Medicina (Kaunas) 2013;49(1):9-14

Comparison of Changes in Blood Glucose, Insulin Resistance Indices, and Adipokine Levels in Diabetic and Nondiabetic Subjects With Morbid Obesity After Laparoscopic Adjustable Gastric Banding

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Key Words: *adiponectin; leptin; laparoscopic adjustable gastric banding.*

Summary. *Objective. The aim of the study was to evaluate blood glucose, insulin resistance indices, and adipokine (leptin and adiponectin) levels in morbidly obese individuals with and without type 2 diabetes mellitus and to compare the changes in these parameters 1 year after laparoscopic adjustable gastric banding surgery.*

Material and Methods. In total, 103 patients (37 subjects with and 66 subjects without type 2 diabetes mellitus) were studied preoperatively and again 1 year after laparoscopic adjustable gastric banding.

Results. One year after laparoscopic adjustable gastric banding, the leptin concentrations decreased significantly in both treatment groups, while the adiponectin levels increased significantly in the nondiabetic patients (11.19 μg/mL [SD 7.20] vs. 15.58 μg/mL [SD 7.8], P=0.003) and tended to increase in the group of the patients with type 2 diabetes mellitus (8.98 μg/mL [SD 6.80] vs. 13.01 μg/mL [SD 12.14], P>0.05). A considerable decrease in the insulin resistance indices was noted in the patients with type 2 diabetes mellitus 1 year after the intervention, and it was followed by a partial or complete remission of type 2 diabetes mellitus in 23 (85.19%) of the 27 investigated diabetic patients. The postoperative insulin resistance indices in the patients with type 2 diabetes mellitus became similar to the values in the nondiabetic subjects.

Conclusions. Weight loss after laparoscopic adjustable gastric banding is associated with a significant increase in adiponectin secretion in nondiabetic morbidly obese patients and with improvement in adiponectin secretion in type 2 diabetes individuals. In subjects with type 2 diabetes, this surgical intervention results in a significant reduction in blood glucose and insulin resistance.

Introduction

Obesity is a well-known risk factor for type 2 diabetes mellitus, and about 90% of the humans affected by this disease are overweight or obese in developed countries (1). Obese individuals develop insulin resistance (2); in turn, insulin resistance is the most important pathogenic factor for type 2 diabetes mellitus. Considerable efforts have been directed at understanding the mechanisms linking obesity with the development of insulin resistance, impaired glucose tolerance, and type 2 diabetes mellitus. This research has led to the concept that adipose tissue is more than just a simple energy storage compartment, but is also an important endocrine organ secreting many bioactive substances. These substances, named adipokines, were proved to be involved in a variety of functions, including glucose homeostasis, lipid metabolism, regulation of hunger and satiety, and energy balance (3). Adiponectin is an adipokine that seems to be secreted exclusively by adipocytes and is the most abundant adipose tissue-derived protein. In contrast to other adipokine levels (such as leptin, interleukin 6, and others) that are often elevated in obese subjects, the adiponectin level is reduced (4).

Other adipokine, leptin, plays an important role in controlling body weight by regulating energy intake and energy expenditure (5). Obese humans were shown to have an increased secretion of leptin, whereas weight loss was associated with a reduction in the leptin level (6). Besides the regulation of food intake, body weight, energy balance, and numerous other important processes, leptin was shown to have an impact on glucose metabolism by inhibiting β-cell insulin secretion and enhancing peripheral tissue insulin sensitivity (7). However, several cross-

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sectional studies demonstrated that leptin concentrations positively correlated with the indices of insulin resistance (8) irrespective of body mass index (9).

Scientific investigations have proven that morbid obesity is associated with the changes in adiponectin and leptin secretions (10). Surgical intervention is considered an efficient method of reducing body weight in morbidly obese patients and can be considered as a model to study the beneficial effects of a pronounced weight loss on glucose metabolism, insulin resistance, and adipokine levels. Bariatric surgery was proven to have numerous beneficial effects on a variety of metabolic disorders associated with obesity, causing the complete resolution of type 2 diabetes mellitus in up to 76.8% of diabetic patients (11). However, it is still not clear whether a significant weight loss after gastric banding in morbidly obese subjects with type 2 diabetes is accompanied by the changes in insulin resistance and adipokine levels similar to the ones that occur in nondiabetic patients. It is still not certain if adipokine levels are restored to the reference range in patients with type 2 diabetes mellitus after bariatric surgery and a significant weight loss.

The main aim of our study was to examine and compare the effect of a prolonged weight loss after laparoscopic adjustable gastric banding on adiponectin and leptin concentrations and their possible correlation with the changes in the parameters of body weight and insulin sensitivity in nondiabetic and diabetic morbidly obese patients.

Material and Methods

This prospective study included 103 morbidly obese patients referred for laparoscopic adjustable gastric banding. The study subjects were evaluated before and 1 year after the surgical intervention. The Lithuanian Bioethics Committee issued a permit to carry out this research, and all the subjects before the study procedures signed the written informed consent form.

The evaluation of the study participants involved medical history and physical examination, including anthropometric measurements (weight and height). Body mass index (BMI) was calculated as weight in kg divided by height in meters squared.

Venous blood samples were taken in the morning after 12–14 hours of fasting. The laboratory tests (fasting plasma glucose, HbA1c, and insulin concentrations) were performed in the Centre of Laboratory Diagnostics, Vilnius University Hospital Santariškių Klinikos, using standard laboratory methods.

Insulin resistance was estimated by calculating the homeostasis assessment-insulin resistance (HOMA-IR) index, using the formula introduced by Matthews in 1985 (12):

$$\text{HOMA-IR} = [\text{insulin } (\mu\text{U/mL}) \times \text{glucose (mmol/L)}]/22.5$$

The adipokine levels were determined using commercially available reagents. The serum adiponectin levels were measured by a radioimmunoassay using a Human Adiponectin RIA Kit (LINCO research, Missouri, USA). The leptin levels were determined by the immunoradiometric method, using Human Leptin IRMA DSL-23100 (Diagnostic Systems Laboratories Inc., Texas, USA) reagents.

Based on the diagnostic fasting plasma (blood) glucose value ($\geqslant$7.0 mmol/L), the subjects were divided into type 2 diabetes mellitus (DM(+), n=37) and nondiabetic (DM(–), n=66) groups, using the WHO 1998 diagnostic criteria (13). The study subjects underwent laparoscopic adjustable gastric banding in the Department of Surgery, Vilnius University Hospital Santariškių Klinikos. All the study patients were offered a re-examination 1 year after the surgical treatment; 64 subjects from DM(–) and 27 from DM(+) group consented to repeat the evaluation. The majority (n=20, 54%) of our DM(+) patients were recently or newly diagnosed and were on diet alone, 8 patients (21.6%) received treatment with metformin, and 9 (24.4%) were given 2 or more antidiabetic drugs.

Statistical Analysis. Statistical analysis was performed using the SPSS (Statistical Package for the Social Sciences) 15.0 software. The data were summarized using standard procedures. Descriptive statistics are presented as mean and standard deviation. The Student *t* test was used to analyze the data with normal distribution, whereas the Mann–Whitney *U* test was applied to compare the nonparametrically distributed parameters. The Spearman correlation coefficient *r* was calculated to explore the correlation between the variables. A *P* value of <0.05 was considered statistically significant.

Results

The baseline characteristics were evaluated in 66 DM(–) and 37 DM(+) subjects. Before the surgical intervention, the subjects from both study groups had similar BMI (47.0 kg/m^2 [SD, 6.9] vs. 48.4 kg/m^2 [SD, 8.1]). The mean age of the subjects was higher in the DM(+) group (50.2 [SD, 11.4] vs. 43.5 years [SD, 11.2], $P<0.005$); the proportion of the women in this study group was higher as compared with the DM(–) group (male-to-female ratio 1:1.63 vs. 1:2.3, respectively) ($P<0.01$). As expected, the DM(+) group had higher baseline blood glucose (7.9 mmol/L [SD, 2.8] vs. 5.4 mmol/L [SD, 0.7], $P<0.0001$), HbA1c (7.0% [SD, 1.49] vs. 5.7% [SD, 0.6], $P<0.0001$), insulin levels (36.7 μU/mL [SD, 40.5] vs. 18.0 μU/mL [SD, 10.0], $P<0.001$), and HOMA-IR index (14.37 [SD, 19.62] vs. 4.44 [SD, 2.78], $P<0.0001$).

One year after laparoscopic adjustable gastric banding, BMI decreased significantly and to the same extent in both study groups (40.4 kg/m² [SD 7.8] in DM(−) vs. 41.9 kg/m² [SD 9.4] in DM(+)).

Effect of Body Weight Loss on Glucose Metabolism and Insulin Resistance. Blood glucose was reduced 1 year after the surgical treatment in the DM(+) group (7.9 mmol/L [SD, 2.8] vs. 6.1 mmol/L [SD, 1.5], P=0.01)) (Table). Based on a previously proposed definition of diabetes cure (14), we observed a partial or complete remission of type 2 diabetes mellitus in 23 (85.19%) of the 27 patients in the DM(+) group 1 year after laparoscopic adjustable gastric banding, of whom 11 were in a complete remission of diabetes; in 4 patients (14.81%), type 2 diabetes mellitus was persisting. There were no data available on the glucose metabolism status postoperatively in 10 subjects of the DM(+) group. The comparison of the subjects from the DM(+) group with persistent and remittent type 2 diabetes mellitus revealed that the patients with persistent diabetes mellitus postoperatively had a significantly higher BMI and HOMA-IR index; they also tended to have a lower adiponectin level, although this difference did not reach statistical significance due to a small number of the subjects studied.

The subjects of the DM(−) group had a statistically significant reduction in the HbA1c level 1 year after the surgical treatment (Table). The changes in HbA1c could be caused by the reduction in postprandial glycemia, which was not measured in our study because fasting blood glucose in this study group was similar before and after the surgical intervention.

In the DM(−) group, the HOMA-IR index was significantly higher preoperatively when compared with the postoperative values (4.44 [SD, 2.78] vs. 2.98 [SD, 1.81], P=0.001). An even more prominent reduction in insulin resistance was observed in the DM(+) group: the HOMA-IR index dropped from 14.37 (SD, 19.63) to 3.67 (SD, 2.50) (P=0.03). After the surgical treatment, the HOMA-IR index became similar in the DM(+) and DM(−) groups (3.67 [SD, 2.50] vs. 2.98 [SD, 1.82]). Analogous changes were noted in the insulin concentrations. Before laparoscopic adjustable gastric banding, prominent hyperinsulinemia in the DM(+) group was observed; the insulin concentration in this group was almost 2 times higher than in the DM(−) group. After the surgical intervention, the insulin levels became comparable in the diabetic and nondiabetic subjects (12.9 μU/mL [SD 8.1] vs. 12.4 μU/mL [SD 6.7]).

Effect of Body Weight Reduction on Adipokine Levels in Subjects With and Without Type 2 Diabetes Mellitus. The surgical intervention caused similar changes in the adipokine levels in our study groups (Table). The adiponectin level significantly increased (11.19 μg/mL [SD, 7.20] vs. 15.58 μg/mL [SD, 7.80], P=0.003), and the leptin level decreased (38.74 ng/mL [SD, 17.43] vs. 29.07 ng/mL [SD, 17.79], P=0.01) 1 year after adjustable gastric banding in the nondiabetic subjects (Fig.). Similar changes were observed in the leptin levels of the diabetic

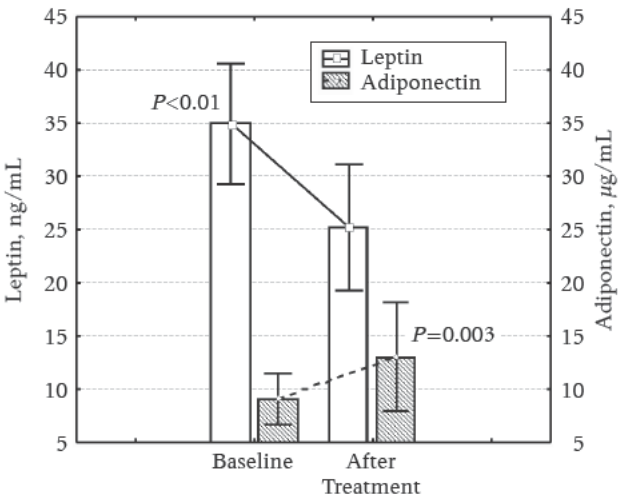

Fig. Adipokine levels before and 1 year after laparoscopic adjustable gastric banding in the DM(−) group

Table. Comparison of Anthropometric and Laboratory Characteristics of Study Groups Before and 1 Year After Laparoscopic Adjustable Gastric Banding

Variable	DM(−)		P	DM(+)		P
	Before Banding (n=66)	1 Year After Banding (n=64)		Before Banding (n=37)	1 Year After Banding (n=27)	
BMI, kg/m²	47.0 (6.9)	40.4 (7.8)	0.0001	48.7 (8.1)	41.9 (9.4)	0.003
Fasting plasma glucose, mmol/L	5.4 (0.7)	5.2 (0.6)	NS	7.9 (2.8)	6.1 (1.5)	0.01
HbA1c, %	5.7 (0.6)	5.4 (0.5)	0.01	7.0 (1.5)	5.9 (0.7)	0.003
HOMA-IR index	4.44 (2.78)	2.98 (1.81)	0.001	14.37 (19.63)	3.7 (2.5)	0.03
Insulin, mU/L	18.0 (10.0)	12.4 (6.7)	0.001	36.7 (40.5)	12.9 (8.2)	0.005
Leptin, ng/mL	38.74 (17.43)	29.07 (17.79)	0.01	34.91 (15.54)	25.17 (14.17)	0.03
Adiponectin, μg/mL	11.19 (7.20)	15.58 (7.80)	0.003	8.98 (6.80)	13.01 (12.14)	NS

Values are mean (standard deviation).
BMI, body mass index; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis assessment-insulin resistance; NS, not significant.

patients (34.91 ng/mL [SD, 15.54] vs. 25.17 ng/mL [SD, 14.17], P=0.003); adiponectin tended to increase, but the difference did not reach statistical significance probably due to a small number of the studied individuals in the DM(+) group (8.98 μg/mL [SD 6.80] vs. 13.01 μg/mL [SD 12.14], P>0.05).

The correlation analysis revealed that the adiponectin level did not significantly correlate with BMI in both study groups, whereas leptin had a strong and significant positive association (r=0.74, P<0.0001).

Effect of Glucose Metabolism Status and Insulin Resistance on Adipokine Levels. To assess the impact of the glucose metabolism status on the adiponectin levels, the baseline adiponectin concentrations were compared in our DM(+) and DM(–) groups. The groups were similar with regard to BMI, whereas fasting plasma glucose, HbA1c, and insulin resistance indices were higher in the DM(+) group. Although there was a trend toward a lower adiponectin level in the diabetic subjects when compared with the nondiabetic subjects (8.98 μg/mL [SD, 6.80] vs. 11.19 μg/mL [SD, 7.20]), the difference did not reach statistical significance.

In the pooled study population, there was a significant negative correlation between the adiponectin level and the HOMA-IR index before the surgical intervention (r=–0.26, P<0.01). This dependence became more prominent 1 year after the surgical treatment (r=–0.37, P<0.01). The leptin levels correlated negatively with the HOMA-IR index before gastric banding (r=–0.22, P<0.05); however, this correlation turned positive 1 year after the surgical intervention (r=0.26, P<0.05). The leptin and adiponectin levels correlated negatively with the plasma glucose concentration, but did not correlate with each other both before and 1 year after laparoscopic adjustable gastric banding.

The analysis in the study groups revealed that there was a significant negative correlation between the adiponectin level and the HOMA-IR index in the nondiabetic subjects (r=–0.20, P<0.05); however, the associations with blood glucose and HbA1c were not significant (P>0.05). In the diabetic subjects, there was a significant negative correlation between the adiponectin level and HbA1c before the surgical intervention (r=–0.46, P<0.05); however, this association was lost 1 year after gastric banding (P>0.05). Like in the nondiabetic subjects, there was a significant negative association between the adiponectin level and the HOMA-IR index in the diabetic subjects (r=–0.3, P<0.05).

Discussion

The treatment of morbid obesity with conservative measures and pharmacotherapy often fails to produce a permanent reduction in body weight. Bariatric surgery is the only option to date resulting in a substantial and durable long-term weight loss (15). Our results correspond to the results of other studies (15, 16) and confirm the effectiveness of laparoscopic adjustable gastric banding in treating morbid obesity and causing a reduction of about 14% of weight both in diabetic and nondiabetic patients.

Obesity is clearly linked to insulin resistance and hyperglycemia, and weight loss is associated with the improvement in glucose metabolism. Like other authors (17–19), we also observed a significant reduction in the insulin resistance and HbA1c level in the nondiabetic and diabetic morbidly obese patients after gastric banding. The reduction in weight and insulin resistance caused a partial or complete remission of type 2 diabetes mellitus in at least 85% of our diabetic patients 1 year after the surgical intervention. These results confirm a highly beneficial effect of laparoscopic adjustable gastric banding in subjects with type 2 diabetes mellitus on weight reduction and glucose metabolism showed by other researchers (11, 20).

To our knowledge, there have been no studies published by now comparing the effect of weight loss after laparoscopic adjustable gastric banding on insulin resistance indices in diabetic and nondiabetic patients. Our study revealed that the effect of weight loss on insulin resistance and glucose metabolism was more prominent in the patients with type 2 diabetes mellitus when compared with the nondiabetic patients. The insulin level and the HOMA-IR index, being significantly higher in the subjects with type 2 diabetes mellitus preoperatively, reduced substantially and did not differ from the nondiabetic subjects 1 year after the surgical treatment. The significantly higher fasting plasma glucose and HbA1c values postoperatively in our diabetic subjects as compared with the nondiabetic subjects could be explained by the reduced β-cell function in patients with type 2 diabetes mellitus.

In several cross-sectional studies, the lower plasma levels of adiponectin in comparison with the healthy controls were documented in human subjects with obesity, insulin resistance and type 2 diabetes, and the adiponectin blood level was shown to be negatively correlated with anthropometric variables and indices of insulin resistance (21–23).

Although the associations of a low adiponectin concentration with obesity and type 2 diabetes mellitus are rather well studied, the data on adiponectin metabolism in morbidly obese diabetic patients and on the changes following a significant weight loss after bariatric surgery in these patients are still lacking. Our (24, 25) and other studies (23) have previously demonstrated that patients with type 2 diabetes mellitus have the reduced levels of adiponectin when compared with nondiabetic subjects

with similar anthropometric characteristics. In our present study, there was no significant difference in the adiponectin levels in the morbidly obese nondiabetic and diabetic subjects. This finding indicates that morbid obesity could be associated with a marked alteration in adiponectin secretion in both nondiabetic and diabetic patients, and this alteration is ameliorated by a significant weight loss. In human trials, the leptin concentration was shown to be either reduced or unchanged because of type 2 diabetes mellitus (8, 26). The variable results are not surprising because subjects differed with respect to the extent of obesity and treatment regimens. Thus, a controversy concerning leptin concentrations in type 2 diabetes mellitus still exists, and there is a lack of knowledge about leptin levels in morbidly obese diabetic patients.

Previous studies demonstrated that weight loss after bariatric surgery resulted in a reduction in leptin levels and an increase in adiponectin levels in nondiabetic or mixed populations (17–19, 27, 28), but to our knowledge, no study comparing the effect of weight loss on adipokine levels in diabetic and nondiabetic patients has been performed. The results of our study indicated that the beneficial effect of weight loss on the adiponectin secretion after laparoscopic adjustable gastric banding was evident in the nondiabetic morbidly obese patients and tended to increase 1 year after gastric banding in the diabetic subjects, although this increase did not reach statistical significance probably due to a small number of the investigated individuals. Our data suggest that adiponectin might play an important role in the improvement in insulin resistance and glucose metabolism in morbidly obese individuals during a significant weight loss.

The findings of our present study are consistent with the results of other studies (29, 30) and our previous studies (24, 25) and demonstrate that the adiponectin level correlates negatively with the indices of insulin resistance rather than with the measures of overall obesity such as BMI in both diabetic and nondiabetic morbidly obese patients. The leptin concentration correlates positively with BMI, but the association of this adipokine level and insulin resistance is more complex and warrants further investigation.

Conclusions

Our study demonstrates that laparoscopic adjustable gastric banding results in a similar weight loss in nondiabetic and diabetic morbidly obese patients. This significant weight loss is associated with an increase in adiponectin secretion in nondiabetic patients and the tendency for the adiponectin level to increase together with a significant reduction in blood glucose and insulin resistance in individuals with type 2 diabetes mellitus. In both nondiabetic and diabetic morbidly obese patients, weight reduction is associated with a marked decrease in the leptin level. The adiponectin level correlates negatively with insulin resistance indices, but not with BMI, whereas the association of the leptin concentration and insulin resistance is more complex.

Statement of Conflict of Interests

The authors state no conflict of interest.

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Received 19 October 2011, accepted 21 January 2013