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Association of circulating visfatin concentrations with insulin resistance and low-grade inflammation after dietary energy restriction in Spanish obese non-diabetic women: Role of body composition changes

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KEYWORDS
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Obesity;
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Inflammation

Abstract *Background and Aims:* To assess the influence of body composition changes on circulating serum visfatin after following 12 weeks of energy restricted diet intervention. We also examined the possible role of visfatin in glucose metabolism and in obesity-associated low-grade inflammation.

Methods and Results: A total of 78 obese (BMI 34.0 ± 2.8 kg/m^2) women aged 36.7±7 y volunteered to participate in the study. We measured by DXA body fat mass (FM) and lean mass (LM). Fasting serum visfatin, glucose, insulin, adiponectin, leptin, IL-1β, IL-6, IL-8, TNF-α and CRP concentrations were analyzed before and after the intervention and HOMA and QUIKI indexes were calculated. Mean weight loss 7.7 ± 3.0 kg and HOMA decreased in 24 ± 35%. Serum visfatin concentration change was negatively associated with LM difference ($P < 0.05$), whereas no significant relationship was observed with FM changes after energy restricted diet intervention. Changes in circulating serum visfatin levels were significantly and inversely associated with HOMA-IR ($P < 0.01$) and positively with QUICKI index ($P < 0.02$) after energy restricted diet intervention, regardless of achieved body weight loss. We did not find any significant association between changes in visfatin levels and IL-1β, IL-6, IL-8, TNF-α and CRP levels after dietary intervention (all $P > 0.2$).

Conclusion: Circulating visfatin concentration is associated with sensitivity improvement achieved after energy restricted diet intervention induced weight loss. Furthermore, LM changes could be an influencing factor on visfatin concentrations and consequently, on the

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improvement of insulin sensitivity after weight loss in obese non-diabetic women. Our findings did not provide any evidence for a role of visfatin increase on low-grade inflammation after weight loss.

Introduction

Obesity and various components of the metabolic syndrome are strongly linked due to the differential secretory function of adipose tissue [1]. Obesity is also characterized by the infiltration of macrophages into adipose tissue promoting a low-grade inflammation state implicated in the development of many complications such as, atherosclerosis and type 2 diabetes [2]. Thus, adipokines and cytokines, including interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor (TNF)-α and visfatin, might play an important role in the pathogenesis of insulin resistance and cardiovascular disease [1].

Visfatin, also known as nicotinamide phosphoribosyl transferase (NAMPT) and pre-β-cell colony-enhancing factor (PBEF), is a ubiquitously expressed cytokine potentially involved in the control of glucose homeostasis [3] and in inflammation [4]. However, the physiological relevance of visfatin remains controversial [5]. Several studies suggested an important role of visfatin in the control of glucose metabolism by regulating of β-cell function through the NAD biosynthetic activity [3]. However, other recent reports suggest that visfatin is involved in inflammation [6,7]. In this sense, a new functional link between NAD metabolism and inflammation has been reported, suggesting a potential role of NAD-dependent enzymes in the regulation of proinflammatory cytokine production [4]. Likewise, visfatin has been shown to upregulate IL-6, IL-β1 and TNF-α in human monocytes [7].

In humans, circulating visfatin concentrations have been reported to be higher in obese subjects as compared to lean subjects [8]. However, the association between obesity and elevated serum visfatin levels has not been confirmed yet [9]. The effect of weight loss on serum visfatin levels is also controversial. Thus, while most authors find increased visfatin plasma levels after weight loss in obese subjects who underwent bariatric surgery [10—12]; other investigators observed either reduced [2, 13] or no changes in plasma concentrations [14]. Finally, several studies showed that individuals following energy restricted diets diminished their plasma visfatin levels as a function of weight loss [9, 15]. Similar results have been observed when weight loss has been achieved by increased physical activity [16, 17]. However, no study has examined the influence of body composition specific compartments changes on serum visfatin levels after weight loss treatment.

In this study we assessed the influence of both lean mass and fat mass changes as measured by DXA, on circulating serum visfatin concentration in premenopausal obese women after following an energy restricted diet intervention. We also examined the possible role of visfatin in glucose metabolism and in obesity-associated low-grade inflammation in this well characterized sample of non-diabetic obese women before and after weight loss.

Methods

Study population

A total of 83 non-morbid obese (body mass index (BMI) inclusion criteria: 30—39.9 kg/m^2) women from Vitoria (North Spain), aged between 19 and 49 years volunteered to participate in this study, and underwent a comprehensive medical examination. Participants were premenopausic, non-athletic and showed weight stability (body weight changes <3 kg in the last 3 months). Exclusion criteria included history of cardiovascular disease or diabetes, pregnancy, total cholesterol levels >300 mg/dL, levels of triglyceride >300 mg/dL and blood pressure level >140/90 mm Hg. We also excluded women under medication (except oral contraceptives). All women received verbal and written information about the nature and purpose of the survey, and all of them gave written consent for participation in the study. This study was in accordance with the Helsinki II declaration and was approved by the Ethical Committee in Hospital of Txagorritxu (Vitoria).

Four participants left the study due to inability to follow the research protocol and 1 due to pregnancy. Only data from women who finished the 12 weeks diet intervention program, i.e. $N = 78$ are included in the analyses (dropout rate = 6%).

Design

The present study was designed as a 12 weeks controlled weight loss program. Body weight reduction was induced by a low energy mixed (55% carbohydrates, 30% lipids and 15% proteins) diet providing 600 kcal less than individually estimated energy requirements based on resting metabolic rate (RMR). The individual energy requirements were estimated using a ventilated hood system at baseline and multiplied by a factor of 1.3, as corresponds to a low physical activity level. Energy content and macronutrient composition of diets were according to the American Diabetes Association nutrition recommendations [18, 19]. Diets were designed to achieve weight losses of 0.5—1 kg per week, such diets are considered as a low risk intervention [18, 20]. To optimize compliance, dietary instructions were reinforced weekly by a dietician.

The study examinations were performed before and after 12 weeks of dieting in the Unit of Clinic Assays of LEIA Foundation (Txagorritxu Hospital, Vitoria). Fasting blood samples were taken from an antecubital vein after gas exchange measurement. Samples were processed after collection and stored at −80 °C for later analysis. Body weight (±10 g) was measured after voiding using a digital integrating scale (SECA 760). Height was measured to the nearest 5 mm using a stadiometer (SECA 220) at the start of the study BMI was calculated as weight (kg)/height (m)^2.

Body composition

Dual Energy X-ray Absorptiometry (DXA) measurements were performed within ±3 days of the pre- and post-intervention examinations. A DXA scanner 140 (HOLOGIC, QDR 4500W) with QDR software for windows version 12.4 was used to estimate fat mass (FM), bone free lean tissue mass (LM) and bone mass (BM).

Indirect calorimetry

RMR was estimated by respiratory exchange measurements, as described elsewhere [21, 22]. Fasting urine was collected to determine nitrogen output and thereafter non-protein respiratory quotient (NPRQ) [23].

Biochemical assays

Fasting serum glucose (mmol/L), total cholesterol (mmol/L), HDL-cholesterol (mmol/L) and triglycerides (TG) (mmol/L) were measured by enzymatic spectrophotometric technique with an autoanalyzer (COBAS FARA; Roche Diagnostics, Basel, Switzerland). Serum insulin (μU/mL), leptin (ng/mL), visfatin (ng/mL), adiponectin (μg/mL) and IL-6 (pg/mL) concentrations were measured by Enzyme-Linked Immunosorbent Assay kits (EZHI-14K, EZHL-80SK, EZHADP-61K, EK-003-80, LINCO Research, Missouri, USA and EK-003-80, Phoenix Europe, GMBH, Karlsruhe, Germany and 45-ILHU-E01, Alpco Diagnosis Salem, NH, USA, respectively). Cytokine analysis of IL-β1, IL-8 and TNF-α was performed on the collected serum samples using multiplex assays (Millipore, Leiden, Netherlands) and read on a Luminex100TM platform. Serum fasting high sensitive C-reactive protein (CRP) concentrations were measured by enzyme immunoassay (IBL international GMBH, Hamburg, Germany). Samples were prepared according to the manufacturer's recommendation and cytokine levels were assessed by LuminexTM multiplex analysis. All samples were measured in duplicate and the mean was scored. Insulin resistance was assessed by the homeostasis assessment model (HOMA-IR) and insulin sensitivity by quantitative insulin sensitivity check index (QUICKI) [24, 25]. The adiponectin to leptin (A/L) ratio was also calculated [26].

Statistical analysis

Characteristics of the study sample at baseline and after weight loss intervention program are presented as means and standard deviation, unless otherwise stated. Differences in the study variables before and after the diet intervention program were analyzed by paired-samples Student's *t* test.

Linear regression analysis was also used to examine the associations of lean mass (model 1) and fat mass (model 2) changes with serum circulating visfatin level differences after adjusting for age as a constant confounding factor. Relative changes of variables after weight loss program were calculated as Δ (%): [(Data 12 wk after weight loss period − Data at baseline)/Data at baseline] × 100.

The relationship between circulating visfatin concentrations at baseline, insulin resistance and sensitivity, and proinflammatory markers was examined by linear regression analysis controlling for BMI before dietary treatment (model 1). The effect of circulating visfatin changes on insulin sensitivity and resistance and proinflammatory marker levels after energy restricted diet intervention was tested by linear regression analysis adjusting for body weight loss (model 2).

Variables with skewed distribution were logarithmically transformed to obtain a more symmetrical distribution. Analyses were performed using the SPSS, v. 17.0 (SPSS Inc, Chicago) and the level of significance was set to 0.05.

Results

The effect of diet intervention on body composition, metabolic variables and serum proinflammatory cytokine levels

Table 1 summarizes the descriptive characteristics of obese women at baseline and after 12 weeks of energy restricted diet intervention. Body weight, BMI, FM, LM and RMR were significantly decreased ($P < 0.001$) after 12 weeks of diet intervention, while no significant differences were found in BM and NPRQ. On the other hand, serum glucose ($P < 0.02$), insulin ($P < 0.001$), leptin ($P < 0.001$), HOMA-IR ($P < 0.001$), A/L ratio ($P < 0.001$), total and HDL-cholesterol ($P < 0.05$) and CRP ($P < 0.02$) significantly decreased, whereas serum visfatin concentrations and QUICKI significantly increased ($P < 0.05$) after weight loss. There was a tendency to decrease TG concentration ($P < 0.06$), while no significant changes were found in serum IL-β1, IL-6, IL-8 and TNF-α concentrations after energy restricted diet intervention.

The effect of lean and fat mass changes on serum visfatin level changes

As a result of body weight loss, circulating serum visfatin concentrations increased (Table 1). Thus, we found that body weight loss and BMI change were negatively correlated ($r = -0.253$; $P = 0.026$ and $r = -0.233$, $P = 0.040$, respectively) with serum visfatin change (%). Our next step was to test the effect of body composition specific compartments on this relationship. Table 2 presents linear regression statistics showing the estimated differences in circulating visfatin percentage decrease in body LM and FM in obese women after energy restricted diet intervention. LM difference was negatively associated with serum visfatin concentration change ($P < 0.05$), whereas no significant association was observed between changes in FM and serum visfatin level changes after energy restricted diet intervention.

Circulating visfatin levels, glucose metabolism and proinflammatory cytokine levels at baseline and after dietary treatment

Circulating concentrations of visfatin were positively correlated with IL-β1 and HDL-cholesterol ($P < 0.05$) and negatively with IL-6 ($P < 0.01$) and IL-8 ($P < 0.02$) independently of BMI at baseline (Table 3, model 1).

Table 1 Characteristics of the study sample before and after the 12 weeks energy restricted diet intervention.

	Before	After	*P*
Age (y)	36.7 (7.0)		
Weight (kg)	88.9 (10.1)	81.2 (9.9)	**<0.001**
BMI (kg/m^2)	34.0 (2.8)	31.0 (2.7)	**<0.001**
Body composition (DXA)			
Body fat percentage (%)	42.4 (3.9)	40.3 (4.1)	**<0.001**
Fat mass (kg)	37.4 (6.2)	32.6 (6.2)	**<0.001**
Lean mass (kg)	48.3 (5.3)	45.7 (5.2)	**<0.001**
Bone mass (kg)	2.1 (0.3)	2.1 (0.3)	0.750
RMR (kJ/min)	4.53 (0.5)	4.07 (0.42)	**<0.001**
NPRQ	0.78 (0.10)	0.80 (0.10)	0.493
Cholesterol (mmol/L)	4.95 (0.83)	4.45 (0.77)	**<0.001**
HDL-cholesterol (mmol/L)	1.49 (0.33)	1.29 (0.24)	**<0.001**
Triglycerides (mmol/L)	3.73 (0.42)	1.37 (0.15)	0.051
Glucose (mmol/L)	5.01 (0.44)	4.92 (0.44)	**0.010**
Insulin (μU/mL)	8.84 (4.90)	6.42 (3.92)	**<0.001**
Adiponectin (μg/mL)	9.32 (6.84)	8.21 (6.31)	**0.118**
HOMA	2.0 (1.1)	1.4 (0.9)	**<0.001**
QUICKI	0.35 (0.03)	0.38 (0.04)	**<0.001**
Leptin (ng/mL)	48.1 (17.3)	28.2 (14.8)	**<0.001**
A/L ratio[a]	0.21 (0.14)	0.35 (0.24)	**<0.001**
Visfatin (ng/mL)[a]	17.6 (7.6)	19.7 (8.2)	**0.007**
IL-β1 (pg/mL)[a]	1.4 (2.1)	1.5 (2.7)	0.150
IL-6 (pg/mL)[a]	0.58 (0.29)	0.55 (0.28)	0.444
IL-8 (pg/mL)[a]	9.5 (12.7)	10.0 (17.2)	0.708
TNF-α (pg/mL)[a]	8.9 (7.7)	8.7 (6.8)	0.912
CRP (mg/L)[a]	2.15 (2.06)	1.79 (1.94)	**0.011**

Values are means (SD). DXA: dual energy x-ray absorptiometry; BMI: body mass index; RMR: resting metabolic rate; NPRQ: non-protein respiratory quotient; HOMA: homeostasis model assessment; QUICKI: quantitative insulin sensitivity check index; A/L: adiponectin to leptin; IL: interleukin; TNF: tumor necrosis factor; CRP: C-reactive protein.

[a] Analysis was performed with log-transformed data.

Changes in circulating serum visfatin levels were significantly and inversely associated with HOMA-IR ($P < 0.01$) and positively with QUICKI index ($P < 0.02$) after energy restricted diet intervention, regardless of achieved body weight loss (Table 3, model 2). These relationships did not substantially change when waist circumference change was entered into the model instead of body weight loss ($P = 0.020$ and $P = 0.035$, respectively). Nevertheless, we did not find any significant association between changes in visfatin levels and neither TG and HDL-cholesterol concentrations, nor with IL-1β, IL-6 IL-8, TNF-α and CRP levels after dietary intervention (all $P > 0.2$).

Discussion

The most interesting findings of this study are: [1] that body composition changes after weight reduction influence circulating visfatin concentrations in obese non-diabetic women, and [2] that increasing serum visfatin improves insulin sensitivity, while no significant relationship was found with low-grade inflammation estimates changes after dietary treatment. Our results suggest that lean mass changes could be an influencing factor on visfatin concentrations and consequently, on the improvement of insulin sensitivity after weight loss in obese non-diabetic women. As far as we are aware, this would be the first study

Table 2 Lineal regression coefficients (β) and standard errors (SE) examining the association of lean mass (LM) and fat mass (FM) changes with circulating serum visfatin concentration changes after following an energy restricted diet intervention in obese women.

	ΔLM adjusted with age			ΔFM adjusted with age		
	β	SE	*P*	β	SE	*P*
ΔVisfatin (%)	−3.866	1.653	**0.022**	−0.155	0.401	0.699

Δ(%): [(Data 12 wk after weight loss period − Data at baseline)/Data at baseline] × 100.

Table 3 Lineal regression coefficients (β) and standard errors (SE) examining the associations of circulating visfatin with HOMA-IR, QUIKI, A/L ratio, total cholesterol, TG, HDL-cholesterol, IL-1β, IL-8 and TNF-α and CRP levels at baseline (model 1) and the relationship of circulation visfatin changes (%) with HOMA-IR, QUIKI, A/L ratio, total cholesterol, TG, HDL-cholesterol, IL-1β, IL-8 TNF-α and CRP after energy restricted diet intervention (model 2).

	β	SE	*P*
Model 1. Circulating visfatin concentrations (ng/ml) adjusted with BMI at baseline			
HOMA-IR at baseline[a]	−0.249	0.140	0.080
QUIKI at baseline[a]	0.037	0.022	0.087
A/L ratio at baseline[a]	−0.087	0.174	0.619
Cholesterol at baseline (mmol/L)	0.084	0.047	0.079
TG at baseline (mmol/L)[a]	−0.139	0.130	0.287
HDL-cholesterol at baseline (mmol/L)[a]	0.172	0.079	**0.034**
IL-1β at baseline (pg/mL)[a]	0.596	0.282	**0.038**
IL-6 at baseline (pg/mL)[a]	−0.862	0.267	**0.003**
IL-8 at baseline (pg/mL)[a]	−0.778	0.320	**0.017**
TNF-α at baseline (pg/mL)[a]	−0.107	0.274	0.696
CRP at baseline (mg/L)	−1.064	0.695	0.131
Model 2. Changes in circulating visfatin concentrations adjusted with body weight loss			
HOMA-IR after[a]	−0.014	0.005	**0.009**
QUICIK after[a]	0.002	0.001	**0.017**
A/L ratio after[a]	−0.106	0.198	0.595
Cholesterol after (mmol/L)[a]	−0.096	0.057	0.098
TG after (mmol/L)[a]	−0.006	0.003	0.117
HDL-cholesterol after[a]	0.001	0.001	0.306
IL-β1 after (pg/mL)[a]	0.002	0.008	0.775
IL-6 after (pg/mL)[a]	0.008	0.008	0.306
IL-8 after (pg/mL)[a]	−0.006	0.009	0.533
TNF-α after (pg/mL)[a]	0.004	0.008	0.609
CRP after (mg/L)	0.020	0.019	0.305

Changes in visfatin: Circulating visfatin concentration at baseline − circulating concentration of visfatin after energy restricted diet intervention. Body weight loss: body weight at baseline − body weight after energy restricted diet intervention. A/L: adiponectin to leptin; TG: triglycerides; IL: interleukin; TNF: tumor necrosis factor; CRP: C-reactive protein.

[a] Analysis was performed with log-transformed data.

examining the effect of body composition compartments on circulating visfatin concentrations after an energy restricted diet intervention.

As expected, in our study metabolic syndrome related parameters were clearly decreased after weight loss, while serum visfatin concentrations significantly increased. The effect of weight loss on circulating visfatin levels is controversial. Indeed, while most authors find in obese subjects who underwent bariatric surgery increased visfatin plasma levels after weight loss [10]; other investigators observed either reduced or no changes in visfatin plasma concentrations [13]. Finally, several studies showed that individuals following energy restricted diets diminished their plasma visfatin levels as a function of weight loss [15]. The reason for these discrepancies in the literature is unclear, but may have been caused by factors as the degree of obesity [13], the presence of diabetes or glucose intolerance [27,28], sex [29], age [30] or lifestyle [31], which have been previously associated with different results and conclusions.

Insulin resistance is the principal cause of glucose intolerance and type 2 diabetes and induces progression of atherosclerosis. HOMA-IR and QUIKI index are the methods to effectively evaluate insulin resistance and sensitivity in the situation where insulin secretion capacity is sustained to some extent [24]. Additionally, the A/L ratio has been reported to predict insulin sensitivity and it has been proposed as a potential atherogenic index in obese patients with type 2 diabetes [26]. Although potential influence of visfatin on glucose homeostasis and in the pathophysiology of diabetes has been previously suggested, in our study the relationships between visfatin concentrations and variables of insulin resistance and sensitivity, i.e. HOMA-IR and QUICKI, did not reach statistically significance after BMI adjustment at baseline. Nevertheless, our study provides evidences that women increasing their circulating visfatin concentrations after diet induced weight loss, diminished insulin resistance estimated with both HOMA-IR and QUICKI indexes, while no relationship was found with A/L ratio. These results were independent of either achieved weight loss or waist circumference reduction. Although, the results do not allow us to establish the directionality and causality of the associations, these findings could lead us to speculate that circulating visfatin seems to act directly in the glucose metabolism and could play a role in the weight loss induced insulin sensitivity improvement.

We detected significant associations between lean mass changes with circulating concentrations of visfatin, while

no relationship was found with fat mass changes. Although visfatin is predominantly produced by visceral adipose tissue, controversy exists over the contribution of this fat depot to serum visfatin in humans [32,33]. Thus, previous studies showed no association between circulating concentrations of visfatin and the mRNA expression levels of visfatin in adipose tissue [8]. Our data support recent reports either in animal or human studies suggesting that one of the highest amounts of mRNA of visfatin is found in the muscle tissue [34]. Other authors showed that visfatin levels correlate with muscle mitochondrial content and that exercise increased the visfatin expression [31]. One possible explanation of our findings could be that decreasing muscle mass, decreases one important source of serum visfatin in obese women.

Chronic low-grade inflammation constitutes a mediator in the development of obesity-related diseases [35]. Adipose tissue produces a number of adipokines linked to inflammation, including adiponectin, IL-1β, IL-6, TNF-α [36]. Circulating levels of TNF-α and IL-6 are directly correlated with adiposity and insulin resistance [37,38]. The association of visfatin with inflammatory markers together with its increased production and release by macrophages supports its proinflammatory properties [39]. Furthermore, a strong association between visfatin and TNF-α and IL-8 in peripheral blood cells has been described [7,40]. However, Varma et al. [41] found a negative association between visfatin and CD68, as well as with circulating TNF-α, suggesting an anti-inflammatory role for visfatin. Our results did not provide any evidence for a role of visfatin increase on low-grade inflammation levels after weight loss. However, circulating visfatin concentrations were positively correlated with IL-1β and negatively with IL-6 and IL-8 at baseline regardless of BMI. These results suggest a potential involvement of visfatin on inflammation, but its implications for its role are inconclusive. CRP is an acute phase protein produced exclusively by the liver in response to inflammation. Our results did not concur with previous studies reporting significant relationships between visfatin and CRP [6,8], which is an established predictor of future cardiovascular disease. Nevertheless, Catalan et al [6] conducted their study with morbidly obese individuals with high concentrations of CRP, and the association was lost after adjusting for BMI. Oki et al. [6], showed a significant relationship between visfatin and CRP in a sample of old Japanese adults, but this association was not adjusted for BMI. Manco et al. [14], in a small sample of obese female ($n = 10$) who underwent bariatric surgery observed that visfatin concentration was negatively correlated with insulin levels, but not with inflammatory markers in agreement with our own results. Further research will provide more insight into the still unclear role of visfatin in the inflammatory response of obese subjects.

The most important limitation of the current study includes its small sample size. However, our sample was more homogeneous than other previously reported due to its inclusion criteria and to the highly controlled intervention. Thus, subjects were all Caucasian, non-diabetic and non-morbid obese women and followed energy restricted diet with similar macronutrient composition based on Mediterranean dietary habits. Second, we cannot discard that the lack of differences in the multiplex-derived cytokine measures (TNF-α, IL-1β and IL-8) after energy restricted diet could be due to the low sensitivity of this analytical method [42]. Third, we did not measure visceral adiposity, which is highly correlated with visfatin concentrations and we used waist circumference as surrogate of abdominal adiposity. Finally, the accurate technique used to assess body composition gave strength to the adjustments. However, we need to be very cautious before extrapolating our conclusions to other populations and replication of our findings is essential.

In conclusion, our results suggest that increased circulating visfatin concentration is associated with insulin sensitivity improvement achieved after energy restricted diet intervention induced weight loss. Furthermore, lean mass changes could be an influencing factor on visfatin concentrations and consequently, on the improvement of insulin sensitivity after weight loss in obese non-diabetic women. Our findings did not provide any evidence for a role of visfatin increase on low-grade inflammation levels after weight loss.

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