Central European Journal of Medicine
DOI: 10.2478/s11536-006-0015-x
Research article
CEJMed 1(2) 2006 136–147

The relationship between features of metabolic syndrome and blood adipocytokine concentrations in the morbid obese patients during dynamic weight loss

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Received 11 February 2006; accepted 10 May 2006

Abstract: Bariatric surgery is the most effective method to achieve weight loss in obese subjects. The aim of this study was to evaluate some adipocytokines and insulin, as well as parameters of metabolic syndrome of the obese patients, for three and six months after vertical banded gastroplasty, in the time of dynamic weight loss.

Seven males and two females aged 28 to 49 years, with long lasting simple obesity and the presence of metabolic syndrome, were studied. After surgical treatment the values of the body mass index, waist circumference, systolic and diastolic blood pressure, total cholesterol, LDL cholesterol, triglycerides, and blood concentrations of leptin decreased significantly.

Before surgical operation of all obese patients no statistically significant correlations between studied parameters were noted. Three and six months later a lot of correlations between studied parameters appeared.

In conclusion, (a) vertical-banded gastroplasty is a valuable method in treatment of obese subjects, leading to a significant decrease in body weight and improvement in some parameters of metabolic syndrome in a few months after surgery, (b) adipocytokines, together with an unknown gastric factor, may be key factors in the control of some features of the metabolic syndrome.

Keywords: Obesity, metabolic syndrome, adiponectin, leptin, resistin

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1 Introduction

Obesity is a long-term disease associated with the presence of too much fat. The global pandemic of obesity has increased over 75% since 1980 [1]. An imbalance in energy homeostasis leading to obesity has been recognized as a regulatory process involving hormones such as insulin and leptin that circulate in the peripheral blood in proportion to body fat content and act on the hypothalamus to reduce food intake and fat stores [2]. Obesity is closely associated not only with insulin resistance but also with elevated triglyceride levels, low HDL and high LDL cholesterol levels, and elevated blood pressure. It produces a complex medical condition called metabolic syndrome [3, 4], leading to atherosclerosis. A surrogate marker for body fat content is the body mass index (BMI) [3].

Regional body-fat distribution has an important influence on metabolic and cardiovascular risk factors. Multiple environmental and genetic factors are thought to influence a manifestation of abdominal obesity [5].

The development of metabolic syndrome, the complex set of risk factors including glucose intolerance, hyperinsulinemia, hypertension, and dyslipidemia, dramatically heightens a cardiovascular risk. The National Cholesterol Educational Program (Adult Treatment Panel III-ATP III) and other authors have recently suggested the use of the term metabolic syndrome to identify a common cluster of metabolic abnormalities, defined when at least three out of five criteria are fulfilled: 1) abdominal obesity [waist circumference, >102 cm in men and >88 cm in women], 2) hypertriglyceridemia [≥150 mg/dl], 3) low HDL [<40 mg/dl in men and <50 mg/dl in women], 4) hypertension [≥130/85 mm Hg], and 5) elevated fasting glucose [≥110 mg/dl] [4, 6, 7]. Even normal weight individuals with increased amounts of abdominal adipose tissue can be metabolically obese, with insulin resistance and dyslipidemia [8, 9]. Visceral fat is a potent modulator of insulin action on hepatic glucose production [10]. The cells of the human fat tissue are able to produce several hormonal factors influencing the development and severity of the clinical outcome of the metabolic syndrome. Leptin, adiponectin, and resistin are among crucial factors called adipocytokies [5].

Leptin is a product of the obese (ob) gene and is generated predominantly in white adipose tissue [11]. It is involved in the maintenance of energy balance and body weight. In humans, peripheral blood leptin concentration is strongly correlated with the amount of body fat and body mass index [12]. The arcuate nucleus (ARC) of the hypothalamus serves as the leptin signaling center. It is known that the insulin/leptin-arcuate nucleus of the hypothalamus axis regulates energy homeostasis through control of appetite and energy expenditure. Both hormones rise in direct proportion to adipose mass; they cross the blood-brain barrier and have receptors in the ARC [13].

Adiponectin is another adipocyte-derived cytokine that plays an important role in regulating energy homeostasis and insulin sensitivity. Adiponectin is found in high concentrations in the peripheral circulation [14], and its circulating levels are diminished in obese patients and those with type 2 diabetes [15]. Moreover, adiponectin concentrations are inversely associated with central or overall adiposity [16, 17].

Resistin, a plasma protein, induces insulin resistance in rodents. Whereas rodent resistin is produced in adipocytes, macrophages are its major source in humans. Therefore resistin may be an inflammatory marker of atherosclerosis in humans [18–20].

At present, bariatric surgery is the most effective method to achieve the major goal in obesity treatment, long-term weight loss [21, 22]. It was documented that postsurgical weight loss improves almost all obesity-related comorbidities [23].

The aim of the study was to evaluate some adipocytokines and insulin, as well as parameters of metabolic syndrome of the obese patients for three and six months after vertical banded gastroplasty, in the time of the dynamic weight loss.

2 Statistical methods and experimental procedures

Seven males and two females, aged from 28 to 49 years (38.2±3.4) with long-lasting, simple obesity and the presence of metabolic syndrome (by ATP III criteria) were studied before vertical banded gastroplasty, and after three and six months after it. Blood serum leptin (DSL, USA kit; sensitivity-0.05 ng/mL; intra-assay precission-3.0%), adiponectin (R & D Systems kit, USA; sensitivity-0.25 ng/mL; intra-assay precission-4.7%) and resistin (R & D Systems kit, USA; sensitivity-0.026 ng/mL; intra-assay precission-5.3%) concentrations before and after treatment were evaluated by ELISA and insulin (IRI) by MEIA (Abbott, USA; sensitivity < 1 μU/ml; intra-assay precision – 4.1%) methods. The serum concentrations of total cholesterol (TCH), HDL-cholesterol (HDL), LDL-cholesterol (LDL), triglycerides (TG), and blood sugar (BS) were also performed. Furthermore, systolic (RR-S) and diastolic (RR-D) blood pressure (patients were without any hypotensive medication) as well as the body mass index (BMI) were measured. Waist circumference and insulin resistance index (HOMA-IR) were calculated.

All comparisons were carried out using Statgraphics Plus software. Statistical verifications were made using the normality Kolomogorov-Smirnov test. The statistical significance of differences among the groups was determined by Student's t-test or Cochran-Cox Q-test and Student's paired t-tests. The relationship between features was evaluated using the Pearson's correlation coefficient analyses. The values are presented as the mean ±SEM. P values$\leq$0.05 or less were considered statistically significant.

The study was approved by the Local Ethical Committee of the Medical University of Lodz.

3 Results

Three months after surgical treatment the values of BMI, waist circumference, RR-S, RR-D, and the blood concentrations of leptin decreased significantly (Table 1). We did not observe any significant differences in IRI, glucose, HOMA-IR, lipids profile (TCH, LDL, and TG), and blood levels of adiponectin and resistin after treatment (Table 1).

Table 1 Statistical comparisons between the studied parameters in obese subjects before (I) and 3 (II), as well as 6 (III) months after ventricular banded gastroplasty (VBG); x ± SEM, NS- not significant.

	Before operation (I)	Three months after surgery (II)	Six months after surgery (III)	Statistical significance
BMI (kg/m^2)	46.16±3.47	39.81±3.04	36.96±3.29	I vs.II, $p<0.001$ I vs. III, $p<0.001$ II vs III, $p<0.01$
Waist circumference (cm)	132.11±4.86	117.22±5.48	113.75±6.24	I vs. II, $p<0.01$ I vs. III, $p<0.001$ II vs. III, $p<0.05$
RR-S (mm Hg)	144.44±6.20	121.67±5.00	118.75±5.72	I vs. II, $p<0.001$ I vs. III, $p<0.01$ II vs. III, NS
RR-D (mm Hg)	92.78±4.64	82.22±4.64	73.75±4.60	I vs. II, $p<0.01$ I vs. III, $p<0.05$ II vs. III, NS
glucose (mg/dL)	85.44±2.17	83.44±2.94	80.75±2.32	NS
IRI (μU/mL)	11.43±1.84	8.68±1.51	8.00±1.81	NS
HOMA-IR	2.41+0.36	1.83+0.37	1.65±0.42	NS
TCH (mg/dL)	204.00±11.84	191.33±10.28	170.50±9.03	I vs. II, NS I vs. III, $p<0.05$ II vs. III, NS
LDL (mg/dL)	128.56±8.98	119.56±9.19	101.86±7.39	I vs. II, NS I vs. III, $p<0.05$ II vs. III, NS
HDL (mg/dL)	50.56±4.50	47.67±3.79	47.50±3.73	NS
TG (mg/dL)	131.56±11.37	119.67±11.67	106.00±12.80	I vs. II, NS I vs. III, $p<0.01$ II vs. III, NS
Leptin (ng/mL)	67.64±3.95	50.61±6.85	41.53±8.50	I vs. II, $p<0.05$ I vs. III, $p<0.05$ II vs. III, NS
Adiponectin (μg/mL)	9.46±2.40	11.95±3.09	11.44±3.14	NS
Resistin (ng/mL)	22.69±1.90	20.75±2.43	19.43±4.58	NS

Before surgical operation of all obese patients, no statistically significant correlations between studied parameters were noted. Three months later there were positive correlations between BMI and HOMA-IR, waist circumference and HOMA-IR, waist circumference and BMI, adiponectin and TCH, adiponectin and HDL, as well as negative correlations between adiponectin and RR-S, leptin and RR-S, adiponectin and insulin, and adiponectin and TG (Fig. 1, 2).

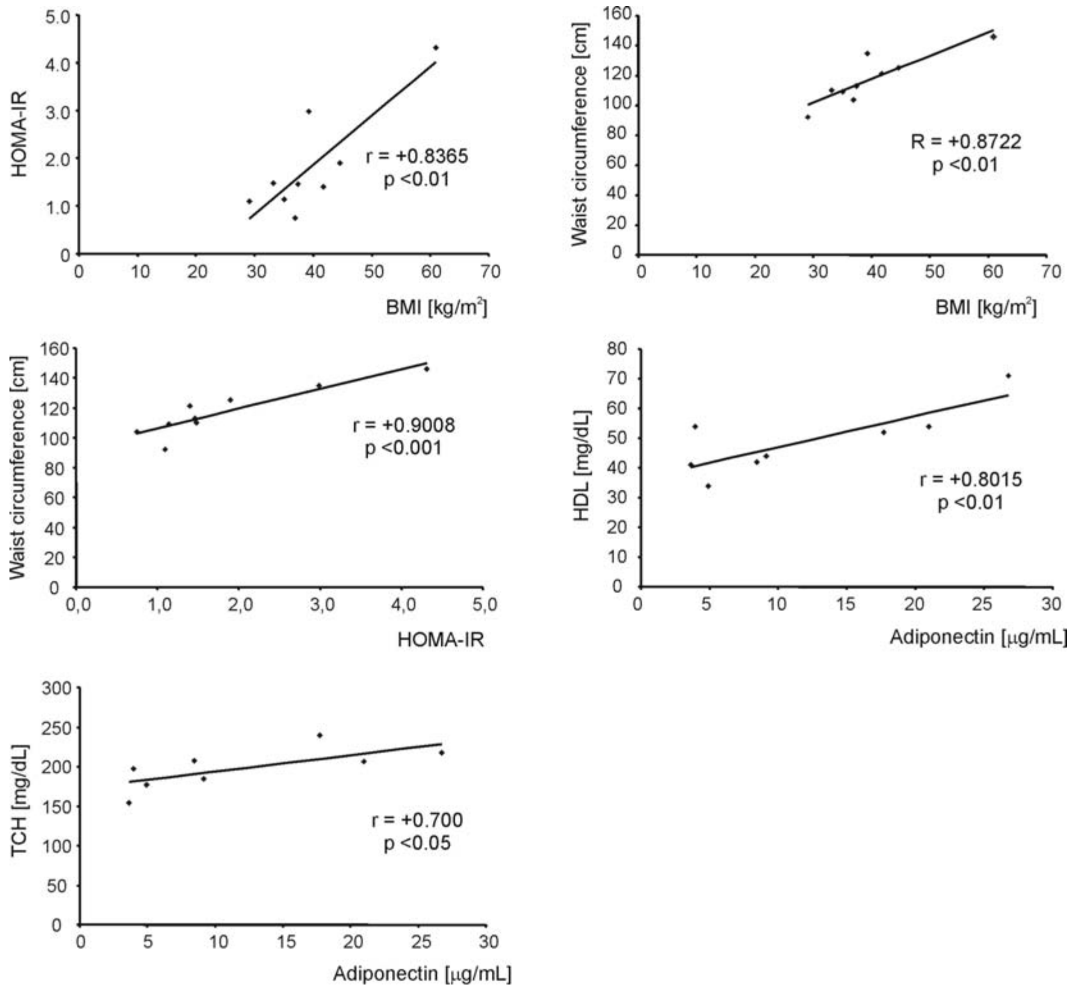

Fig. 1 Positive correlations of the studied parameters in obese patients 3 months after surgery.

Six months after surgical treatment, the values of BMI, waist circumference, RR-S, RR-D, and the blood concentrations of leptin, TCH, LDL, and TG decreased significantly (Table 1). We did not observe any significant differences in HOMA-IR, HDL, blood levels of glucose, IRI, adiponectin, and resistin after treatment (Table 1).

Six months later there were positive correlations between resistin and BMI, resistin and HOMA-IR, leptin and TG, TG and BMI, waist circumference and BMI, and waist circumference and HOMA-IR, as well as negative correlations between adiponectin and insulin, and between waist circumference and adiponectin (Fig. 3, 4).

4 Discussion

Intestinal malabsorption and gastric restriction are the two most obvious mechanisms that explain weight loss after bariatric surgery. The vertical banded gastroplasty (VBG) causes weight loss by limiting the capacity of the stomach to accommodate food and by constricting the flow of ingested nutrients [21–23]. VBG effectively limits the amount of

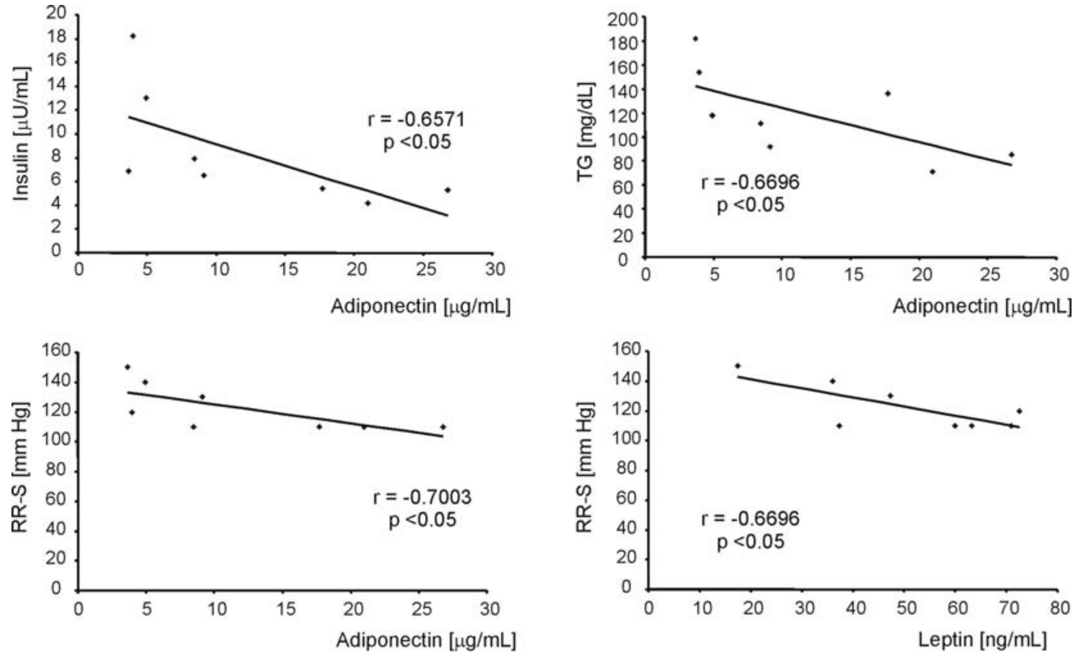

Fig. 2 Negative correlations of the studied parameters in obese patients 3 months after surgery.

food that can be consumed at one sitting and causes 30-50% reduction of excess body weight within the first 1-2 yr [22, 23].

All of our studied patients did not have any complications in the course of the operation as well as during post-operative period. They were very impressed and satisfied with postsurgical weight loss in such a short period of time (6 months). As expected, three and/or six months after surgical treatment, all our studied subjects lost body weight. The values of weight loss, BMI, waist circumference, RR-S, RR-D, lipids (TCH, LDL, TG), and leptin improved. Many studies also show that postsurgical weight loss improves all obesity-related comorbidities, including hypertension, dyslipidemias, diabetes, nonalcoholic steatohepatitis, sleep apnea and obesity-hypoventilation syndrome, reflux esophagitis, cardiac dysfunction, pseudotumor cerebri, arthritis, infertility, stress incontinence, and venous stasis ulcers [21, 23–28]. In our study, after a short period of medication, many interesting correlations between the studied parameters appeared. After VBG at the 6^{th} month, the correlations (positive) between resistin and BMI, resistin and HOMA-IR, as well as a negative relationship between adiponectin and insulin levels were the most impressive.

For a long time it has been known that obesity is linked to insulin resistance. Recently, many investigators have reported that adiposities secrete a bunch of bioactive peptides called adipocytokines, which play a pivotal role in energy homeostasis by affecting insulin sensitivity, glucose and lipid metabolism, food intake, and inflammation. A lot of evidence from animal and human studies suggests that adiponectin plays an important role in insulin sensitivity [29–33], inflammation [34], atherogenesis [35, 36], and lipid metabolism [29, 37], and thus influences hyperlipidemia and cardiovascular disease [34]. The relation

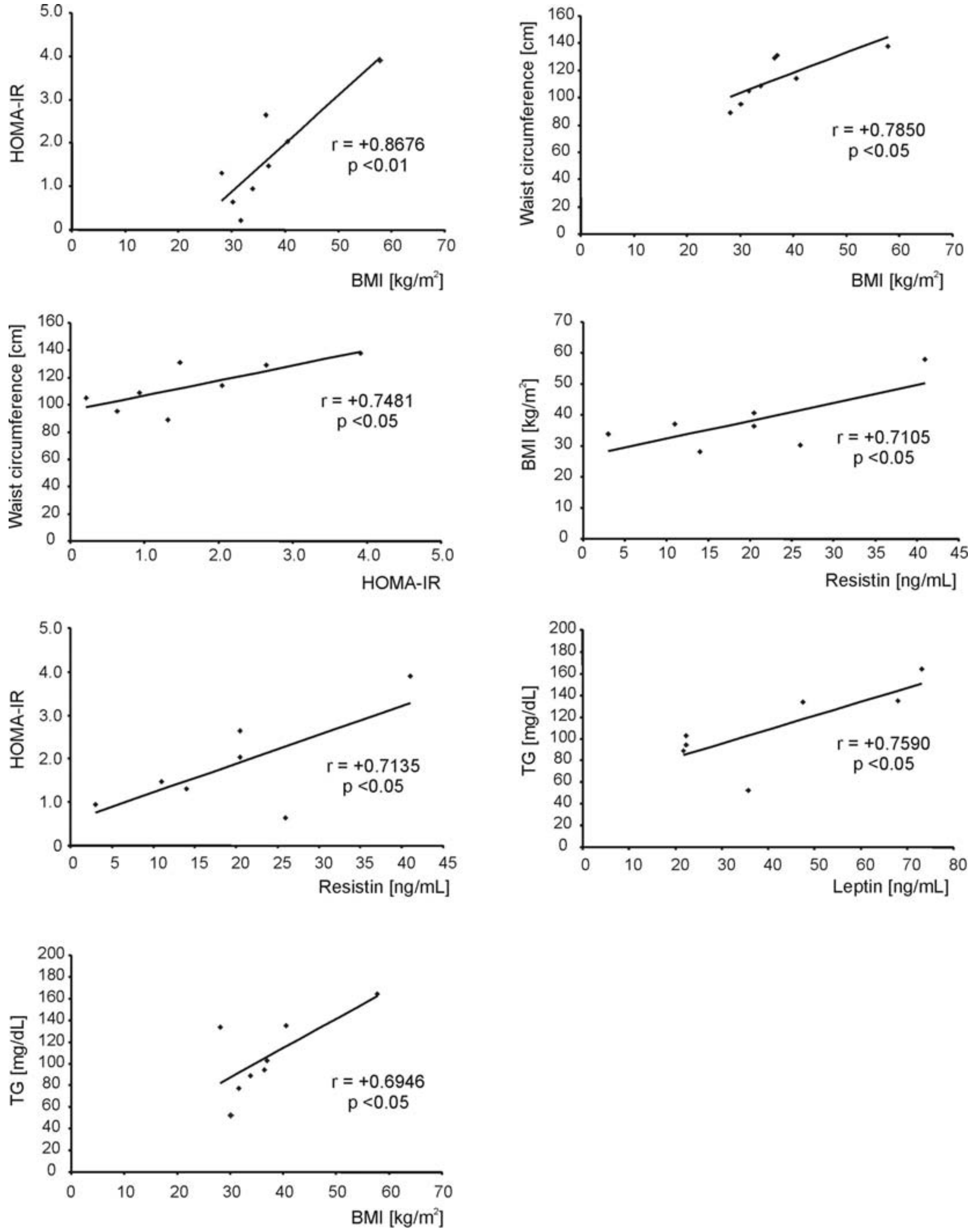

Fig. 3 Positive correlations of the studied parameters in obese patients 6 months after surgery.

between adiponectin and insulin sensitivity has been established in an animal model in which adiponectin administration reversed insulin resistance in lipoatrophic mice [30]. Moreover, the levels of adiponectin are lower in patients with type 2 diabetes or insulin resistance [38] and higher in humans treated with thiazolidinediones [39, 40]. It has been recently proposed that resistin plays a role in obesity-mediated insulin resistance [40, 41] and is also a proinflammatory molecule [14, 42]. It was also shown that increasing levels of

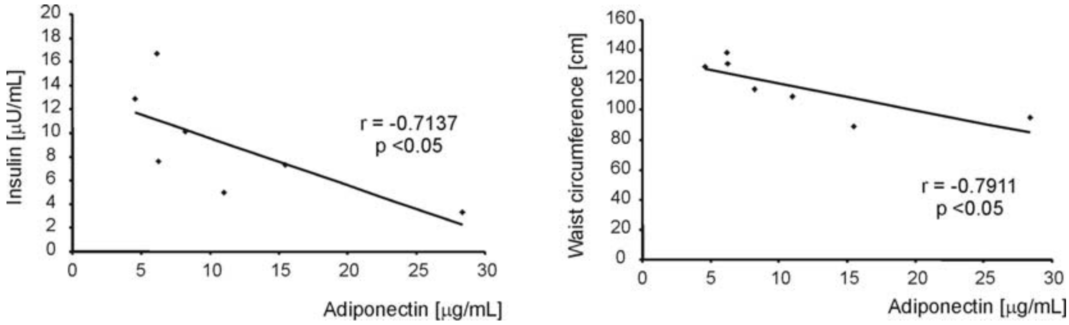

Fig. 4 Negative correlations of the studied parameters in obese patients 6 months after surgery.

leptin and decreasing levels of adiponectin correlated with worsening of insulin resistance in obese individuals [43]. Moreover, it was documented that leptin levels decreased and adiponectin rose following bariatric surgery. These changes correlate with weight loss and improvement in insulin [43]. Although resistin may play an important role in explaining insulin resistance, current animal and human studies show conflicting results.

Our study clearly shows that after VBG in our patients with metabolic syndrome, an unknown gastric factor appeared, influencing all the correlations in the studied variables. However, it is also possible that the lack of significant correlations between the studied parameters at baseline could be due to the small sample size of studied subjects.

In conclusion:

Vertical-banded gastroplasty is a valuable method in treatment of obese subjects, leading to a significant decrease in body weight and improvement in the main parameters of the metabolic syndrome in a few months after surgery;

Adipocytokines secreted by the adipose tissue, together with an unknown gastric factor, may be key factors in the control of some features of the metabolic syndrome.

Acknowledgment

Supported by the Medical University grant No 502-11-189 to J.K.

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