass index (BMI) ≤ 25 kg/m^2 while considered obese if their BMI ≥ 30 kg/m^2.

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Calculation of BMI, LBM, HOMA-β, HOMA-IR and HOMA-HIS

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Lean body mass (LBM) was calculated according to Hume, R [12] as follows: LBM (kg) = 0.32810 × weight (kg) + 0.33929 × height (cm) − 29.5336 in men and LBM (kg) = 0.29569 × weight (kg) + 0.41893 × height (cm)−43.2933 in women.

Homoeostasis model assessment β-cell index (HOMA-β) was used to estimate the pancreatic β-cell secretory capacity using the formula introduced by Hosker et al [13]: HOMA-β = 20 x FI/(FPG – 3.5) where FI is fasting insulin (μU/ml) and FPG is fasting plasma glucose (mg/dl). Insulin resistance (IR) was evaluated by the HOMA introduced by Matthews et al. [14] as follows: HOMA-IR = FI (μU/ml) x FPG (mmol/L)/22.5. Hepatic insulin sensitivity (HIS) was assessed using the following formula HOMA-HIS = 405/[FPG (mg/dl) x FI (μU/ml)] [15].

Biochemical assays

Venous blood samples were obtained after an overnight fast. Serum was separated by centrifugation at 14,000 rpm for 5 minutes and stored at -70 °C. Plasma samples were prepared using fluoride-vacutainer tubes, and centrifuged at 3,000×g for 15 min at 4 °C. Total cholesterol, HDL-cholesterol, and triglycerides were assayed in serum using fully enzymatic methods (Bio-Merieux Co. France) as described by Allain et al., (1974), Finley et al., (1978), and Nagele, (1984), respectively [16], [17], [18]. Low density lipoprotein cholesterol (LDL-C) was calculated by Friedwald's formula [19], LDL-C = total cholesterol − (triglycerides/5 + HDL-C). Serum urea and creatinine were determined using standard methods (Boehringer Mannheim Co, Germany). Plasma glucose was determined by the glucose oxidase method (Spinreact diagnostic kit, San antonio, Claret, Texas) according to Trinder et al 1969 [20]. Glycosylated hemoglobin was measured in the whole blood by the method described by Trivelli, (1971) [21] using a commericial kit (Stanbio Laboratory, North Main, Boerne, Texas). Plasma insulin levels were assayed using a solid phase sandwich ELISA kit for human insulin (BioSource International, Inc. Europe S.A.). Resistin was measured in plasma using a commercially available ELISA kit (Biovendor Laboratory Medicine Inc, USA) which is a sandwich-type assay using a rabbit polyclonal antihuman resistin antibody that detects homodimeric resistin.

Statistical analysis

Statistical analyses were performed using IBM, SPSS program (version 22 Inc., Chicago, USA). All data were expressed as means ± SEM; values of $p < 0.05$ were considered significant. Comparisons between groups were made using Student's t-test. Pearson correlation coefficient test was used to associate circulating resistin levels and various parameters.

RESULTS

Data presented in table (1) are showing that serum resistin level is significantly higher (p<0.001) in diabetic subjects than their normal controls. Also, diabetic patients showed a highly significant increase (p<0.001) in fasting plasma glucose (FPG), HbA1c, HOMA-β, and insulin resistance (HOMA-IR), compared to their normal controls. In addition, total cholesterol, triglycerides, and LDL-C were also detected in significantly increased levels in diabetic patients than their normal volunteers. In contrast, plasma insulin, hepatic insulin sensitivity (HOMA-HIS), serum urea and HDL-C were detected in significantly lower amounts (p<0.001) in diabetic group. Moreover, statistically no significant difference was observed in the levels of body mass index (BMI), lean body mass and creatinine between the two groups.

The effect of gender on the levels of resistin and other parameters was investigated through subdividing type 2 diabetics and their matching controls into male and female groups (Table 2). Height values were recording a significant difference in females but not in males; however this difference has no observable effect on the calculated BMI. In addition, the significant increase recorded in resistin levels were higher in males (p=0.002) than in females (p=0.013). No other significant gender differences were observed in the levels of FBG, HbA1c, HOMA-β, HOMA-IR, HOMA-HIS, cholesterol, TG, HDL-C, LDL-C, and urea (Table 2).

Diabetic patients were further subgrouped into two age groups, 40-49 years and 50-60 years (Table 3). On comparing the two groups, a more significant increase in the level of resistin was noticed in the younger group. In addition, both the two age groups are still exhibiting a significant increase in the levels of FBG, HbA1c, HOMA-β, HOMA-IR, HOMA-HIS, cholesterol, TG, and LDL-C (Table 3).

To study the effect of obesity on resistin levels and the other clinical parameters, diabetic patients were divided into two subgroups according to BMI: lean (BMI ≤ 25) and obese (BMI ≥ 30). Levels of resistin were recording a significantly higher increase in lean diabetics (p<0.001) than that in obese diabetics (p=0.002) compared with their matched controls (Table 4). However, levels of insulin were significantly different in lean diabetics but not in obese subjects, compared to their matched controls. No other significant BMI-based differences were detected in any other parameters, such as FBG, HbA1c, cholesterol, TG, HDL-C, LDL-c, urea, HOMA-β, HOMA-IR, and HOMA-HIS (Table 4).

Table 5 shows that circulating plasma resistin levels were highly significantly correlated with obesity markers such as weight (r=0.57, p<0.001), BMI (r=0.56, p <0.001), LBM (r=0.50, p <0.001) as well as parameters of insulin resistance such as HOMA-β (r=0.49, p <0.001), and HOMA-IR (r=0.49, p <0.001). Also, positive correlations were observed with total cholesterol (r=0.31, p <0.05), LDL-C (r=0.32, p <0.05), and insulin levels (r=0.38, p <0.01). In addition, a strong significant negative correlation was observed with HOMA-HIS (r=−0.44, p <0.01) while moderately correlated with HDL-C (r=−0.30, p <0.05).

Table 1: Demographic and biochemical characteristics of diabetic patients and their matched controls

Parameter	Group		
	Controls (n=41)	Diabetics (n=43)	P value
Age (years)	49.90 ± 1.09	50.40 ± 1.07	N.S.
Height (cm)	164.09 ± 0.96	164.48 ± 0.87	N.S.
Weight (Kg)	78.22 ± 2.65	78.32 ± 2.59	N.S.
Body mass index (kg/m²)	28.98 ± 0.96	29.01 ± 1.01	0.980
Lean body mass (kg)	50.60 ± 1.17	49.90 ± 0.93	N.S.
Fasting blood glucose (mg/dl)	95.60 ± 1.30	262.74 ± 9.01	< 0.001*
HbA1c (%)	4.82 ± 0.06	8.53 ± 0.22	< 0.001*
Insulin (µU/mL)	12.95 ± 0.39	8.88 ± 0.58	< 0.001*
Resistin (ng/mL)	6.51 ± 0.44	10.39 ± 0.78	< 0.001*
HOMA-β	2.96 ± 0.06	5.29 ± 0.19	< 0.001*
HOMA-IR	54.32 ± 1.16	96.14 ± 3.51	< 0.001*
HOMA-HIS	0.33 ± 0.007	0.195 ± .007	< 0.001*
Total cholesterol (mg/dl)	190.07 ± 2.84	260.97 ± 6.16	< 0.001*
Triglycerides (mg/dl)	89.92 ± 2.22	160.02 ± 5.65	< 0.001*
HDL-C (mg/dl)	42.60 ± 1.37	34.76 ± 0.51	< 0.001*
LDL-C (mg/dl)	129 ± 3.21	194.22 ± 6.36	< 0.001*
Urea (mg/dl)	28.26 ± 0.54	22.0 ± 0.57	< 0.001*
Creatinine (mg/dl)	0.86 ± 0.02	0.91 ± 0.02	N.S.

Results are expressed as Mean ± SEM
*Statistically significant difference
Abbreviations: HbA1c, glycated hemoglobin; HOMA-β, homeostasis model assessment β-cell index; HOMA-IR, homeostasis model assessment insulin resistance; HOMA-HIS, homeostasis model assessment hepatic insulin sensitivity; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Table 2: Levels of various parameters by sex in diabetic patients and their matched controls

Parameter	Male			Female		
	Controls (n=20)	Diabetics (n=19)	*P* value	Controls (n=21)	Diabetics (n=24)	*P* value
Age (years)	49.80 ± 1.59	53.16 ± 1.54	N.S.	50.0 ± 1.53	48.21 ± 1.36	N.S.
Height (cm)	169.45 ± 0.58	167.15 ± 1.33	N.S.	159.0 ± 0.80	162.37 ± 0.97	0.011*
Weight (Kg)	83.35 ± 3.41	78.31 ± 3.84	N.S.	73.33 ± 3.81	78.33 ± 3.58	N.S.
BMI (kg/m2)	28.97 ± 1.17	28.21 ± 1.60	N.S.	28.99 ± 1.53	29.65 ± 1.32	N.S.
Lean body mass (kg)	55.27 ± 1.16	52.77 ± 1.16	N.S.	46.16 ± 1.45	47.62 ± 1.23	N.S.
FPG (mg/dl)	95.90 ± 1.75	276.31 ± 9.07	< 0.001*	95.33 ± 1.97	252.0 ± 14.25	< 0.001*
HbA1c (%)	4.93 ± 0.09	8.45 ± 0.31	< 0.001*	4.71 ± 0.09	8.59 ± 0.31	< 0.001*
Insulin (µU/mL)	12.40 ± 0.56	8.00 ± 0.64	< 0.001*	13.47 ± 0.52	9.58 ± 0.90	0.001*
Resistin (ng/mL)	6.49 ± 0.61	11.47 ± 1.28	0.002*	6.54 ± 0.64	9.54 ± 0.95	0.013*
HOMA-β	2.84 ± 0.09	5.23 ± 0.29	< 0.001*	3.09 ± 0.08	5.35 ± 0.26	< 0.001*
HOMA-IR	52.17 ± 1.71	94.99 ± 5.25	< 0.001*	56.38 ± 1.49	97.05 ± 4.80	< 0.001*
HOMA-HIS	0.34 ± 0.01	0.19 ± 0.01	< 0.001*	0.32 ± 0.009	0.19 ± 0.009	< 0.001*
Cholesterol (mg/dl)	187.65 ± 4.13	259.78 ± 8.70	< 0.001*	192.38 ± 3.95	261.91 ± 8.78	< 0.001*
Triglycerides (mg/dl)	89.40 ± 3.95	145.42 ± 5.48	< 0.001*	90.42 ± 2.26	171.58 ± 8.54	< 0.001*
HDL-C (mg/dl)	43.45 ± 2.66	34.52 ± 0.78	0.004*	41.80 ± 0.94	34.95 ± 0.69	< 0.001*
LDL-C (mg/dl)	126.73 ± 4.93	196.17 ± 8.90	< 0.001*	132.43 ± 4.17	192.68 ± 9.12	< 0.001*
Urea (mg/dl)	27.20 ± 0.89	21.52 ± 0.81	< 0.001*	29.28 ± 0.58	22.37 ± 0.79	< 0.001*
Creatinine (mg/dl)	0.84 ± 0.03	0.90 ± 0.04	N.S.	0.88 ± 0.03	0.92 ± 0.04	N.S.

Results are expressed as Mean ± SEM
*Statistically significant difference

DISCUSSION

In the present study, we detected a significant increase in the level of plasma resistin in diabetic patients compared with that of control subjects. This finding is in agreement with several reports that have correlated type 2 diabetes with high levels of resistin [8], [22], [23] however, contradictory results were also reported by Stejskal et al (2003) and Lee et al (2003), respectively[24], [25]. In addition, significantly higher levels of FBG, HOMA-β, HOMA-IR as well as total cholesterol, triglycerides, LDL-C and urea were also detected in Egyptian diabetics compared to their controls.

Table 3: Levels of various parameters by age in diabetic patients and their matched controls

Parameter	Age = 40-49 Y Controls (n=23) Diabetics (n=22)	Age = 50-60 Y Controls (n=18) Diabetics (n=21)
Height (cm)	NS	NS
Weight (Kg)	NS	NS
BMI (kg/m2)	NS	NS
Lean body mass (kg)	NS	NS
FPG (mg/dl)	< 0.001*	< 0.001*
HbA1c (%)	< 0.001*	< 0.001*
Insulin (μU/mL)	0.001*	< 0.001*
Resistin (ng/mL)	0.003*	0.009*
HOMA-β	<0.001*	< 0.001*
HOMA-IR	<0.001*	< 0.001*
HOMA-HIS	<0.001*	< 0.001*
Cholesterol (mg/dl)	< 0.001*	< 0.001*
Triglycerides (mg/dl)	< 0.001*	< 0.001*
HDL-C (mg/dl)	< 0.001*	0.004*
LDL-C (mg/dl)	< 0.001*	< 0.001*
Urea (mg/dl)	< 0.001*	0.001*
Creatinine (mg/dl)	NS	NS

Results are expressed as Mean ± SEM
NS: non-significant
*Statistically significant difference

Table 5: Pearson's correlation coefficients between resistin and various parameters in diabetic patients

Parameter	Pearson *r*	*P* (two-tailed)
Age (years)	0.162	N.S.
Height (cm)	- 0.114	N.S.
Weight (Kg)	0.570	<0.001**
BMI (kg/m2)	0.567	<0.001**
Lean body mass (kg)	0.504	0.001*
FPG (mg/dl)	- 0.132	N.S.
HbA1c (%)	0.271	N.S.
Insulin (μU/mL)	0.388	0.01*
HOMA-β	0.498	0.001**
HOMA-IR	0.497	0.001**
HOMA-HIS	- 0.442	0.003**
Cholesterol (mg/dl)	0.313	0.041*
Triglycerides (mg/dl)	0.001	N.S.
HDL-C (mg/dl)	- 0.304	0.047*
LDL-C (mg/dl)	0.327	0.032*
Urea (mg/dl)	- 0.061	N.S.
Creatinine (mg/dl)	0.117	N.S.

r: correlation coefficient;
* Statistically significant correlation.
** Highly statistically significant correlation.

Analysis of the gender effect revealed that the changes in both male and female diabetic patients' parameters, including resistin, were consistent with the parameters seen in the whole group. However, a more significant difference in resistin levels is observed in men than in women subgroup. In fact, several studies have reported a significant gender differences in concentration of circulating resistin [7], [25], [26] although others did not encountered such effect [8], [27]. Moreover, a less pronounced significant decrease was also observed in the level of HDL-C in male diabetic patients than the female diabetic subgroup, compared to their respective controls.

Table 4: Characteristics of diabetic patients and their matched controls according to their BMI

Parameter	Lean (BMI ≤ 25)			Obese (BMI ≥ 30)		
	Controls (n=21)	Diabetics (n=20)	*P* value	Controls (n=20)	Diabetics (n=23)	*P* value
Age (years)	49.38 ± 1.25	49.45 ± 1.55	N.S.	50.45 ± 1.84	51.22 ± 1.50	N.S.
Height (cm)	164.14 ± 1.30	166.0 ± 1.35	N.S.	164.05 ± 1.45	163.17 ± 1.08	N.S.
Weight (Kg)	63.09 ± 1.46	61.35 ± 1.14	0.354	94.10 ± 1.47	93.08 ± 1.32	N.S.
Lean body mass (kg)	45.52 ± 1.17	45.45 ± 1.07	N.S.	55.94 ± 1.22	53.76 ± 0.89	N.S.
FPG (mg/dl)	92.57 ± 1.78	261.0 ± 8.74	< 0.001*	98.80 ± 1.68	264.26 ± 15.23	< 0.001*
HbA1c (%)	4.81 ± 0.08	7.88 ± 0.29	< 0.001*	4.82 ± 0.10	9.10 ± 0.28	< 0.001*
Insulin (μU/mL)	13.76 ± 0.58	7.50 ± 0.41	< 0.001*	12.10 ± 0.45	10.08 ± 0.97	N.S.
Resistin (ng/mL)	4.06 ± 0.20	7.20 ± 0.38	< 0.001*	9.10 ± 0.33	13.17 ± 1.15	0.002*
HOMA-β	3.05 ± 0.08	4.67 ± 0.94	< 0.001*	2.88 ± 0.44	5.84 ± 1.30	< 0.001*
HOMA-IR	55.82 ± 1.57	84.93 ± 3.79	< 0.001*	52.76 ± 1.69	105.89 ± 4.88	< 0.001*
HOMA-HIS	0.32 ± 0.01	0.21 ± 0.01	< 0.001*	0.34 ± 0.01	0.17 ± 0.008	< 0.001*
Cholesterol (mg/dl)	189.14 ± 3.10	236.45 ± 7.62	< 0.001*	191.05 ± 4.91	282.30 ± 6.87	< 0.001*
Triglycerides (mg/dl)	86.85 ± 3.14	152.85 ± 7.65	< 0.001*	93.15 ± 3.06	166.26 ± 8.14	< 0.001*
HDL-C (mg/dl)	43.09 ± 2.57	35.40 ± 0.61	0.008*	42.10 ± 0.90	34.21 ± 0.79	< 0.001*
LDL-C (mg/dl)	128.68 ± 3.78	170.48 ± 8.23	< 0.001*	130.67 ± 5.34	214.87 ± 7.22	< 0.001*
Urea (mg/dl)	28.47 ± 0.64	21.60 ± 0.91	< 0.001*	28.05 ± 0.91	22.34 ± 0.72	< 0.001*
Creatinine (mg/dl)	0.84 ±0.02	0.90 ± 0.04	N.S.	0.89 ± 0.03	0.93 ± 0.03	N.S.

Results are expressed as Mean ± SEM
*Statistically significant difference
Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HIS, hepatic insulin sensitivity.

Investigation of the age effect on the levels of resistin in type 2 diabetic Egyptian subjects showed no difference between the two age subgroups (40-49 Y versus 50-60 Y) and change in resistin levels in the two subgroups is also consistent with that of the whole diabetic group. Such finding could also be indicated from the lack of association of resistin with age (Table 5). These results are not in agreement with those of Gharibeh et al. (2010) who observed a pronounced age effect on resistin levels in elderly Jordanian diabetic patients (> 60 years) and have explained that by the development of obesity and insulin resistance with ageing [22]. In fact, age effect on the levels of plasma resistin in diabetic patients was postulated (with others) to explain the controversial data of resistin levels among such patients [9], [24], [25].

Data obtained from the present study also reflects a link between plasma resistin and insulin resistance in Egyptian diabetics and indicated by the significant correlation of resistin values with insulin, HOMA-β, HOMA-IR, and HOMA-HIS (Table 5). In fact, these findings contradict with previous studies on Japanese [8] and Pima Indians [28] diabetics. However, such discrepancies could be due to ethnic variations or different methodologies used in determinations. Pearson's analysis also demonstrates a significant positive correlation between circulating resistin and obesity expressed by BMI. This observation could be potentiated by the less significant increase in resistin level detected in obese than lean diabetics, indicating that obesity itself is associated with high resistin levels (Table 4). Such results are in accordance with previous results carried out on Saudi [29] and Jordanian [22] type 2 diabetics and detected a highly significant correlation between resistin levels and obesity markers; BMI, waist-to-hip ratio, and waist circumference.

Pearson's analysis also reveals no association between resistin and blood glucose or HBA1c in diabetic patients; such result is also reported in previous report [30]. Taken altogether, these data links circulating plasma resistin levels, obesity, and insulin resistance with type 2 diabetes. Moreover, it suggests an indirect role of resistin in the pathogenesis of type 2 diabetes among Egyptian patients.

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