Role of Visfatin in Glucose and Insulin Homeostasis in Fatty Albino Rats

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Abstract: Visfatin is a novel adipokine that is secreted by visceral and subcutaneous fat, human bone marrow, liver, and muscle., also called pre-B cell colony-enhancing factor 1 (PBEF1). In this study, we investigated the role of serum visfatin, adipokine, concentrations in alterations of glucose and insulin homeostasis in fatty albino rats. For this purpose, animals were kept in three groups -each of them twelve rats- under three different feeding conditions: (a) *Control group:* the rats were fed a semipurified standard diet; (b) F*atty group:* the rats were fed a semipurified high fat high sucrose diet for 7 weeks, to increase their body fat content and (c) R*estricted group:* These animals were fed a semipurified standard diet similar to that used in the control group, but supplemented with a 5 g/kg diet of linoleic acid, provided by sunflower oil . It was observed that fatty diet did not modify serum visfatin concentration . Nevertheless, energy restriction led to a significant increase in serum visfatin level. No significant differences in concentrations of fasting glucose and lipids profiles were observed between the 3 groups. Insulin level and resistance measured by HOMA-IR, was significant higher in the fatty group than in the restricted group. a positive significant correlation was found between serum visfatin and triacylglycerols confirmed that triacylglycerols were the only significant predictor of visfatin concentrations . We observed that there is inversely relationship between visfatin and glucose, insulin levels and insulin resistance in both fatty and restricted groups and the feeding models play an important mediator in the role of the effect of visfatin on glucose and insulin homeostasis through regulating triacylglycerol metabolism. Further study of visfatin's physiological role may lead to new insights into glucose and insulin homeostasis and or new therapies for metabolic disorders such as diabetes.

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1. Introduction

Visfatin is a novel adipokine that is secreted by visceral and subcutaneous fat, human bone marrow, liver, and muscle., also called pre-B cell colony-enhancing factor 1 (PBEF1), **(Fukuhara *et al.,* 2005)[13].** PBEF1 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 (**Samal *et al.,* 1994)[26].** Visfatin was found to be released predominantly from macrophages rather than from adipocytes in visceral adipose tissue. In this regard, there is sufficient evidence to consider that visfatin is expressed by the macrophages infiltrating adipose tissue and is produced in response to inflammatory signals (**Pedro *et al.,* 2010)[21].** 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 **(Skop *et al.,* 2009)[30].** Recently, visfatin was shown to be involved in the development of obesity-associated insulin resistance and type 2 diabetes mellitus in human and animal models **(Chen *et al.,* 2006)**[8]. The concentration of visfatin in plasma increases during the development of obesity, and it was shown to exert insulin-mimetic effects in cultured myocytes and adipocytes and to lower plasma glucose concentrations in mice **(Fukuhara *et al.,* 2005)**[13]. Furthermore, plasma visfatin was also found to be elevated in patients with type 2 diabetes (C**hen *et al.,* 2006)**[8]. It was proposed that visfatin mimicked the effects of insulin by binding to the insulin receptor at another site than that of insulin. The insulin-mimetic action of visfatin has been reported in isolated adipocytes, myocytes, and hepatocytes (**Sommer *et al.,* 2008**)[31].

Changes in nutritional status such as overfeeding, underfeeding, and exercise have important effects on adipose tissue metabolism (**Enveoldsen *et al.,* 2004**)[11] and may affect visfatin concentrations. Although visfatin is considered to be a link between obesity and diabetes (**Sethi *et al.,* 2005**)[27], to date, data related to the nutritional regulation of visfatin are lacking. Recent data have pointed to an important role of visfatin in pancreatic β-cell function. In contrast to the results **(Fukahara *et al.,* 2005[13] and Revollo *et al.,* 2007[24])**., failed to obtain evidence to reproduce the

reported insulin-mimetic effects of visfatin on adipogenesis, glucose uptake, cellular insulin signaling, and blood glucose levels in mice. They described that visfatin functions as an intracellular and extracellular NAD biosynthetic enzyme playing an important role in the regulation of glucose-stimulated insulin secretion in pancreatic β cells. **Brown *et al.*, 2010**[6] demonstrated that Visfatin caused a significant increase in insulin secretion compared to control at low glucose, and suggested that visfatin can significantly regulate insulin secretion, insulin receptor phosphorylation, and expression of a number of genes associated with beta-cell function in mice.

The information obtained from examining the response to these nutritional changes will provide insight into the mechanisms and roles of this adipokine in obesity and the metabolic syndrome **(Ronti *et al.*, 2006)**[25]. The available results are insufficient to properly define the functions and the regulation of recently discovered visfatin adipokine. Moreover, in some cases, reported studies have produced contradictory results. Consequently, more detailed and better controlled *in vivo* and *in vitro* studies are necessary to shed more light on these issues. The present work was designed to improve and show the relationship between changes in serum visfatin concentration and alterations in glucose and insulin homeostasis in fatty albino rats.

2. Material and Methods

Animals, Diets, and Experimental Design

We used thirty six (36) Adult male Albino rats of local strain, three months old age from Helwan Farm. Their initial body weight 100 gm. Each four rats were put in a cage (37 X 22 X 20 cm) for 1 week before experiment for adaptation in laboratory room temperature between 20-25 ^{o}C with the natural light-dark cycle. After a 7-day adaptation period, 12 rats were fed a semipurified standard diet **(control group)** and the remaining 24 hamsters were fed a semipurified high fat high sucrose (HFHS) diet for 7 weeks, to increase their body fat content. The standard diet consisted of 200 g/kg of casein (Sigma, St. Louis, MO, United States), 4 g/kg of L-methionine (Sigma, St. Louis), 390 g/kg of wheat starch (Vencasser, Bilbao, Spain), 235 g/kg of sucrose (local markets), 70 g/kg of sunflower oil (local markets), 46 g/kg of cellulose (Vencasser), 4 g/kg of choline-HCl (Sigma, St. Louis), 11 g/kg of vitamin mix, and 40 g/kg of mineral mix. The HFHS diet consisted of 200 g/kg of casein, 4 g/kg of L-methionine, 220 g/kg of wheat starch, 320 g/kg of sucrose, 150 g/kg of palm oil (Agra-Unilever, Leioa, Spain), 5 g/kg of sunflower oil, 46 g/kg of cellulose, 4 g/kg of choline-HCl, 11 g/kg of vitamin mix, and 40 g/kg of mineral mix (**Reeves *et al.*, 1993)**[23]**.**

After this experimental period, animals from the control group and 12 animals from the HFHS diet **(fatty group)** were sacrificed. The 12 remaining rats were subjected to energy restriction for 3 weeks. These animals were fed a semipurified standard diet similar to that used in control group, but supplemented with a 5 g/kg diet of linoleic acid, provided by sunflower oil (local markets) **(restricted group).** All experimental diets were freshly prepared once a week, gassed with nitrogen, and stored at 0°C to 4°C to avoid rancidity. Body weight and food intake were measured daily.

At the end of each experimental period, the rats were sacrificed after 12 hours of fasting under anesthesia (chloral hydrate) by exsanguinations. Adipose tissue from different anatomical locations (perirenal, epididymal, and subcutaneous) was dissected and weighed, then immediately frozen. Serum was obtained from blood samples after centrifugation. All samples were stored at −80°C until analysis.

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Serum concentrations of glucose, triacylglycerol, total cholesterol, and HDL cholesterol were measured with the use of Synchron reagents and performed on an Lx20 analyzer (Beckman Coulter Inc). LDL cholesterol was calculated with the use of the following formula: (total cholesterol) – (HDL cholesterol) – (triacylglycerols/2.2). The calculated value is reliable in the absence of severe hyperlipidemia insulin and visfatin, by enzyme-linked immunosorbent assay (ELISA) (EZRMI 13K, Linco, St. Charles, MO, United States; EK-003-80 and EK-057-23, Phoenix Europe GMBH, Karlsruhe, Germany, respectively). The homeostatic model assessment for insulin resistance (HOMA-IR) was calculated from insulin and glucose values using the formula of **Matthews *et al.*, 1985**.[19]

Statistical Analysis

Results are presented as mean ± standard error of the mean. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 12.0 (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. Multiple regression analyses were used to examine the predictors of fasting serum concentrations of visfatin.

3. Results

Table (1): Final body weight and adipose tissue weights of rats fed on the experimental diets

	Control group	Fatty group	Restricted group	*P* value
Final body weight/ g	109±3	129±1	110±2	$P < 0.01$*
Epididymal (EP) weights / g	1.57±0.15	2.89±0.15	1.28±0.17	$P < 0.001$*
Perirenal (PR) weight / g	1.03±0.12	2.11±0.20	1.67±0.19	$P < 0.05$*
Subcutaneous (SC) weight / g	2.77±0.36	4.41±0.28	2.59±0.23	$P < 0.001$*
EP+PR+SC	5.37 ±0.62	9.41±0.56	5.54±0.46	$P < 0.001$*

- n=12 in each group - Data are represented as mean ± standard deviation * Significant ($P < 0.05$)

Fatty diet for 7 weeks resulted in a significantly increased body weight, which was accompanied by heavier adipose tissues in all anatomical locations analyzed. Three weeks of energy restriction completely abolished the increase in body fat produced by the HFHS feeding because no significant differences were found between restricted groups and the control group in terms of body weight and adipose tissue weights

Table (2): Serum Parameters of rats fed on the experimental diets

	Control group	**Fatty group**	**Restricted group**	*P* **value**
Visfatin (ng/mL)	29.3 ± 3.3	25.5 ± 6.6	35.7 ± 4.6	$P < 0.01$*
Glucose (mmol/L)	7.10 ± 0.60	8.32 ± 0.45	6.79 ± 0.45	$P < 0.05$*
Insulin (pmol/L)	65.16 ± 11.36	112.76 ± 26.07	48.78 ± 4.20	$P < 0.05$*
Cholesterol (mmol/L)	4.3 ± 0.2	4.5 ± 0.3	4.7 ± 0.1	$P > 0.05$
Triacylglycerol (mmol/L)	0.91 ± 0.06	0.93 ± 0.11	1.26 ± 0.14	$P > 0.05$
HDL cholesterol (mmol/L)	1.36 ± 0.05	1.35 ± 0.09	1.25 ± 0.40	$P > 0.05$
LDL cholesterol (mmol/L)	2.51 ± 0.14	2.73 ± 0.25	2.86 ± 0.13	$P > 0.05$
HOMA-IR	3.05 ± 0.67	4.60 ± 0.44	2.15 ± 0.28	$P < 0.05$*

- n=12 in each group - Data are represented as mean ± standard deviation * Significant ($P < 0.05$)

As far as visfatin is concerned, it was observed that HFHS feeding did not modify serum concentration . Nevertheless, energy restriction led to a significant increase in serum levels. No significant differences in concentrations of fasting glucose, total cholesterol, triacylglycerol, HDL cholesterol, and LDL cholesterol were observed between the 3 groups. Insulin resistance, measured by HOMA-IR, was higher in the obese subjects than in the lean subjects.

Table (3): Linear regression analysis of variables related to fasting serum visfatin (ng/ml)

Variables	**r**	***P***
Body fat (%)	−0.01	NS
Glucose (mmol/L)	−0.13	NS
Insulin (pmol/L)	0.01	NS
Cholesterol (mmol/L)	0.08	NS
Triacylglycerol (mmol/L)	0.36	S
HDL cholesterol (mmol/L)	−0.02	NS
LDL cholesterol (mmol/L)	−0.03	NS
HOMA-IR	−0.01	NS

No significant correlations were found between serum visfatin concentration and serum concentrations of glucose, insulin, lipids, insulin resistance or body fat compositions . a positive significant correlation was found between serum visfatin and triacylglycerols confirmed that triacylglycerols were the only significant predictor of visfatin concentrations .

4. Discussion

In the present study, fatty diet through high fat high sucrose feeding produced a significant increase in body fat accumulation, as well as higher serum glucose concentrations. Consequently, the HOMA-IR value was also significantly increased, suggesting the development of insulin resistance. These features are in good accordance with other published works in which HFHS diets have been shown to enlarge adiposity and to impair whole-body insulin action [**Boyd *et al.*,1990[5] and Yaspelkis *et al.*,2004[34]**]. Also in line with the literature, energy restriction reduced body fat and ameliorated glucose homeostasis **[Barzilai *et al.*,1998[2] and Dhahbi *et al.*,2001[10]].**

Conflicting results have been reported in the literature concerning the relationship between visfatin and body fat accumulation, as well as its potential involvement in glucose homeostasis. In the present study, fatty feeding had no effect on serum concentration of visfatin, suggesting that this adipokine does not have a major role in the insulin resistance development associated with fatty feeding. These results are in good accordance with those reported by **Klöting and Klöting , 2005[16]** who were unable to find any relationship between visfatin and the metabolic syndrome in rats, and with those published by **Mercader *et al.*,2008[20]** who did not find significant changes in visfatin serum levels in rats fed a cafeteria diet. However, **Pérez-Echarri *et al.*,2009[22]** observed that feeding rats on a cafeteria diet impaired visfatin gene transcription in adipose tissue, without changes in circulating levels. Also, **Fukuhara *et al.*, 2005[13]** reported that visfatin is predominantly secreted by visceral fat and that plasma visfatin concentration increases during the development of obesity in mice. Therefore, it is reasonable to expect an association between circulating serum visfatin concentration and trunk fat, which is a reflection of the amount of visceral fat. Reasons underlying the discrepancy among these studies are not clear. Furthermore, the regulation of visfatin during overfeeding has also been studied in humans, and it has been observed that effects on this adipokine may differ from those found in rodents. **Sun *et al.*,2007[32]** observed that short-term overfeeding resulted in a significant reduction in serum visfatin concentration in healthy young men. Similarly, **Shea *et al.*,2007[28]** found reduced visfatin levels in overfed lean and overweight humans.

In restricted groups, serum visfatin was significantly increased and reduced HOMA-IR value were observed. this suggests a potential role of this adipokine in the improvement of insulin sensitivity induced by energy restriction. As far as we know, no studies have shown the effects of calorie restriction on visfatin in rodents. With regard to human studies, **Haider *et al.*, 2006**,[15] as well as **Swarbick *et al.*,2008**,[33] observed reduced visfatin concentrations in obese patients after bariatric surgery. **Sheu *et al.*, 2008[29] and De Luis *et al.*,2008[9]** found similar results in obese nondiabetic subjects after caloric restriction. In contrast, **Krzyzanowska *et al.*,2006,[17] Botella-Carretero *et al.*,2008[4] and García-Fuentes *et al.*, 2007[14]** showed increased serum visfatin concentrations in morbidly obese women after bariatric surgery.

The insulin function impairment induced by fatty diet does not seem to be mediated by visfatin. However, visfatin can contribute in an improvement of insulin sensitivity associated with energy restriction. These results suggest that visfatin may not have evolved as a molecule that reserves the action of insulin when food is easily available, but rather that its function seems to be associated with energy restriction adaptation. Evidence from animals suggests that visfatin is an adipokine that exerts insulin-like action. Visfatin is able to mimic insulin function and lower plasma concentrations of glucose by binding to the insulin receptor as shown in c57BL/6J mice, insulin-resistant KKAy mice, and streptozotocin-treated insulin-deficient mice (**Fukuhara *et al.*,2005**)[13]. We can expect an association of fasting visfatin concentrations with fasting glucose concentrations. However, none of the biochemical variables associated with glucose metabolism correlated with serum visfatin concentrations in response to the overfeeding and fatty diet. This is consistent with the earlier findings that show no correlation of plasma visfatin with fasting plasma glucose in a heterogeneous group of white humans **(Berndt *et al.*,2005)[3].** The absence of correlation is likely due to the low concentration of visfatin at physiologic conditions . In addition, our results indicate that visfatin is likely not an important regulator of glucose metabolism or insulin resistance in overfeeding rats . Other studies found that the serum concentrations of visfatin were raised in diabetic patients (**Chen *et al.*,2006**)[8] and gestational diabetic women **(Krzyzanowska *et al.*,2007)[18]**, suggesting that visfatin may act as a compensatory factor in glucose metabolism. Its low concentration at physiologic conditions results in its limited role in this metabolic process. However, in situations of impaired insulin functioning such as in type 2 diabetes and

gestational diabetic women, visfatin may be elevated and may partially compensate for insulin function.

We found that serum visfatin concentrations were positively correlated with serum triacylglycerols independently %BF. Thus, visfatin may act an independent role in regulating triacylglycerol metabolism in a similar fashion as adiponectin, which was also linked with triacylglycerols **(Baratta *et al.*,2004)[1] and (Chan *et al.*,2005)[7].** The lack of association between the changes in triacylglycerols with visfatin warrant further study. Because elevated serum triacylglycerols is a marker of the metabolic syndrome, these results may have clinical implications. We concluded that there is inversely relationship between visfatin and glucose, insulin levels and insulin resistance in both fatty and restricted groups and the feeding models play an important mediator in the role of the effect of visfatin on glucose and insulin homeostasis through regulating triacylglycerol metabolism. Further study of visfatin's physiological role may lead to new insights into glucose and insulin homeostasis and or new therapies for metabolic disorders such as diabetes.

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