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Original Article

Effect of Weight Reduction Following Bariatric Surgery on Serum Visfatin and Adiponectin Levels in Morbidly Obese Subjects

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Key Words

Adiponectin · Visfatin · Morbid obesity · Bariatric surgery · Weight loss

Abstract

Objective: Adipokines are signaling and mediator proteins secreted from adipose tissue. A novel adipokine, visfatin, was reported as a protein which was mainly expressed in visceral adipose tissue. Controversial results have been shown regarding the changes of adipokines following weight reduction. So we investigated the effects of weight reduction on serum concentrations of adiponectin and visfatin in morbidly obese subjects. **Methods:** 35 severely obese patients (26 females and 9 males), aged 15–58 years, were studied. Anthropometric parameters and biochemical parameters as well as adiponectin and visfatin were analyzed before and 6 weeks after weight reduction. **Results:** Anthropometric indices decreased significantly. Blood levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride were reduced significantly. The reduction of visfatin and the elevation of adiponectin were significant as well. However, other parameters like fasting glucose and insulin did not change. Moreover, we could not find any significant correlation between the change of serum visfatin and that of adiponectin. **Conclusions:** 6-week weight reduction after bariatric surgery resulted in decreased serum visfatin and increased adiponectin levels. However, we cannot find any significant correlation between changes of adiponectin, visfatin, BMI, waist circumference, and insulin resistance. Further studies with different design are suggested to clarify these associations.

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Introduction

It has been widely confirmed that obesity is a major cause of morbidity and mortality. Obesity as a chronic low-grade inflammatory state is associated with many disorders such as diabetes mellitus, cardiovascular disease, and atherosclerosis [1, 2]. The exact mechanism linking obesity with these complications has not been elucidated [3, 4].

Recent studies suggested that bariatric surgery interventions had increased in morbidly obese patients because of more successful weight loss, longer-term weight maintenance, and enhancement of health-related quality of life [5]. A number of reports showed that bariatric surgery was associated with a notable reduction of all-cause mortality. Also comorbid conditions, including diabetes, hypertension, dyslipidemia and insulin resistance, have been improved [6]. Therefore, this method may be considered as a favorable option for treatment of morbidly obese patients. However, further studies are needed to elucidate the mechanisms resulting in decreased mortality among these patients after bariatric surgery [7].

It has been shown that adipose tissue has an important endocrine function under physiological and pathophysiological conditions [8–10]. Adipokines which are secreted from white adipose tissue could explain at least a part of the pathologic changes accompanying obesity [11]. The metabolism of almost all known adipokines is markedly dysregulated in obesity. The serum levels of most of them are increased, others, like adiponectin, are decreased [11, 12].

Visfatin (pre-B-cell colony enhancing factor) was previously described as a modulator of B-cell differentiation. It is also recognized in lymphocytes, bone marrow, muscle, and liver [13]. However, visfatin has recently been identified as a new adipokine which is produced mainly by visceral adipose tissue [14] and is involved in the process of glucose metabolism and inflammation [15, 16]. It has been shown that visfatin exerts insulin-mimetic effects and stimulates glucose utilization in peripheral tissues [14, 17, 18]. However, its biological role and the underlying mechanisms are not entirely clear yet. It is hypothesized that visfatin secretion could be a compensatory mechanism or part of the pathophysiology of diabetes [19]. In fact, the relationship between visfatin and diabetes or insulin resistance was not clear, and the results of different studies were inconsistent [20, 21]. Thus further studies are needed to clarify the role of visfatin in insulin resistance and related metabolic disorders [22]. Previous studies showed inconsistent results regarding changes of serum visfatin levels in obesity and metabolic syndrome; both increasing and decreasing [14, 21, 23–27] and even unchanged [28, 29] levels of visfatin had been found. The observed changes of visfatin levels after bariatric surgery and weight reduction were also inconsistent [21, 30, 31]. In some of these studies the serum levels of this adipokine actually remained unchanged [31]. In addition, many studies suggested that this adipokine is related to inflammation in obesity via different mechanisms [32]. With these conflicting results in mind, it remains a matter of ongoing discussion whether or not there is an association between obesity, weight reduction and serum visfatin concentrations [33].

Further studies investigated if there is any difference in the visfatin mRNA expression of visceral (VAT) and subcutaneous adipose tissue (SAT) in lean and obese individuals. Berndt et al. [34] found a positive correlation between visfatin mRNA expression of VAT, BMI and %body fat. Moreover, they found a negative correlation between BMI and visfatin expression of SAT. Pagano et al. [25] indicated that visfatin mRNA expression was lower in SAT and higher in VAT of obese than of lean individuals. Varma et al. [20] also found a positive correlation between BMI and visfatin gene expression in VAT and a negative correlation between BMI and visfatin gene expression in SAT.

Adiponectin, another adipokine which is secreted from adipocytes, has anti-inflammatory and anti-atherogenic effects [35] by suppressing pro-inflammatory cytokines such as

TNF- α and inducing other anti-inflammatory factors [36]. Many studies showed that the adiponectin level is lower in the insulin-resistant stage and increased with improved insulin sensitivity after weight loss [12, 37, 38]. In vivo studies demonstrated that adiponectin enhanced the energy consumption and fatty acid oxidation in the liver and muscles, resulting in a decrease of the tissue triglycerides and an improvement of insulin sensitivity [39].

It has been suggested that weight loss is accompanied by changes in the inflammatory state and adipokine levels. However, the changes of inflammatory and anti-inflammatory adipokines during short-term and rapid weight loss in young morbidly obese subjects are not exactly understood, and conflicting results have been reported [40]. So the aim of our study was to evaluate the changes in circulating visfatin and adiponectin levels following weight loss in morbidly obese subjects and whether or not there are associated changes of other metabolic parameters.

Material and Methods

35 morbidly obese subjects (26 females and 9 males), aged 33.5 ± 9.1 years (range 15–58 years), were recruited to study the changes of adiponectin and visfatin levels after bariatric surgery at university hospitals. These patients received bariatric surgery after failure of other weight loss strategies. Patients were treated by laparoscopic gastric banding (LAGB), laparoscopic total gastric vertical plication (LTGVP), or gastric bypass according to the evaluation and choice of the surgeon.

Subjects with the following conditions were excluded from the study: presence of type 2 diabetes mellitus or use of antidiabetic medications (metformin, thiazolidinediones, insulin), hypo- or hyperthyroidism, hypertension and/or use of anti-hypertensive drugs, ischemic heart disease or stroke, any malignancy, chronic kidney or liver disease, obesity caused by an endocrine disorder, Cushing syndrome, psychiatric disorders, pregnancy or lactating, rheumatoid arthritis, smoking and alcohol intake, and use of lipid-lowering medications (statins, fibrates). The study protocol was approved by the ethics committee of the university, and all subjects signed written informed consent.

Study Protocol

Patients underwent a clinical assessment including medical history, physical examination and co-morbidity evaluation by a multidisciplinary consultation team and anthropometric measurement; fasting blood samples were collected prior to and 6 weeks after surgery.

Measurements of Anthropometric Indices and Blood Pressure

Anthropometric indices and blood pressure were measured prior to, and 6 weeks after surgery by using standard methods. Body weight was measured to the nearest 0.1 kg using a calibrated manual weighing scale (Seca 709, Les Mureaux, France). Height was measured to the nearest 0.5 cm on a standardized wall-mounted height board. Waist circumference (WC) was measured at the minimum circumference between the iliac crest and the rib cage at minimal respiration. Hip circumference was measured at the maximum protuberance of the buttocks. Using these data, waist-to-hip ratio (WHR) was calculated. BMI was defined as weight in kilograms divided by height in meters squared (kg/m^2). Blood pressure was measured after at least 10 min rest in a sitting position.

Bariatric Surgery

All patients met the criteria detailed by the National Institutes of Health for selection of morbidly obese patients undergoing bariatric surgery [41]. Patients underwent restrictive bariatric surgery using one of three techniques: LAGB, LTGVP, or gastric bypass. All patients were operated by a single team.

Laboratory Assays

Blood samples were collected between 8:00 a.m. and 10:00 a.m. after 10–12 h overnight fasting. Blood samples were centrifuged at $3,000 \times g$ for 10 min. Plasma samples were stored at -80°C until further analysis. Fasting plasma glucose was measured using the glucose oxidation method (Pars Azmoon, Tehran, Iran), and total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) were determined by enzyme colorimetric assay (Pars Azmoon) using an Eppendorf autoanalyzer (Eppendorf Corp., Hamburg,

Table 1. Clinical and biochemical variables in morbid obese subjects before and after bariatric surgery (n = 35)

	Before surgery	After surgery	p value
Sex (F/M)	26/9	26/9	
Weight, kg	128 ± 20.7	111.2 ± 17.9	0.000
BMI, kg/m ²	45 ± 4.7	39.2 ± 4.6	0.000
WC, cm	123.1 ± 14.4	111.3 ± 12.9	0.000
WHR	0.89 ± 0.09	0.87 ± 0.09	0.000

Table 2. Biochemical variables in morbid obese subjects before and after bariatric surgery (n = 35)

	Before surgery	After surgery	p value
Fasting glucose, mmol/l	98 ± 10.7	94.2 ± 7.7	0.07
HDL-C, mmol/l	39.3 ± 8.8	37.3 ± 6.7	0.05
LDL-C, mmol/l	114.5 ± 27.5	105.2 ± 24.7	0.006
TC, mmol/l	190.8 ± 38.9	180.4 ± 36.5	0.08
Adiponectin, ng/ml	36.5 ± 11	41.3 ± 11	0.01
Visfatin, ng/ml	5 ± 3.5	3.4 ± 3.2	0.01

Germany). High-density lipoprotein cholesterol (HDL-C) was measured using a precipitation-based method. The serum insulin level was assayed using an immunoradiometric method (Biosource Europe SA, Nivelles, Belgium). The insulin sensitivity was determined using the Homeostasis Model Assessment Index of insulin resistance (HOMA-IR) according to the following formula: $HOMA-IR = \text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose concentration (mmol/l)} / 22.5$ [42].

The serum concentrations of visfatin and adiponectin were determined by commercially available ELISA kits (Human Visfatin ELISA Kit and Human Adiponectin ELISA Kit; AdipoGen Pharmaceuticals Belmont, Seoul, South Korea). The intra- and inter-assay coefficient of variation of both kits was <9.1% and <5.5%, respectively. The sensitivity of the visfatin and the adiponectin ELISA kit was 300 and 100 pg/ml, respectively.

Statistical Analysis

The Kolmogorov-Smirnov test was applied to examine normal distribution of continuous variables. Continuous variables with normal distribution are presented as mean ± SD; for non-normal variables median (25th and 75th percentiles) were used. Differences between preoperative and postoperative data were tested by paired t-test or Wilcoxon sign rank test as appropriate. Correlations between changes of variables were explored using Pearson's or Spearman's correlation where appropriate. Comparisons of plasma levels of visfatin and adiponectin between three surgery methods were made using one-way analysis of variance (ANOVA). Statistical analyses were performed using the statistical package SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, USA). p values less than 0.05 were considered significant.

Results

Baseline Characteristics

35 morbidly obese patients, 26 women and 9 men, participated in the study. Their mean age was 33.5 ± 9.1 years and their mean BMI at baseline 45 ± 4.7 kg/m². 14 patients were submitted to LAGB, whereas LTGVP was performed in 14 patients; 7 patients underwent gastric bypass surgery. The anthropometric and biochemical characteristics of the patients before and after bariatric surgery are given in tables 1–3. There were no differences in serum visfatin and adiponectin levels between patients submitted to LAGB, those submitted to LTGVP and those submitted to gastric bypass at baseline as well as after weight reduction.

Table 3. Biochemical variables in morbid obese subjects before and after bariatric surgery (n = 35)^a

	Before surgery	After surgery	p value
Fasting insulin, pmol/l	13.1 (9–20.7)	11.7 (10.1–15.0)	0.15
HOMA-IR	3.1 (2–4.6)	2.7 (2.3–3.5)	0.09
TG, mmol/l	148 (110–194)	128 (102–148)	0.009

^aAll data are presented as median (25th and 75th percentile).

After bariatric surgery, a significant decrease in weight, BMI, WC, and WHR was shown (table 1). Serum visfatin as well as HDL-C, LDL-C, and TG levels also decreased, whereas adiponectin concentrations increased. No changes were observed in serum TG levels, fasting glucose concentrations, insulin concentrations, and HOMA-IR (tables 2, 3). Furthermore, we analyzed the changes of anthropometric and biochemical variables according to the type of surgery (LAGB, LTGVP, and gastric bypass). Reductions of weight, WC, and BMI were significant and similar in the three groups. The changes of insulin levels were significant only in those patients who had bypass surgery. However, in neither group, a significant change of HOMA-IR could be detected.

We did not observe any significant correlations between changes of circulating visfatin or adiponectin levels and changes of other metabolic variables. This remains true also after adjustment for age and sex.

Discussion

In the present study, we have shown that serum visfatin concentrations decreased and adiponectin concentrations in morbidly obese subjects increased significantly after weight reduction following bariatric surgery. Previous studies have reported inconsistent results as to the changes of serum visfatin and adiponectin levels after weight reduction. Obesity is considered as a low-grade inflammation, which is improved following weight loss [6, 31, 43]. Therefore, it is expected that weight reduction modulates secretion of adipokines from adipose tissue. Visfatin has been considered as a new pro-inflammatory adipokine [32]. Since the main site of visfatin secretion is VAT [14, 25], it was suggested that its plasma concentration is correlated with visceral obesity [14]. In recent years contradictory results have been published as to whether serum visfatin levels in obesity increase [23] or decrease [25], indicating that the association between obesity and visfatin is more complex than a simple dependency on body fat mass [44]. Also, the changes of serum visfatin concentrations following different kinds of weight reduction strategies in morbidly obese subjects, such as gastroplastic surgery [30], intestinal bypass [45], LAGB [46] and lifestyle modifications [47], were inconsistent. Some studies found decreased levels of circulating visfatin [21, 48] in line with our present results, but others reported increased plasma visfatin levels [30, 44, 45]. Moreover, some studies could not find any significant change of visfatin levels [31]. De Luis et al. [49] reported that visfatin concentrations did not change after 1 year of surgically induced weight loss. As demonstrated in our series, the type of bariatric surgery did not influence on changes of visfatin and adiponectin levels. The discrepant results could be explained by the a more complex relationship between visfatin and body fat level and its distribution; glucose homeostasis status and other factors such as iron metabolism [50], vascular endothelial function [51], genetic and race variation [47, 51], pattern of macronutrient intake, and dietary restriction of adipokin response [47, 52], may also influence visfatin metabolism.

It has been shown that VAT is considerably decreased following weight loss [47] as demonstrated by reduction of WC [44, 53]. A decreased amount of VAT following weight loss would suggest a reduction in visfatin concentrations after bariatric surgery. These results are in accordance with the hypothesis that visfatin is over-produced in obesity – possibly to compensate insulin resistance caused by increased adipose tissue. Following weight reduction, the need for this mechanism would be diminished [30, 48]. Berndt et al. [34] showed that plasma visfatin concentrations correlated with BMI, but not with WHR. This is why plasma visfatin is decreased following weight and BMI reduction. On the other hand, the inconsistent findings may be due to different inclusion criteria of patients, such as mean BMI, rate of weight reduction, and follow-up period [47]. Another potential explanation for short-time serum changes of adipokines following weight loss are rapid changes of adipokine production by the liver. Moschen et al. [46] indicated that serum concentrations and hepatic visfatin expression was reduced after bariatric surgery-induced weight loss. They concluded that weight loss in severely obese subjects enhances circulating levels and liver expression of the anti-inflammatory adipokine adiponectin while serum levels and/or liver expression of the pro-inflammatory adipocytokines such as visfatin are significantly reduced.

An additional reason for the discrepancy in results may be the use of C-terminal assays for detection of visfatin in some studies which was not reliable [54]; only an ELISA assay could detect full-length visfatin [54].

In the present study, we found significant changes of adiponectin levels following weight loss. Adiponectin has already been shown to have insulin-sensitizing and anti-inflammatory properties [55] and is known as a main mediator of glucose metabolism [56]. It is the only secretory protein of adipose tissue the expression of which is decreased or diminished in morbidly obese subjects [57].

An increase of adiponectin levels after weight reduction as a consequence of bariatric surgery procedures or dietary methods have been shown in several studies [58–60], being in accordance with our results. In contrast, other studies failed to observe such an increase [61]. The threshold of weight loss could be one of the possible reasons to promote adiponectin levels. It had been noted that a weight loss of 10% or more is required to induce an increase in plasma concentrations of adiponectin [57].

Many publications have evaluated long-term effects of bariatric surgery-induced weight reduction (6 months) on serum adipokine levels. In other words, the short-term effect of bariatric procedures on adipokines is unclear. We therefore planned to investigate short-term effects of weight loss on visfatin and adiponectin levels after bariatric surgery. Swarbrick et al. [62] reported no changes of plasma adiponectin 1 month after bariatric surgery. They suggested that adiponectin-increasing effects of weight loss were obtained not until 3 months and with more pronounced weight loss [63]. However, we observed such changes after 6 weeks already. It seems that these changes were compatible with longer-term follow-up studies. This may help to clarify short-time metabolic adaptation induced by bariatric surgical procedures. Further studies should confirm these results.

In our series, the decrease of visfatin concentrations and the increase of adiponectin levels were accompanied by a decrease in BMI, WC, and WHR [21]. However, we did not observe any significant decreases of plasma insulin, glucose, and insulin sensitivity. Pro-inflammatory cytokines such as TNF- α and IL-6 can inhibit the synthesis and secretion of adiponectin. Thus, decreasing TNF- α and IL-6 level as a result of weight loss may contribute to the increase in adiponectin levels [64]. Therefore, reduction of adiposity may contribute to increasing adiponectin levels [35]. Some studies suggested that this relationship is mainly modulated by the degree of insulin resistance rather than adipose tissue accumulation or blood glucose levels [65, 66]. Insulin is modulated by adiponectin via glucose and fatty acid metabolism [67], and adiponectin can improve insulin sensitivity in the liver [57,

68]. This means that insulin sensitivity is dependent on plasma adiponectin concentration [12, 38].

We could not find any significant association between changes of visfatin or adiponectin levels and changes of blood glucose or HOMA-IR. Small sample size might partly explain these findings. Another reason might be the normal fasting blood glucose before surgery. With a normal range of blood glucose, the need for increased visfatin as a compensatory mechanism to overcome hyperglycemia could be diminished. The increased level of visfatin before surgery therefore may be the result of a higher fat mass rather than of a compensatory mechanism. Another explanation would be that normal level of fasting blood glucose might be the result of increased visfatin levels to mimic insulin action. All these hypotheses could only explain in part the absence of any correlation between the changes of adipokines, like visfatin or adiponectin, and those of blood glucose and insulin sensitivity.

We also investigated whether or not the type of surgery has an influence on the changes of anthropometric variables, insulin levels, and HOMA-IR. Reductions of weight, WC and BMI were significant in the three surgical groups, but the changes of insulin levels were significant only in those patients who had bypass surgery as shown in other studies [35]. However, in neither group, a significant change of HOMA-IR could be detected.

We were not able to show any significant correlation between visfatin or adiponectin levels and anthropometric indices such as WC and BMI. It seems that these associations are more complex and not entirely understood thus far. Since patients with a narrow range of BMI (BMI 35–55 kg/m²) were compared, we could not expect to find significant correlation between anthropometric indices and adipokine levels. In other words, with wider range of BMI the correlation would be more obvious. Furthermore, we could not find any significant correlation between the changes of circulating visfatin and plasma adiponectin concentrations, confirming results of other studies [21, 69, 70]. It has been suggested that counter-regulatory adaptations in high-molecular-weight adiponectin and visfatin interaction might have an effect on glucose homeostasis and possibly on adipoinsular axis, contributing to the maintenance of normal glucose tolerance [22].

Our study has some limitations. The patients in our study only showed a narrow range of BMI and insulin resistance, and correlations might be more obvious if the ranges of BMI and insulin resistance are wider. Moreover, we did not measure high-molecular-weight adiponectin. Many studies have reported that the ratio of high-molecular-weight to total adiponectin determines or predicts insulin sensitivity more correctly than total adiponectin levels [22, 71].

In conclusion, weight reduction after bariatric surgery is associated with a significant decrease in circulating concentrations of the adipokine visfatin in morbidly obese subjects. In addition, weight loss in severely obese subjects increases anti-inflammatory adiponectin levels and modifies biochemical and anthropometric parameters. Further research is needed to clarify different aspects of adipokine action and their influence on the pathogenesis mechanisms of obesity and insulin-resistant disorders.

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Disclosure Statement

All contributing authors declare that they have no conflicts of interest.

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