Serum Visfatin, Resistin and IL-18 in A Group of Egyptian Obese Diabetic and Non Diabetic Individuals

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Resistin and visfatin have been proposed as playing a role in the pathogenesis of insulin resistance. We assessed the relationship between their serum concentrations and insulin resistance in lean, obese diabetic and obese non-diabetic. We explore their relationship with inflammatory markers and anthropometric parameters in obese patients. We measured serum resistin, visfatin levels in obese diabetic, obese non-diabetic patients and in lean subjects. The concentrations of serum resistin showed significant differences among the three groups. Higher levels of visfatin occurred in obese diabetic and non diabetic compared to lean subjects. Higher levels for HOMA-IR occurred in obese diabetic and non diabetic compared to lean subjects. Resistin correlated positively with insulin, HOMA-IR and with hs-CRP in obese diabetic subjects. Visfatin correlated positively with insulin and HOMA-IR in obese diabetic and non-diabetic subjects. Resistin might be involved in the pathogenesis of diabetes. Additionally, IL-18 might be a predictor of insulin resistance.

Besides its role in energy storage, white adipose tissue (WAT) is now recognized as an active secretory organ through its production of adipokines. Adipokines have been involved in the modulation of glucose and lipid homeostasis via central effects of leptin or the peripheral actions of resistin, adiponectin and visfatin on the liver and muscle. In addition, adipokines include proinflammatory factors and chemokines, the production of which has been shown to be increased in obesity (Rasouli & Kern, 2008). Recent data indicate that obese WAT is infiltrated by macrophages, which may be a major source of locally-produced pro-inflammatory cytokine (Bastard *et al.,* 2006).

Resistin and visfatin are produced by both the macrophages infiltrating the WAT and by the adipocytes (Bastard *et al.,* 2006). Resistin has been initially postulated as a risk factor for insulin resistance (IR), however, the subsequent available data on it have revealed contradictory findings in both humans and rodents (Bokarewa *et al.,* 2005). On the other hand, visfatin has been suggested to be a beneficial adipokine with insulin-mimicking/-sensitizing effects, but regulation of visfatin production and its physiological importance in the conditions of obesity and type 2 diabetes mellitus are still not completely understood (Hajer *et al.,* 2008). Despite the opposing effects of resistin and visfatin on the regulation of insulin sensitivity, both adipokines have pro-inflammatory properties by triggering cytokine production and NF-kappa B activation. New insight into the role of adipokines makes them attractive targets for novel therapeutic strategies in chronic inflammatory diseases or subclinical inflammation relating to obesity and various metabolic abnormalities (Stofkova, 2010).

Additionally, high circulating levels of IL-18 are associated with an increased risk of IR. In apparently healthy non obese persons, high IL-18 levels are associated with future diabetes incidence. This association was independent of well-known risk factors for diabetes, including obesity and dietary intake (Hivert *et al.,* 2009).

Plasma C-reactive protein (CRP) concentration is increased in the metabolic syndrome. It is not known, however, whether CRP is merely a marker of accompanying inflammation or whether it contributes causally to insulin resistance (Xi *et al.,* 2011).

The aim of this work was to assess the relation between visfatin and resistin to insulin resistance and correlate these parameters to two inflammatory markers, namely IL-18 and CRP as measured by a high-sensitivity CRP (hs-CRP) test.

Subjects and Methods

The study included 24 obese diabetic individuals (16 females and 8 males) aged 32.4 ± 9 years and with body mass index (BMI) 53.7±5.43 kg/m^2 and 29 obese non diabetic individuals (10 females and 19 males) aged 30 ± 8.8 years and with BMI 52.5±6 kg/m2, presenting at outpatient clinics of Ain-Shams University Hospitals and Ahmad Maher Teaching Hospital. In addition, 30 healthy individuals (18 females and 11 males) aged 30.4 ± 7 years and with BMI values 22.3±0.8 kg/m were also included in the study as controls. Study exclusion criteria included hypertension, acute inflammation or infection. A written informed consent was taken from all participants. Ain Shams Medical Research Ethics Committee approved this study.

Anthropometric parameters including body weight, height, BMI, waist–circumference (WC) and hip circumference (HC), were determined.

Serum visfatin concentration (ng/ml) was evaluated using the visfatin enzyme immunoassay (ELISA) kit (RayBiotech Inc., Georgia, USA), according to the instructions of the manufacturer. The minimum detectable concentration was =379 pg/ml. Additionally, Serum resistin and IL-18 concentration (ng/ml), were evaluated using the resistin enzyme immunoassay (ELISA) kit (BioVender Europe, Czech Republic) and (RayBiotech Inc., Georgia, USA), respectively, according to the instructions of the manufacturers. The minimal detection limits were 33 pg/ml for resistin and 20 pg/ml for IL-18.Fasting insulin was determined using INS-EASIA (Biosource Europe S.A., Belgium), according to the instructions of the manufacturers. Insulin resistance-was estimated using the Homeostasis Model Assessment (HOMA) index = fasting serum insulin concentration (μIU/mL) × fasting serum glucose concentration (mmol/L)/22.5 (Arya *et al.,* 2002). According to Lebovitz *et al.,* (2002), Cut off value of HOMA is more than or = 2.7. Finally, hs-CRP was determined using DRG CRP ELISA kit (DRG, International, Germany). Fasting blood sugar was assayed by enzymatic procedure using Beckman Synchron CX7 Clinical System (Beckman Coulter Inc. California, USA).

Statistical Analysis

Statistical analysis was done using SPSS version15.0.1 for windows (SPSS Inc, Chicago, IL, 2001). Continuous data were summarized as mean ± standard deviation, and categorical data were expressed as percentage. Comparison of variables between groups was made by one analysis of variance (ANOVA) and post Hoc test. Pearson correlation coefficient test was used to rank different variables against each other. $P < 0.05$ was considered significant.

Results

Table 1 summarizes the anthropometric and biochemical measurements observed in study groups, obese diabetic, obese non diabetic and controls. The concentrations of fasting serum resistin showed significant differences among the three groups (P<0.01). Mean serum resistin concentrations increased from lean (5.9±0.4) 11.59 to obese non-diabetic (27.7±2.7) to obese diabetic (51±8.2 ng/mL). Higher levels of visfatin occurred in the obese diabetic (41.7±3.3) and the obese non diabetic (51.4±6.1) compared to the lean subjects(8.3±1.9) (P<0.01). Higher levels for homeostasis model assessment ratio (HOMA-R) occurred in the obese diabetic and the obese non diabetic compared to the lean subjects (P<0.01); (Table 1).

Table 1. Comparison of physical and metabolic characteristics of study subjects (Values are mean± SD)

Variables	Obese diabetic (n=24)	Obese non diabetic (n=29)	Lean (n =30)	*P* value
Waist circumference (cm)	149±14.3	141±19.4	85±9	P_1 (NS) P_2<0.01 P_3 <0.05
Body mass index (kg/m^2)	53.7±5.43	52.5±6	22.3 ± 0.8	P_1 >0.05 P_2<0.05 P_3 <0.05
Resistin (ng/ml)	51±8.2	27.7±2.7	5.9±0.4	P_1 < 0.01 P_2<0.01 P_3 <0.01
Visfatin (ng/ml)	41.7±3.3	51.4±6.1	8.3±1.9	P_1 (NS) P_2<0.01 P_3 <0.01
IL-18 (pg/ml)	3181±970	2896±985	170.6±139.4	P_1 (NS) P_2<0.01 P_3 <0.01
hsCRP (ng/ml)	4±0.7	7.8±0.9	0.45±0.12	P_1 <0.01 P_2<0.01 P_3 <0.01
Insulin (µIU/mL)	17.7±1.8	14.11±1.6	7.0±2.1	P_1 (NS) P_2<0.01 P_3 <0.05
Fasting serum glucose (mg/dl)	161.8 ±23.9	86.2±8.7	87±7.6	P_1 <0.01 P_2<0.01 P_3 (NS)
HOMA-IR	5.4±0.65	2.4±0.5	1.2±0.3	P_1 <0.01 P_2<0.01 P_3 <0.01

P_1 = between A and B, P_2 = between A and C, P_3 = between B and C, A=obese diabetic, B=obese non diabetic, C=lean subjects

P>0.05 is not significant (NS)

Visfatin correlated positively with each of insulin (r=0.53, *P*<0.01) and HOMA-IR (r=0.6, *P*<0.01) in obese diabetic subjects (Figure 1). In obese non-diabetic subjects, visfatin correlated with insulin (r=0.49, P<0.05) and HOMA-IR (r=0.44, *P*<0.05) (Figure 2). Noteworthy, resistin correlated positively with each of insulin (r=0.43, *P*<0.05), HOMA-IR (r=0.56, *P*<0.01) and hs-CRP (r=0.58, *P*<0.01) in obese diabetic subjects (Figure 3). Resistin showed no correlation with insulin and HOMA-IR, in the lean and obese non-diabetic groups. Additionally, resistin was more strongly associated with inflammatory markers (hs-CRP, IL-18) in diabetics (table 2).

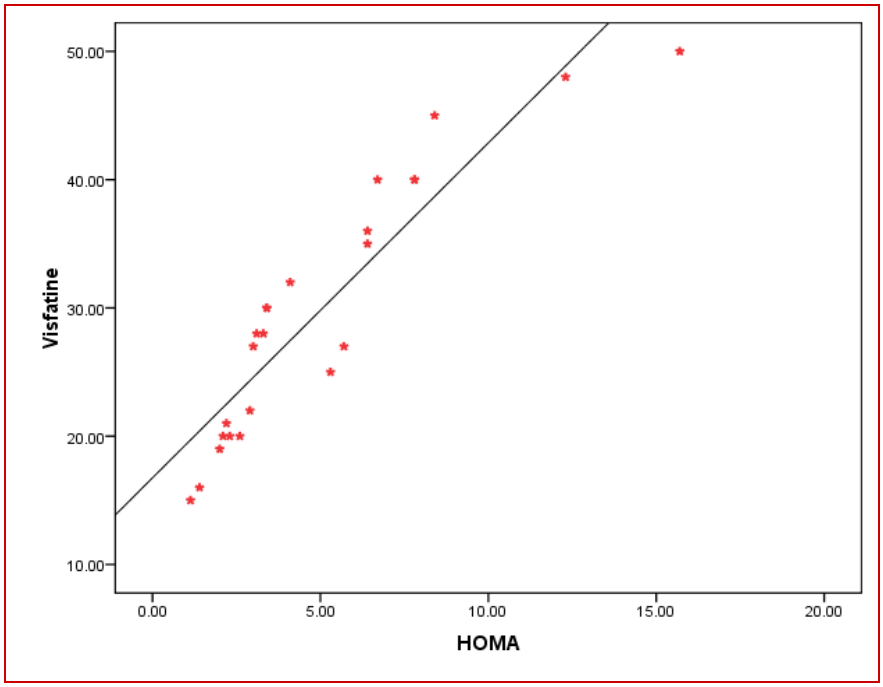

Figure 1. Showing significant positive correlation between serum visfatin and HOMA (r = 0.61, *P* <0.01) in obese diabetic.

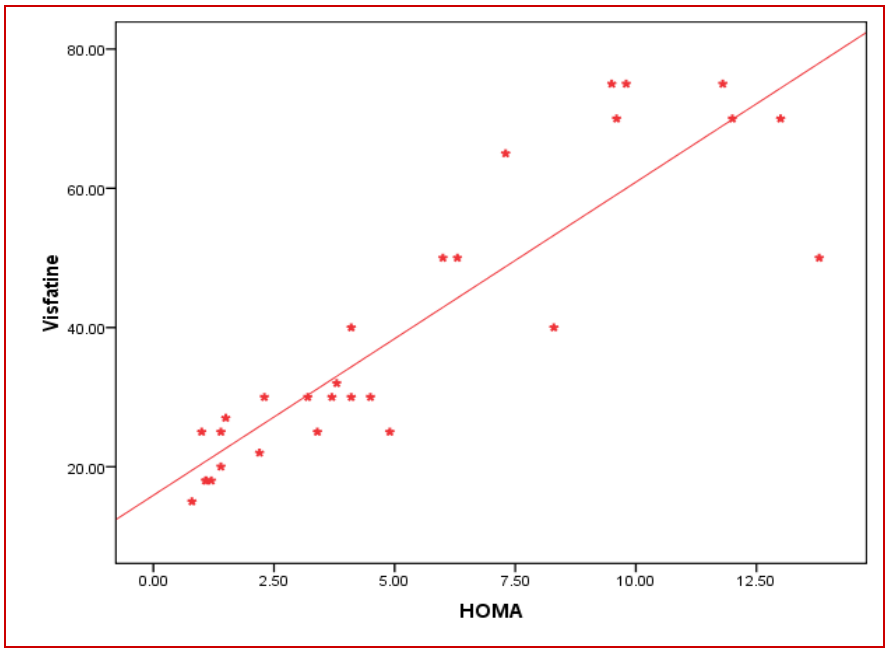

Figure 2. Showing significant positive correlation between serum visfatin and HOMA (r = 0.44, *P* <0.05) in obese non diabetic.

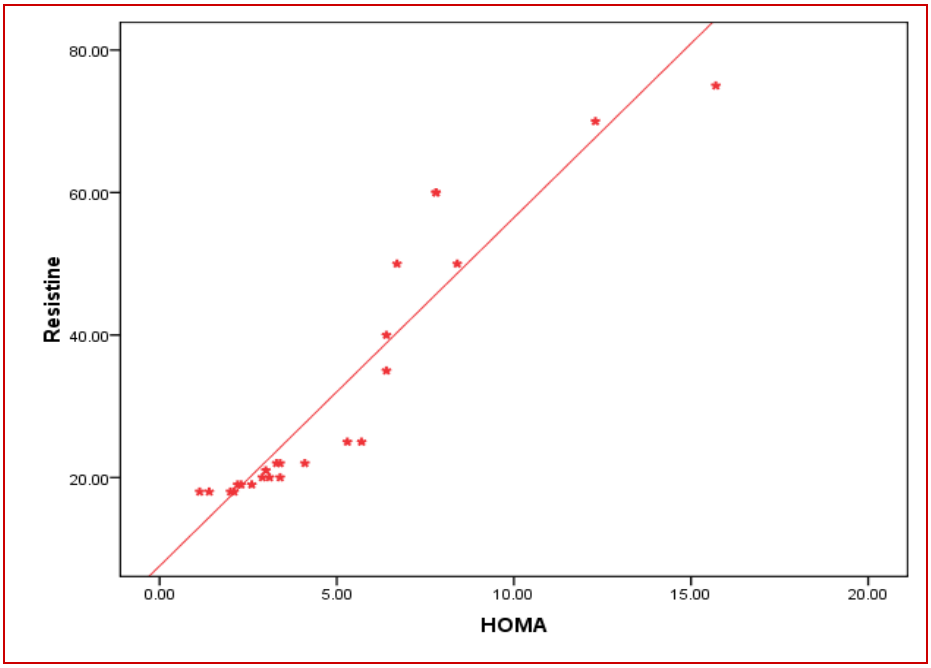

Figure 3. Showing significant positive correlation between serum resistin and HOMA (r = 0.56, *P* <0.01) in obese diabetic.

Table 2. Correlation between IL-18 and each of resistin and visfatin, in diabetics.

Variables	r	*P* value
Resistin	0.44	<0.05
Visfatin	0.23	NS

P>0.05 is not significant (NS)

Whereas IL-18 correlated significantly and positively with HOMA-IR in both obese and normal controls. In comparison to resistin, visfatin and hs-CRP, IL-18 might be a strong predictor of insulin resistance (Table 3 & 4).

Additionally, we categorized patients according to HOMA, patients with HOMA < 2.7, and other with HOMA ≥ 2.7. There was no significant correlation between HOMA and IL-18 in the patients group with HOMA <2.7. On the other hand, there was significant correlation between HOMA and IL-18 on patients group with HOMA ≥ 2.7. Also we categorized controls according to HOMA, controls with HOMA < 2.7, and other with HOMA ≥ 2.7. There was no significant correlation between HOMA and IL-18 in the controls group with HOMA <2.7. On the other hand, there was significant correlation between HOMA and IL-18 on controls group with HOMA ≥ 2.7.

Table 3. Linear Regression Analysis between HOMA as dependent variable and resistin, visfatin, IL-18 and hs-CRP as independent variables in obese diabetics.

Variables	Beta Coefficient	*P* value
Resistin	-0.075	NS
Visfatin	0.200	NS
hsCRP	0.081	NS
IL-18	0.760	<0.001

P>0.05 is not significant (NS)

Table 4. Linear Regression Analysis between HOMA as dependent variable and resistin, visfatin, IL-18 and hs-CRP as independent variables in obese non diabetics.

Variables	Beta Coefficient	*P* value
Resistin	0.089	NS
Visfatin	0.128	NS
hsCRP	0.065	NS
IL-18	0.933	<0.001

P>0.05 is not significant (NS)

Discussion

Increased visceral white adipose tissue is linked to the risk of developing diabetes. Resistin and visfatin as proinflammatory proteins were found to be released predominantly by visceral WAT macrophages (Curat *et al.,* 2005). These adipokines stand at the interface between metabolism and immunity in modulating not only inflammation, but also (IR) (Lago *et al.,* 2007).

The present study demonstrated that obese diabetic and non diabetic subjects had significantly higher serum resistin, visfatin and IL-18 levels than lean individuals.Such data agrees with previous findings (Vendrell *et al.,* 2004; Schaffler *et al.,* 2004; Haider *et al.,* 2006; Zahorska-Markiewicz *et al.,* 2007). Also, Curat *et al.* (2006) suggested that the accumulation of macrophages might be responsible for the enhanced fat mass-derived production of chemokines (as IL-18) as well as resistin and visfatin in obesity.

On the other hand, another group of researchers reported no differences in resistin, visfatin and IL-18 levels between obese and lean subjects (Youn *et al.,* 2004; Hofsr *et al.,* 2009). The reasons for such conflicting results may be due to ethnic heterogeneity, different population characteristics such as gender and age or confounding factors such diabetes mellitus (Jin *et al.,* 2008).

The present study showed that resistin is not correlated with HOMA-IR and insulin in obese non diabetic and lean subjects. This suggests that resistin may induce IR when resistin reaches a certain level. Importantly,

IL-18 was highly significant correlated with HOMA-IR in both patient group and control group. The relationship between IL-18 and insulin resistance in healthy subjects has not been frequently investigated, however, Fischer *et al.* (2005) reported that IL-18 was associated with HOMA-IR in both normal control and diabetics.

On the other hand, HOMA-IR was significantly and positively correlated to visfatin levels in obese diabetic and non diabetic subjects. This may be suggestive of a regulatory role of visfatin in glucose homoeostasis in obese individuals. Other studies regarding that point showed similar results obtained by Zahorska-Markiewicz *et al.,* (2007) and Filippatos *et al.,* (2008). According to their findings, the former group of investigators suggested that visfatin might compensate for the impairment of insulin action in the early stage of development of insulin resistance. Furthermore, combined components of metabolic syndrome, as central obesity with either insulin resistance or hyperinsulinemia, were associated with increased circulating visfatin levels (Krzystek-Korpacka *et al.,* 2011). It is also worth noting that human visfatin gene shown to be located at 7q22.3 was reported to be a linkage region for insulin resistance syndrome (Arya *et al.,* 2002).

Additionally, serum resistin levels were significantly higher in obese diabetic than obese non diabetic subjects. Such data agrees with previous findings *of (Silha et al.,* 2003; Smith *et al.,* 2003; Fujinami *et al.,* 2004). Shen *et al.* (2006) had demonstrated that resistin inhibited insulin signaling by up-regulating PTEN (phosphatase and tensin homolog deleted on chromosome ten) expression. Additionally, it has been shown, in liver, muscle and adipose tissue, that tissue-specific deletion of PTEN results in insulin hypersensitivity with improved systemic glucose tolerance. In addition, Lazar *et al.* (2005) observed that resistin induced the expression of SOCS (suppressor of cytokine signalling). Both mechanisms lead to inhibition of insulin action.

Regarding IL-18, it was demonstrated that IL-18 acts in synergy with IL-12 to stimulate Th1 polarization, and levels of IL-12 have been reported to be increased in subjects with type 2 diabetes. Hence, it could be speculated that IL-18 in combination with a hyperglycemic proinflammatory milieu might trigger Th1 activation, which was associated with IR (Wegner *et al.,* 2008). Additionally, polymorphisms in the IL-18 gene had been shown to be associated with increased serum levels of IL-18, impaired insulin sensitivity and increased risk of having the metabolic syndrome (Troseid *et al.,* 2010).

Furthermore, it was shown that patients with obesity and type 2 diabetes, or even apparent healthy non obese persons (who have insulin resistance) produce significantly less IFN-γ from peripheral blood mononuclear cells (Th1) in response to IL-18 stimulation compared to lean healthy controls, most likely due to reduced expression of the IL-18 receptor β chain, so IL-18 resistance is a potential explanation of elevated IL-18 levels in such patients (Leick *et al.,* 2007). This new concept of IL-18 resistance may shed further light upon the mechanisms involved in the IL-18-related effect on systemic metabolic disorder. At this point, IL-18-mimetic agents or interventions, including lifestyle modifications, may be novel therapeutic strategies for patients with obesity and type 2diabetes (Yamaoka-Tojo *et al.,* 2011).

In comparison to resistin, visfatin and hs-CRP, the present study showed that IL-18 might be a strong predictor of insulin resistance. This is an important point indicating IL-18 can be used to detect IR in lean control. Therefore, further studies are needed to reevaluate HOMA cut off value in relation to IL-18 value.

In spite of the above data, other studies didn't show any significant correlation between serum visfatin levels and HOMA-IR (Pagano *et al.,* 2006; Chen *et al.,* 2007; Dorgu *et al.,* 2007; de Luis *et al.,* 2008). Additionally, other studies have reported no associations between serum resistin levels and markers of insulin resistance in T2DM patients (Lee *et al.,* 2003; Stejskal *et al.,* 2003) or insulin-resistant patients (Hegele *et al.,* 2003). Moreover, serum and plasma resistin levels were either reduced or increased in T2DM patients with no significant correlation with HOMA-IR (Youn *et al.,* 2004). Some of these researchers explaned these findings that many hormones affect insulin resistance, and resistin may not be a major determinant of IR.

In the present study, no significant correlations between anthropometric parameters and each of serum resistin, visfatin and IL-18, were found in lean individuals. Studies in children and in adults demonstrated the same finding (Davutoglu *et al.,* 2009; Kaminska *et al.,* 2010). According to the former group of researchers, this situation may suggest the existence of a threshold for anthropometric parameters in childhood obesity above which relationships between these parameters and visfatin would have been more prominent. Likewise, we can suppose the same case in adult obesity.

Some researchers suggested that the increased level of resistin and visfatin in humans with obesity is likely an indirect result of elevated levels of inflammatory cytokines characteristics of states of increased adiposity (De Luis *et al.,* 2010; Mojiminiyi & Abdella, 2007). The present study demonstrated a positive correlation between serum resitin levels and high sensitive CRP levels, both in obese diabetic and non diabetic subjects. These findings are in agreement with several groups who had reported a close relationship between resistin and inflammation (Bokarewa *et al.,* 2005; Reilly *et al.,* 2005). Additionally, Hu *et al.* (2007) showed that CRP could significantly increase resistin expression in cultured human PBMC.

Moran *et al.* (2005) found that IR may precede the development of CRP elevation in the evolution of the metabolic syndrome and they explain their findings by that insulin resistance might initiate or contribute to CRP elevation by reducing insulin-induced suppression of hepatic acute-phase reactants. However, other researchers suggested that CRP elevation might precede the development of insulin resistance, as they demonstrated by the use of recombinant CRP that CRP attenuates insulin signaling through the regulation of spleen tyrosine kinase (Syk) on small G-protein RhoA, jun N-terminal kinase (JNK) MAPK, insulin receptor substrate-1(IRS-1) (Xu *et al.,* 2007).

In the present study, hs-CRP was positively associated with both HOMA and BMI in obese diabetic subjects. However, in obese non diabetic subjects, hs-CRP was associated with BMI, only. These findings might suggest that the association between CRP and insulin resistance was obesity dependent and CRP elevation might precede the development of insulin resistance.

These data might indicate that resistin might be involved in the development of diabetes and inflammation in humans.IL-18, in comparison to resistin and visfatin, might be a predictor of insulin resistance.

Additionally, it might be suggested that subjects at risk of IR, might benefit of IL-18 blockers, however, further studies are required regarding this as IL-18 blockers might rise the risk of infections.

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