

# Improvement of Insulin Sensitivity by Rosiglitazone Decreased the Visfatin Level in Obese Rats Induced by High Fat Diet

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**Abstract** Despite the insulin-mimic effect of visfatin, controversy exists over its relation to insulin resistance associated with obesity. Rosiglitazone maleate (RSG) is used as insulin sensitizers in the treatment of type2 diabetes. Aim: the present study had been carried out in a trial to identify the relation of serum visfatin to glucose and insulin homeostasis in fatty albino rats and the effect of RSG treatment in regulation of visfatin level. *Materials and Methods:* A total number of 30 adult male albino rats were divided into 3 equal groups: Group I, rats were served as control. Group II, rats received only high fat diet (HFD). Group III: rats received HFD and treated with RSG for 7 days. In all groups, HOMA-IR and serum levels of glucose, insulin and visfatin were measured. The correlation between visfatin levels and insulin resistance in treated and non treated groups was investigated. *Results:* There was a significant increase in serum visfatin, insulin, glucose levels and HOMA-IR value ( $p < 0.001$  for all) in high fat diet fed group in comparison with control group. However, all these values were significantly decrease ( $p < 0.001$  for all) in HFD fed group treated with RSG in comparison with Group II. There was a significant positive correlation between serum visfatin and HOMA-IR in group II ( $r = 0.935$ ;  $P < 0.001$ ) and group III ( $r = 0.951$ ;  $p < 0.001$ ). *Conclusion:* Rosiglitazone caused improvement of insulin sensitivity and decrease in the visfatin level in the HFD-fed treated rats. The decreased level of visfatin may be a consequent effect for the improvement of insulin resistance.

**Keywords** Visfatin, Rosiglitazone, High Fat, Diabetes, Insulin Resistance

## 1. Introduction

Obesity is highly associated with insulin resistance, increased risk to type2 diabetes and cardiovascular diseases [1-3]. The accumulation of adipose tissue in the abdominal visceral depot is especially correlated with insulin resistance [4,5]. Adipose tissue is a known endocrine organ secreting several soluble factors, known as adipocytokines or adipokines, like adiponectin, leptin, resistin and, visfatin[6]. In addition there are other products of adipocytes like free fatty acids, tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), IL-1, Monocyte chemo-attractant protein-1 (MCP-1), coagulation mediators such as platelet activator inhibitor-1 (PAI-1), and complement components[7]. These adipokines have essential roles in energy homeostasis, glucose and lipid metabolism, insulin resistance, inflammation, and atherosclerosis[8].

Visfatin is one of these adipokines that is secreted by visceral and subcutaneous fat[9], human bone marrow, liver, and muscle, it is also called pre-B cell colony-enhancing

factor 1 (PBEF-1)[10]. PBEF-1 was primarily considered a factor related to the pre-B cell colony formation activity of stem cells and was therefore defined as a cytokine which acts on early B linkage precursor cells, now known as visfatin[11]. Visfatin was found to be released predominantly from macrophages infiltrating the adipose tissue rather than from adipocytes in visceral adipose tissue. In this regard, there is sufficient evidence to consider that visfatin is produced in response to inflammatory signals[12]. It is now believed that visfatin actions can be endocrine, paracrine, and autocrine as well. These autocrine effects of visfatin may play an important role in regulating insulin sensitivity in the liver [13,14].

Despite the insulin-mimic effect of visfatin[10], controversy exists over its role in insulin resistance. Several studies failed to show an association of circulating visfatin with insulin sensitivity[15-17] while others indicated that visfatin was shown to be involved in the development of obesity-associated insulin resistance and type 2 diabetes mellitus in human and animal models[15,18]. In vitro studies showed an insulin-like effect of visfatin on regulation of glucose uptake in 3T3-L1 adipocytes and L6 myocytes, and also in adipocyte differentiation[10].

Thiazolidinediones (TZDs)[Rosiglitazone], an insulin sensitizer which act via stimulation of peroxisome proliferat

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or activated receptor- $\gamma$  (PPAR- $\gamma$ )[19], it enhances the flux of free fatty acids (FFAs) into the tissue and facilitates their enzymatic degradation[20]. TZDs have been shown to improve insulin sensitivity in patients with type 2 diabetes mellitus and insulin resistance. FFAs directly impair insulin sensitivity and are critically involved in the pathophysiology of diabetes mellitus[21]. Rosiglitazone (RSG), an insulin sensitizer, is widely used clinically as an anti-hyperglycemic agent in type 2 diabetes because of its effects on glucose and lipid metabolism[22]. Besides its insulin sensitizing property, RSG also has benefits on cardiovascular functions, including improvement in endothelial function and lowering of blood pressure[23]. Interestingly, these cardiovascular actions of RSG have also been found in type 1 diabetic animals.[24]

In the current study, the relation of visfatin to insulin resistance in obese rats induced by HFD was examined. Furthermore, the effect of improvement of insulin sensitivity by Rosiglitazone maleate administration on the visfatin level was investigated.

## 2. Material and Methods

### 2.1. Experimental Animal

The current study was carried on 30 male adult albino rats (body weight, 180-200 gm) rats were housed under hygienic conditions, in the animal house of the College of Medicine, Zagazig University at 21°C–24°C in a 12 hr/12 hr light/dark cycle[25] for 7 weeks[26]. They were given free access to water and food. The animals were classified into three equal groups:

Group I: (Control group): rats were served as a control group; rats were fed standard rat chow that consisted of 25.8% protein, 62.8% carbohydrates and 11.4% fat (total 12.6 kJ/g)[27].

Group II: (High fat diet fed non treated group): rats were received high fat diet (HFD) for 7 weeks; (HFD; is consisted of 16.4% protein, 25.6% carbohydrate, and 58.0% fat in the form of cotton seed oil added to the laboratory chow diet[27,28]) (a total Cal.=23.4 kJ/g)

The diet was provided from the college of Veterinary Medicine-Zagazig University.

Group III (High fat diet fed treated group): rats were received high fat diet (HFD) and treated with Rosiglitazone maleate (ESG) (Glaxo-Egypt) at a dose of 3mg/kg/day via oral gavages for 7 days.[29]

For all groups, body weight was recorded per week and at the end of the study period (7 weeks for the non treated group and 8 weeks for the treated group).

### 2.2. Sampling of Blood

At the end of the experimental period and after overnight fasting, at 8:00a.m, blood samples were obtained from sinus orbitus vein of each rat after ether inhalation. The blood

samples were allowed to clot at room temperature before centrifuging at approximately 3000rpm for 15 minutes. The serum was stored at -20°C.

### 2.3. Laboratory Analysis

#### 2.3.1. Estimation of Serum Visfatin Level

Rat visfatin ELISA kits: which is an enzyme linked immunosorbent assay for the quantitative measurement of visfatin concentration in rat blood plasma and other biological body fluid (BioVendor-Laboratori medicina, U.S.A.).

#### 2.3.2. Estimation of Serum Glucose Level

According to Trinder using glucose enzymatic (GODPAP) - liquizyme Kits (Biotechnology, Egypt).

#### 2.3.3. Estimation of Serum Insulin Level

By a solid phase enzyme amplified sensitivity immunoassay according to Starr et al. using KAP1251-INS EASIA (Enzyme Amplified Sensitivity Immunoassay) Kits (BioSource Europe S.A., Belgium).

#### 2.3.4. Determination of Insulin Resistance (HOMA-IR)

It was assessed by homeostasis model assessment (where  $HOMA-IR = (\text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting plasma glucose (mg/dl)}) / 405$ .

### 2.4. Statistical Analysis

Results are presented as mean  $\pm$  standard error of the mean. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 17.0 (SPSS Inc., Chicago, IL, United States). Repeated measures of analysis of variance (ANOVA) statistical analysis were applied followed by the Student-Newman-Keuls post hoc test. P value <0.05 was considered to be statistically significant. Pearson's correlation analyses were performed to screen potential factors related to fasting serum concentrations of visfatin.

## 3. Results

The results of the laboratory analysis were represented in table (1).

In group II there were significant increases in the body weight ( $291.28 \pm 20.79$ ), visfatin level ( $33.90 \pm 1.29$ ), insulin level ( $22.89 \pm 2.09$ ), fasting blood glucose level ( $327.67 \pm 25.20$ ) and HOMA-IR ( $18.51 \pm 2.16$ ) in comparison with the control [ $228.4 \pm 16.3$ ;  $26.69 \pm 1.15$ ;  $18.72 \pm 2.78$ ;  $81.69 \pm 8.47$ ;  $3.80 \pm 0.83$  respectively] ( $p < 0.001$  for all). Moreover, there was a significant positive correlation was recorded between the visfatin level and HOMA-IR ( $r = 0.935$ ;  $p < 0.001$ ); Fig. (1).

**Table (1).** The Laboratory Data in Control, HFD-Received Group and RSG-Treated Group

Items	Control group N=10	HFD-fed group N=10	RSG-treated group N=10	P value
Initial BW (gm)	193.36±12.77	194.16±13.86	193.4±12.69	NS
Final BW (gm)	228.4±16.3	291.28±20.79	302.93±21.63 226.5±21.2	<0.001* >0.05 <sup>#</sup> <0.001 <sup>\$</sup> <0.001 <sup>&amp;</sup>
Visfatin level (ng/ml)	26.69±1.15	33.90±1.29	27.72±1.35	<0.001* <0.001 <sup>#</sup> >0.05 <sup>\$</sup>
Insulin level (uIU/ml)	18.72±2.78	22.89±2.09	10.96±1.51	<0.001* <0.001 <sup>#</sup> <0.001 <sup>\$</sup>
Glucose level (mg/dl)	81.69±8.47	327.67±25.20	85.54±7.13	<0.001* <0.001 <sup>#</sup> >0.05 <sup>\$</sup>
HOMA-IR	3.80±0.83	18.51±2.16	2.31±0.33	<0.001* <0.001 <sup>#</sup> <0.05 <sup>\$</sup>

\*= P When GI compared with the Group II

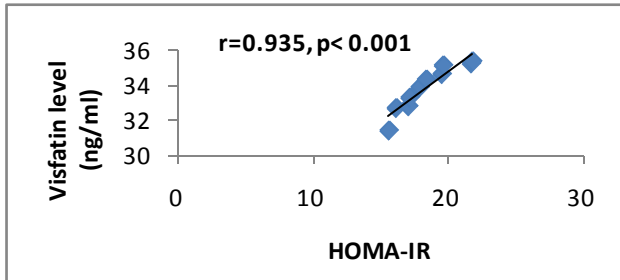
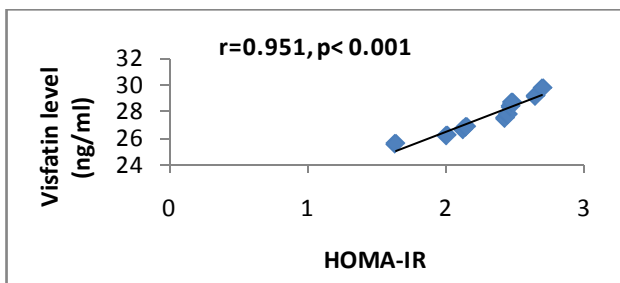
# =P when group II compared with Group III

\$= P when Group III compared with group I

NS= insignificant differences between groups

= the body weight of the HFD group after 7 days of RSG administration

& = P when the final weight of RSG-treated group compared with the weight at the 7th day of administration

**Figure (1).** Correlation Between Visfatin Level and HOMA-IR in Group II Rats**Figure (2).** Correlation Between Visfatin Level and HOMA-IR in Group III Rats

As regard Group III; the HFD-fed treated rats. There was a significant increase in the body weight (302.93±21.63) in comparison to the control group (228.4±16.3;  $P<0.001$ ). However, after administration of Rosiglitazone for 7 days there was a significant decrease in the body weight (226.5±21.2) in comparison to the final weight at the 7<sup>th</sup> week, in addition, visfatin (27.72±1.35), Insulin (10.96±1.51), Blood glucose (85.54±7.13), and HOMA-IR (2.31±0.33) were significantly decreased when compared to group II ( $p<0.001$  for all). Moreover there was significant positive correlation

between the visfatin level and HOMA-IR ( $r=0.951$ ;  $P<0.001$ ); Fig. (2)

## 4. Discussion

The results of the present study revealed that there was a significant increase in serum insulin and glucose level in HFD fed-rats. Consequently, the HOMA-IR value was also significantly increased indicated a development of insulin resistance. These findings are in good accordance with other published works in which high fat/high sucrose diets have been shown to enlarge adiposity and to impair whole body insulin action[32, 33]. Moreover, HFD-fed rats showed a significant higher serum visfatin level. This finding is in line with the finding of Naz et al.[34] that indicated an increase in the visfatin levels in obese mice fed on a high fat diet for 4 months. Moreover, Taşkesen et al.[35] demonstrated higher visfatin level in obese adolescents than non obese adolescents.

Many studies revealed that T2DM patients showed significantly higher serum visfatin levels than non diabetic subjects[15,36,37]. However, the relation between the level of visfatin and insulin resistance still shows controversial results, some studies found positive correlations of circulating visfatin with HOMA-IR and insulin levels[38], Taşkesen et al.[37] indicated positive correlation between visfatin level and HOMA-IR and negative correlation of it with glucose and insulin levels in combined control and obese group of adolescents, while other failed to found any association of circulating visfatin with HOMA-IR[39]. In the current study there was positive correlation indicated between the HOMA-IR and visfatin levels. However, it is yet to be proven whether visfatin production is a compensatory

response to tissue specific insulin resistance or it is a marker for insulin resistance development.

Naz et al.[34] showed that the administration of exogenous recombinant-histidine soluble (mice) visfatin in obese and diabetic groups of mice resulted in significant reduction in their fasting blood glucose levels but it remained higher than the glucose levels of normoglycaemic mice. These results are congruent with the results of Fukuhara et al.[10], who demonstrated an insulin mimetic effect of visfatin. They further established that visfatin used the system of tyrosine phosphorylation - dependent signaling for its action comparable to that of the insulin receptor.

Although visfatin levels had been increased in the HFD received group, the blood glucose also was high. This may be due to the development of visfatin resistance similar to that of insulin resistance as visfatin uses the same receptors used by the insulin for its action[17]. Moreover, in insulin resistant diabetes mellitus, various adipocytokines have been documented to be released such as resistin, which have been proposed to oppose the action of insulin[1]. Naz et al.[34] suggested that increased levels of visfatin in obesity and insulin resistant diabetes mellitus might have been neutralized by other adipocytokines and have resulted in visfatin resistance and hyperglycaemia because visfatin acts on the same receptor as that for the insulin.

In the current study, it was found that treatment of HFD received rats with RSG significantly decreased the serum visfatin, insulin and glucose levels. These findings are in agreement with[40] who revealed that RSG causes significant down-regulation of circulating visfatin concentrations and this effect were normalized by lipid infusion. In contrast Hammarstedt et al.[17] findings indicated that treatment with pioglitazone (one drug belongs the TZDs) unaffected the visfatin levels. This controversial result may be due to several factors including the duration of treatment, the characteristics of the diabetic cohort and the properties of the various TZDs.

In contrast to the findings of this study,[41] demonstrated that RSG treatment increases circulating visfatin concentrations in healthy humans and induces a release of visfatin from isolated adipocytes into the supernatant medium. This effect is counteracted by FFA and can be influenced in vitro by antioxidant strategies. Furthermore, visfatin secretion from adipocytes by rosiglitazone involves activation of PI 3-kinase and Akt. They concluded that the systemic effect of rosiglitazone on plasma visfatin concentrations is not likely the result of altered insulin sensitivity, and the changes observed occurred in the absence of altered circulating insulin concentrations in healthy subjects.

The current study revealed improvement of the insulin resistance and decrease in the HOMA-IR in the RSG treated group. In addition the visfatin levels are significantly and positively correlated with the HOMA-IR in this group.

## 5. Conclusions

The present study revealed higher visfatin production at obese HFD received rats which correlated with HOMA-IR. Moreover, improvement of insulin resistance after Rosiglitazone administration led to down regulation of serum visfatin. However, visfatin's role in the pathogenesis of obesity, T2DM and insulin resistance still shows somewhat of contrivers. Its function and effect may be depending on the metabolic state of the body. Additional researches are needed to clarify the role of visfatin, visfatin receptors and their mechanisms of action in pathogenesis of insulin resistance and obesity.

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