ORIGINAL ARTICLE

Correlation of serum resistin level with insulin resistance and severity of retinopathy in type 2 diabetes mellitus

Naglaa Azab [a], Taher Abdel-Aziz [b,*], Amr Ahmed [a,1], I.M. El-deen [b,1]

[a] *Department of Medical Biochemistry, Faculty of Medicine, Benha University, Egypt*
[b] *Department of Chemistry, Faculty of Science, Port Said University, Egypt*

Abstract Resistin is an adipocyte secreted hormone, to investigate the relationship between levels of serum resistin and C-reactive protein (as an inflammatory marker) together with insulin resistance and the presence of retinopathy in type 2 diabetes mellitus in Egyptian subjects, we measured fasting serum resistin and CRP levels in thirty obese diabetic subjects (with different grades of retinopathy: ten diabetic patients without retinopathy, ten diabetic patients with non-proliferative retinopathy and ten diabetic patients with proliferative retinopathy) and compared them with the results of ten obese non diabetic subjects and ten non obese healthy volunteers. Insulin resistance was assessed using the homeostasis model assessment for insulin resistance (HOMA-IR). All subjects were investigated to analyze the change in their total cholesterol, HDL-C, LDL-C, and triglycerides levels. Fasting glucose and insulin resistance were significantly higher ($P < 0.05$) in diabetic compared with non diabetic subjects. Fasting Serum resistin and CRP were highly significantly different among the groups of study ($P < 0.001$). Fasting serum resistin concentration showed highly significant positive correlation with CRP, BMI (body mass index), serum insulin, HOMA-I.R, and FBS (fasting blood sugar) and it was significantly positively correlated with waist, hip circumferences and triglycerides levels, while it was significantly negatively correlated with HDL-C. Serum resistin was associated with the presence of retinopathy in T2DM.

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1. Introduction

Resistin is a member of a secretory protein family, known as resistin-like molecules (RELMs) (Steppan and Lazar, 2004). It was originally named for its resistance to insulin (Steppan et al., 2001). Resistin is expressed in white adipose tissue with the highest levels in female gonadal adipose tissue (Steppan and Lazar, 2002), besides adipose tissue, human resistin is also expressed in other varieties of human tissues. Real-time PCR showed that human resistin was expressed at the highest level

in the bone marrow followed by the lung (Patel et al., 2003). Human resistin mRNA has also been detected in the nonfat cells of adipose depots (Fain et al., 2003).

Resistin was identified as a possible link between obesity and insulin resistance (Chen et al., 2002). Insulin resistance is a fundamental aspect of the etiology of type 2 diabetes and is also linked to a wide array of other pathophysiologic sequels including hypertension, hyperlipidemia, atherosclerosis and polycystic ovarian disease (Reaven, 1995). A specific complication of diabetes, microangiopathy, includes retinopathy, nephropathy, and neuropathy (Mabley and Soriano, 2005). The development or progression of diabetic microangiopathy could be affected by serum resistin (Osawa et al., 2007a).

Several recent human studies have supported the concept of inflammatory cytokine mediation of resistin (Mattevi et al., 2004), however, resistin associations with inflammatory markers appear to be independent of BMI, suggesting that resistin may have a direct proinflammatory role or mediate its effects via yet to be discovered obesity-independent mechanisms(Greeshma et al., 2004), C-reactive protein (CRP) is an inflammatory biomarker (Sun et al., 2005), involved in endothelial dysfunction and atherogenesis (Torzewski et al., 2000). Inflammation as measured by serum C-reactive protein has been shown to be increased in people with diabetes who have macro vascular complications (Zhao et al., 2011), and microangiopathy (Matsumoto et al., 2002).

In view of this, we investigated the correlation between serum resistin level and insulin resistance in obesity and type 2 diabetes mellitus together with serum resistin and CRP levels in relation to the presence of diabetic retinopathy in fifty Egyptian subjects.

2. Materials and methods

The study was conducted on fifty unrelated Egyptian subjects divided into three groups: group1 (control group) consists of ten non obese non diabetic healthy volunteers, group 2 consists of ten obese, non diabetic subjects and group 3 consists of thirty obese, diabetic subjects divided into 3 subgroups:

- Group 3a: includes ten patients without diabetic retinopathy.
- Group 3b: includes ten patients with non proliferative diabetic retinopathy.
- Group 3c: includes ten patients with proliferative diabetic retinopathy.

Diabetes mellitus was diagnosed based on the American Diabetes Association criteria, as reported in 1998. All subjects were informed of the purpose of the study and their consent was obtained. Physical data for each subject, including weight, height, waist and hip circumferences were recorded. Non diabetic volunteers were judged to be in good health according to their medical history and their fasting blood glucose level (< 100 mg/dL).The subjects in group 3 were subjected to fundus examination for detection of the presence of retinopathy and laboratory investigations including, fasting blood glucose level by colorimetric method and fasting serum insulin level (Pal et al., 2008). Insulin resistance was measured using the homeostasis model assessment of insulin resistance (HOMA-IR), a reliable marker for insulin resistance, was calculated

as fasting insulin × glucose level/22.5 (Katz et al., 2000). Serum resistin was measured using a human resistin ELISA kit (Bender Medsystems, Inc) (Greeshma et al., 2004). Subjects also were assayed for C-reactive protein (Ridker et al., 2002), and Lipid profile (Al-Omar et al.,2010) & (Mehrotra et al.,2009).

2.1. Statistical analysis

The collected data were tabulated and analyzed using SPSS version 16 software. Categorical data were presented as number and percentages, Chi square test (X2) was used as a test of significance while quantitative data were expressed as mean and standard deviation. Comparison of variables among groups of the study was made by one way analysis of variance (ANOVA). The Student "t" test was used to compare the means for pairs of groups. Correlation between serum resistin and other parameters of the subjects was determined by Pearson's Product correlation coefficient (r) to test the strength of association between serum resistin and other variables. Bonferroni's correction was also applied to analyses. Differences were considered statistically significant at $P < 0.05$ and highly significant at $P < 0.01$, to examine the relationship between serum resistin and retinopathy, simple regression analysis involving retinopathy stage as a dependent variable and serum resistin as an independent variable was performed. The receiver operating characteristic (ROC) curve was used to evaluate the performance of fasting serum resistin level as an indicator of developing retinopathy in diabetic subjects, specificity and sensitivity of different cut off values were estimated. An area under the ROC curve of 1.0 indicates perfect discrimination, whereas an area of 0.5 indicates that the test discriminates no better than chance (Zweig and Campbell, 1993).

3. Results

Fasting glucose and insulin resistance, as assessed using the homeostasis model of insulin resistance ratio (HOMA-IR), were similar in non obese and obese subjects, but significantly higher ($P < 0.05$) in diabetic compared with non diabetic subjects.

Fasting serum resistin was highly significantly ($P < 0.01$) different among the five groups (Table 1), mean serum resistin concentration increased in ascending manner in the five groups, showing the highest level in subjects with proliferative diabetic retinopathy. Bonferroni adjustment revealed that there was a significant difference between diabetic non retinopathy subjects and subjects with proliferative diabetic retinopathy.

The serum C-reactive protein levels showed a high significant difference between non diabetic and diabetic groups ($P < 0.01$), the comparison between diabetic non retinopathy group (DNR), and non-proliferative diabetic retinopathy group (NPDR) showed a high significant difference too ($P < 0.01$), so it appears that CRP concentrations were significantly associated with the presence of retinopathy.

Fasting serum resistin concentrations were not correlated with those of LDL-C, whereas there was a highly significant positive correlation between serum resistin concentrations and triglycerides, CRP, serum insulin and FBS concentrations, the same results were seen with BMI and HOMA-R. Serum

Table 1 Fasting serum resistin and other variables in groups of the study (values are mean $\pm$ SD).

Variables	Group1 X ± S.D n = 10	Group 2 X ± S.D n = 10	Group 3a X ± S.D n = 10	Group 3b X ± S.D n = 10	Group 3c X ± S.D n = 10	F	P
Total cholesterol (mg/dl)	177.3 ± 13.8	192 ± 7.6	260 ± 49.6	221.2 ± 35.9	208.3 ± 30.7	10.144	<0.05*
HDL-C (mg/dl)	42.5 ± 7.78	27.3 ± 2.685	27.2 ± 4.07	27 ± 3.605	26.5 ± 4.08	21.126	<0.01*
LDL-C (mg/dl)	108.4 ± 12.22	112.7 ± 5.46	165.5 ± 40.4	130 ± 33.193	119 ± 30.1	6.896	NS
Triglycerides (mg/dl)	132 ± 25.83	259.8 ± 27.8	336.3 ± 42.2	320.3 ± 39.11	314.9 ± 49.2	48.526	<0.01
(HOMA –IR) (mg/dl)	1.37 ± 0.23	2.65 ± 0.53	8.46 ± 3.81	12.77 ± 6.31	17.72 ± 3.91	33.640	<0.01
Resistin (ng/ml)	11.79 ± 2.2	18.82 ± 3.2	20.96 ± 3.19	21.65 ± 3.21	25.55 ± 5.96	18.102	<0.01
BMI (kg/m^2)	21.8 ± 1.6	33.1 ± 1.4	36.00 ± 4.2	36.50 ± 6.5	33.9 ± 2.4	25.79	<0.01
CRP (mg/dl)	3.5 ± 0.45	4.2 ± 0.8	8.9 ± 1.9	12.3 ± 1.2	13.7 ± 1.7	121.16	<0.05

$P < 0.05$ significant and $P < 0.01$ highly significant. NS : non-significant.

Table 2 Pearson's product correlation coefficient (r) of resistin with anthropometric and metabolic parameters in groups of the study.

Variables	r	P
Age (years)	0.4652	<0.01
BMI(kg/m^2)	0.5051	<0.01
Hip (cm)	0.3889	<0.05
Waist (cm)	0.3863	<0.05
FBS (mmol/L)	0.5086	<0.01
HOMA-R (μU/mL-mmol/L)	0.5908	<0.01
Insulin(μU/Ml)	0.6595	<0.01
Total cholesterol	0.2358	<0.01
HDL cholesterol	−0.3958	<0.05
LDL cholesterol	0.0579	NS
Triglycerides	0.6614	<0.01
CRP	0.6678	<0.01

$P < 0.05$ significant, $P < 0.01$ highly significant. NS: non-significant.

resistin is significantly positively correlated with waist and hip circumferences while it is significantly negatively correlated with HDL-C (Table 2).

Serum resistin was also significantly correlated with the stage of retinopathy, simple regression analysis was performed involving retinopathy stage as a dependent variable and serum resistin as an independent variable (Table 3), (Fig. 1).

3.1. Fasting serum resistin cut off points for diabetic retinopathy

ROC curve analysis was performed in order to establish a threshold serum resistin concentration for the existence of diabetic retinopathy. However, there was no statistically signifi-

cant cut-off value of serum resistin for the presence of retinopathy, nevertheless results revealed that resistin concentration is significantly positively correlated with the retinopathy stage (Fig. 1).

4. Discussion

Our study reports the resistin levels in non-obese, obese healthy and obese diabetic Egyptian subjects. Over the past few years, several studies in humans have examined the relationship between circulating resistin levels and obesity or diabetes. The results of these studies have been difficult to interpret and contradictory as a consequence of differences in ethnicity and clinical background of the subjects investigated, or the target epitopes used in the resistin assays.

In the present study, our results showed that circulating levels of resistin were significantly elevated in obese compared to non-obese subjects and obese diabetic subjects had the highest serum resistin levels. This agrees with Al-Harithy & Al-Ghamdi study in 2005 who reported higher serum resistin levels in healthy obese compared to non-obese individuals and highest resistin levels in obese diabetic subjects, also Mcternan et al. (2002) reported higher serum resistin levels in healthy obese compared to non-obese individuals. The results of Youn et al. (2004) and Fujinami et al. (2004) also agree with our results as they revealed that serum resistin levels were significantly higher in diabetic patients compared to control subjects.

On the other side some studies reported that the serum resistin levels were not correlated with body mass index or blood glucose (Takeishi et al., 2007), also Heilbronn et al. (2004) found that there was no significant difference of resistin concentrations among non-obese, obese and obese diabetic subjects.

Table 3 Serum resistin was correlated with retinopathy stage.

	Un standardized regression coefficient	Standardized regression coefficient	Standard error	P
Retinopathy stage (dependent variable)	0.1541	0.1238	0.03	0.0319

For simple regression analysis, each of retinopathy stage (no retinopathy = 0, nonproliferative = 1, and proliferative = 2), was involved as a dependent variable, and serum resistin (ng/ml)as an independent variable. The definition of the stages for retinopathy described in Materials and methods.
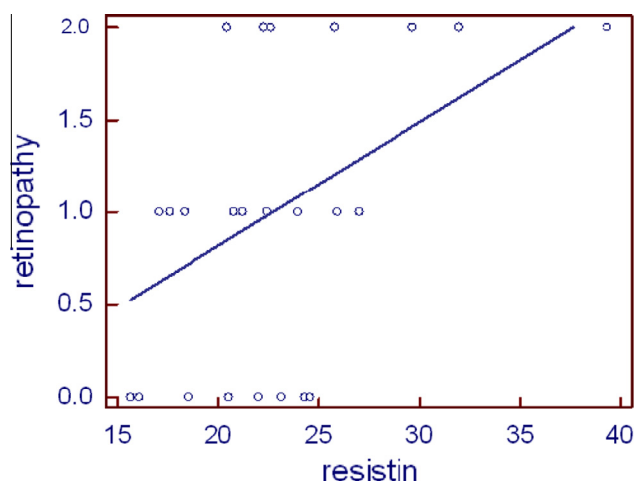
Figure 1 simple regression analysis of the retinopathy stage (no = 0, non-proliferative = 1 and proliferative = 2) as a dependent variable and resistin concentration (ng/ml) (values are mean + SD) as an independent variable reveals that resistin concentration is significantly positively correlated with the retinopathy stage.

The waist and hip circumferences (as measures for central obesity), have been used as indicators or measures of the health of a person, and the risk of developing serious health conditions. Research shows that people with ''apple-shaped'' bodies (with more weight around the waist) face more health risks than those with ''pear-shaped'' bodies who carry more weight around the hip (Reilly et al., 2002).

The current study showed that the waist circumferences ratio was significantly higher in the diabetic groups than in non-diabetic groups. This is in accordance with Reilly et al. (2002). Also the waist circumferences were significantly higher in obese group than in non-obese group, this means that these obese patients may be prone to the development of health problems including diabetes.

Regarding the relationship between insulin level, insulin resistance and resistin, we reported that resistin levels were significantly positively correlated with insulin levels and insulin resistance as assessed by HOMA-IR. Thus our data add to the growing body of evidence indicating that in humans there is a direct relationship between circulating levels of resistin and insulin, and several studies show similar results (Al-Harithy and Al-Ghamdi, 2005; Zhang et al., 1994). Accordingly, several studies have identified positive correlations between resistin levels and insulin resistance in vivo (Silha et al., 2003) and in vitro (Smith et al., 2003). Conversely, other studies reported no associations between serum resistin levels and markers of insulin resistance in Type 2 Diabetes Mellitus patients or insulin-resistant patients. Moreover, serum and plasma resistin levels were either reduced or increased in Type 2 Diabetes Mellitus patients with no significant correlation with HOMA-IR. Consequently, these studies suggest that resistin is unlikely to play a critical endocrine role in insulin resistance or energy homoeostasis in humans (e.g. Urbanek et al., 2003). Nevertheless, a paracrine or autocrine manner of resistin to moderately affect metabolism cannot be ruled out (Kusminski et al.,2005).

Insulin is known to upregulate lipoprotein lipase, a critical factor producing HDL cholesterol through lipoprotein metab-

olism. Therefore, insulin resistance caused by elevated plasma resistin could result in reduced serum HDL cholesterol.

We showed that serum resistin was inversely associated with serum HDL cholesterol. This was in agreement with authors suggesting that resistin was associated with low HDL cholesterol (e.g. Chen et al., 2005), also this was in agreement with Sato et al. (2005), who stated that over expression of resistin in the liver using adenovirus in mice showed enhanced insulin resistance and low serum HDL cholesterol (Osawa et al., 2007b).

Others found no significant correlation between resistin and HDL-cholesterol e.g. (Mohammadzadeh et al., 2008).

A specific complication of diabetes, microangiopathy, includes retinopathy, nephropathy, and neuropathy. Hyperglycemia increases polyol pathway flux, protein kinase C (PKC) activity, and the production of advanced glycation end products (AGE), and reactive oxygen species (ROS) (Mabley and Soriano, 2005). So the development or progression of diabetic microangiopathy could be affected by serum resistin (Osawa et al., 2007a).

Within the diabetic group serum resistin was highly significantly increased in individuals with proliferative retinopathy and it appeared that serum resistin was associated with retinopathy stage; this is consistent with the study of Osawa et al. (Osawa et al., 2007a), Sun Fundun et al. (Fudun et al., 2004) and Wang Jin et al. (Jin et al., 2005), and inconsistent with (Schaffler et al., 2004) who stated that there was no correlation between resistin levels and occurrence of diabetic retinopathy or nephropathy.

Resistin appears to be involved in inflammatory pathways, activating vascular endothelial cells, leading to increased expression of adhesion molecules, and stimulating smooth muscle cell proliferation (Kreçki et al., 2011). Furthermore, some clinical and epidemiological studies revealed positive correlations between plasma resistin levels and pro-inflammatory cytokines (Kawamura et al., 2010).

We reported serum CRP levels (as an inflammatory marker) in the groups of the study, our results showed that there was a significant difference of CRP levels in the diabetic patients, as compared to non-diabetic groups, also a significant difference was seen in patients with retinopathy as compared to diabetic patients without any grade of retinopathy.

This was in agreement with Zhao et al. (2011) who stated that inflammation as measured by serum C-reactive protein has been shown to be increased in people with diabetes and Matsumoto et al. (2002) who concluded that CRP increased in diabetic patients with microangiopathy, however, the associations of CRP with the microvascular complications of diabetes, or diabetic retinopathy in particular, have been inconsistent from the few studies that examined this association. In the European diabetes study (Schram et al., 2005). CRP was found to be positively associated with DR severity, but when BMI was added to the model, the association was no longer significant. Similarly, in a longitudinal study of patients with type 2 diabetes, Spijkerman et al.(2007) reported that CRP was cross-sectionally associated with baseline prevalence of diabetic retinopathy, but this association was not independent of HbA1c levels and BMI and there were also no associations between CRP levels and DR progression. Other studies, however, reported no association between CRP levels and diabetic retinopathy (Van Hecke et al., 2005) and (Nguyen et al., 2009). For example, prospective data from the WESDR (Wisconsin Epidemiologic Study of Diabetic Retinopathy)

([Klein et al., 2009](#)) found that CRP levels were not associated with DR incidence or progression.

5. Conclusion

Resistin is significantly positively correlated with CRP levels, being an inflammatory marker, supporting the inflammatory role of resistin, which may interpret association with the presence of retinopathy.

The association of resistin with the severity of diabetic retinopathy may open up future projects on the early detection and prevention of the condition. However, as we were unable to establish a threshold concentration for the development of retinopathy, we cannot propose the measurement of serum resistin concentration as a candidate test for establishing the risk of developing diabetic retinopathy.

In summary, we report here that serum resistin was higher in diabetic than in healthy subjects, furthermore it is correlated with diabetes linked risk factors, obesity and insulin resistance. It is also higher in patients with diabetic retinopathy than in those without it, and is involved in the generation of diabetes and diabetic retinopathy. Future prospective studies with greater numbers of patient are recommended to establish a direct relationship between serum resistin concentrations and the severity of microangiopathy.

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