A prospective 4-year study of insulin resistance and adipokines in morbidly obese diabetic and non-diabetic patients after gastric banding

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Abstract

Introduction: *There are insufficient data regarding the changes in adipokine levels after laparoscopic adjustable gastric banding (LAGB) in diabetic and non-diabetic patients and their effects on insulin resistance and type 2 diabetes remission.*
Aim: *To assess leptin, adiponectin, and insulin resistance changes after LAGB in diabetic and non-diabetic morbidly obese patients.*
Material and methods: *One hundred and three patients (37 with and 66 without type 2 diabetes) underwent LAGB from January 2009 to January 2010. Glycated hemoglobin, insulin, adipokine levels and insulin resistance were evaluated preoperatively, and 1 and 4 years after LAGB.*
Results: *The mean patient age was 45.9 ±11.7 years and mean preoperative body mass index was 47.5 ±7.3 kg/m^2. A total of 80 of 103 patients (77.6%) completed the 4-year follow-up. After 4 years the mean excess weight loss was 38.8% and 39.5% in diabetic and non-diabetic patients respectively. Leptin levels decreased significantly in both groups at 1 year, but after 4 years this was noted only in non-diabetic patients. After 1 year adiponectin levels increased significantly only in non-diabetic patients ($p = 0.003$) and remained almost the same at 4 years. A significant decrease in insulin resistance was noted in both groups 1 year after LAGB and diabetes remission was observed in 23 (62.1%) patients. There was a negative correlation between preoperative insulin resistance and adiponectin levels throughout the follow-up period. Leptin levels positively correlated with BMI throughout the study period (baseline $r = 0.45$; $p < 0.001$; after 1 year $r = 0.71$; $p < 0.001$; after 4 years $r = 0.68$; $p < 0.001$). There was no significant correlation between leptin and adiponectin concentrations preoperatively or after 1 year; however, at 4 years it was significant ($r = 0.27$; $p < 0.02$).*
Conclusions: *The most significant metabolic changes occurred within 1 year after LAGB. The 4-year follow-up revealed stabilization in metabolic indices rather than significant improvement.*

Key words: *laparoscopic adjustable gastric banding, type 2 diabetes, adiponectin, leptin, insulin resistance.*

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Introduction

The rising prevalence of overweight and obesity has been described as a global pandemic. According to the World Health Organization (WHO), more than 1.9 billion adults were overweight and over 600 million of these were obese in 2014 [1]. Obesity is a major risk factor of type 2 diabetes (T2DM). About 90% of diabetic patients are overweight or obese [2].

Although the etiology of obesity is multifactorial, one element gaining momentum is the role of the adipose tissue and its secreted adipokines [3]. Adipokines are known to act both locally and systemically and express a variety of receptors, thereby allowing them to respond to signals from other hormonal networks and the central nervous system [3, 4]. With the capacity to both direct efferent signals and respond to afferent signals, adipose tissue forms a vast communication network between numerous organs within the body. The excess adipose tissue has been shown to alter the adipokine profile, thereby initiating a detrimental cascade of metabolic disturbances including hyperglycemia, insulin resistance, and dyslipidemia [5]. In turn, insulin resistance is the most important factor in the development of T2DM.

Although the associations of low adiponectin concentration with obesity and T2DM are well studied, the data on the adiponectin changes in morbidly obese diabetic patients undergoing laparoscopic adjustable gastric banding (LAGB) are still fragmented.

Obese humans were shown to have increased secretion of leptin, whereas weight loss was associated with the reduction of leptin level [6]. Besides 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].

Bariatric/metabolic surgery leads to rapid and sustained improvement in insulin resistance and T2DM.

Aim

The main aim of our study was to evaluate the effect of weight loss on adiponectin and leptin concentrations and insulin sensitivity in non-diabetic and diabetic morbidly obese patients undergoing LAGB.

Material and methods

From December 2009 to January 2010 a total of 103 morbidly obese patients underwent LAGB at the University Hospital. Patients were evaluated before, 1 and 4 years after LAGB. All procedures performed in the study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments. The study was reviewed and approved by the Lithuanian Bioethics Committee. Informed consent was obtained from all individual participants included in the study.

Preoperative evaluation was performed by a multidisciplinary team, consisting of an endocrinologist, gastroenterologist, dietitian, cardiologist and bariatric surgeon. Height, waist circumference, and body weight were measured to the nearest 0.1 cm and 0.1 kg respectively. Venous blood samples were taken after an overnight fast.

Blood tests consisted of fasting plasma glucose (enzymatic method), glycated hemoglobin (HbA_{1c}) (automated high-performance liquid chromatography system), and insulin (ELISA method). Serum adiponectin levels were measured by radioimmunoassay using the Human Adiponectin RIA Kit (LINCO Research, Missouri, USA). Leptin levels were measured by an immunoradiometric method using Human Leptin IRMA DSL-23100 (Diagnostic Systems Laboratories Inc., Texas, USA) reagents.

Insulin resistance was estimated by calculating the homeostasis assessment-insulin resistance (HOMA-IR) index: HOMA-IR = insulin (μU/ml) × glucose (mmol/l)/22.5 [8].

Based on American Diabetes Association 2010 diagnostic criteria [9], patients were divided into diabetic (DM) and non-diabetic (ND) groups.

All patients underwent a standard LAGB using the *pars flaccida* technique, which was described earlier [10]. Patients were repeatedly evaluated 1 and 4 years postoperatively.

Statistical analysis

Statistical analysis was performed using SPSS version 21.0 (SPSS Inc., Chicago). The Pearson χ^2 or Fisher's exact test was used to test for differences in categorical variables and the *t*-test or Mann-Whitney 2-sample test for continuous variables depending on the distribution. Spearman's correlation was used to evaluate the correlation between the variables. A p-value < 0.05 was considered statistically significant.

Results

From January 2009 to January 2010, 103 (37 DM and 66 ND) patients underwent LAGB. Baseline characteristics are presented in Table I. The mean preoperative age in both groups was 45.9 ±11.7 years; 69 (67%) patients were women and 34 (33%) were men. Both study groups had similar preoperative body mass index (BMI). The proportion of females was higher in the DM group. The DM group patients had higher baseline blood glucose, HbA_{1c}, insulin levels and HOMA-IR index. Twenty (54%) DM patients were recently or newly diagnosed and were on a diet only, 8 (21.6%) patients were on metformin treatment, and 9 (24.4%) were on two or more antidiabetic drugs.

A total of 91 (88.3%) and 80 (77.6%) patients were repeatedly evaluated after 1 and 4 years respectively. During 4 years 23 (7 DM and 16 ND) patients were lost to follow-up: 4 (3.8%) patients died from unrelated causes, 6 (5.8%) had their band removed, and 13 (12.6%) patients were unable to come. One death was caused by lung cancer, and the others were the result of acute cardiovascular events (1 to 4 years postoperatively).

After 1 year BMI decreased significantly from 47.0 ±6.9 to 40.4 ±7.8 and from 48.7 ±8.1 to 41.9 ±9.4 in ND and DM groups respectively (Table II). After 4 years there was a further significant BMI decrease in both study groups (BMI was 36.3 ±7.8 in the ND group and 37.1 ±8.1 in the DM group). Percentage excess weight loss (%EWL) changes were similar in both groups after 1 and 4 years.

Effect of body weight loss on glucose metabolism

Blood glucose (7.9 ±2.8 vs. 6.1 ±1.5 mmol/l; $p = 0.005$) and HbA_{1c} levels (7.0 ±1.5 vs. 5.9 ±0.7; $p = 0.001$) decreased significantly 1 year after LAGB in the DM group. There was no further significant decrease in glucose or HbA_{1c} level after 4 years. After 1 year ND group patients had a statistically significant reduction only in HbA_{1c} levels, but not in glucose concentration (Table II). The subsequent follow-up did not reveal an additional significant decline in glucose or HbA_{1c} level after 4 years.

After 1 year T2DM remission was observed in 23 (62.16%) patients. One DM patient experienced remission and 1 patient who experienced significant weight regain developed de novo T2DM at 4 years.

Effect of body weight loss on insulin resistance

After 1 year a significant decrease in the insulin resistance index HOMA-IR was noted in DM (9.76

Table I. Baseline characteristics in both study groups

Variable	All patients	ND	DM	*P*-value
Number of patients, *N*	103	66	37	–
Sex (male/female)	34/69	20/46	14/23	–
Age [years]	45.9 ±11.7	43.5 ±11.2	50.2 ±11.4	0.006
Body weight [kg]	137.6 ±24.4	135.7 ±21.8	141.7 ±28.9	> 0.05
BMI [kg/m^2]	47.5 ±7.3	47.0 ±6.9	48.7 ±8.1	> 0.05
EBMI [kg/m^2]	22.5 ±7.4	21.8 ±6.8	23.7 ±8.4	> 0.05
Glucose [mmol/l]	6.3 ±2.2	5.4 ±0.7	7.9 ±2.8	0.0001
HbA_{1c} (%)	6.1 ±1.1	5.7 ±0.6	7.0 ±1.5	0.0001
Insulin [µU/ml]	20.9 ±11.9	17.8 ±9.9	26.6 ±18.3	0.001
HOMA-IR	3.59 ±4.9	4.38 ±2.7	9.76 ±8.3	0.0001
Leptin [ng/ml]	37.6 ±16.6	38.7 ±17.0	37.0 ±16.5	> 0.05
Adiponectin [µg/ml]	10.3 ±6.9	11.2 ±7.0	8.82 ±6.8	> 0.05

ND – non-diabetic patients, DM – diabetic patients, BMI – body mass index, EBMI – excess BMI, EW – excess weight. Values are expressed as mean ± SD unless stated otherwise.

Table II. Comparison of anthropometric and laboratory characteristics in non-diabetic patients before, 1 and 4 years after LAGB

Variable	Before (n = 66)	After 1 year (n = 64)	After 4 years (n = 56)	P^1-value	P^2-value
BMI [kg/m^2]	47.0 ±6.9	40.4 ±7.8	36.3 ±7.8	0.0001	0.01
%EWL	NAP	28.3 ±18.1	39.5 ±24.5	–	0.01
Glucose [mmol/l]	47.0 ±6.9	5.2 ±0.6	5.1 ±0.5	NS	NS
HbA_{1c} (%)	5.7 ±0.6	5.4 ±0.5	5.5 ±0.5	0.01	NS
HOMA-IR	4.3 ±2.7	2.9 ±1.7	2.11 ±2.1	0.001	0.05
Insulin [mU/l]	17.8 ±9.9	12.2 ±6.5	9.0 ±8.3	0.001	0.03
Leptin [ng/ml]	38.7 ±17.0	27.9 ±17.8	19.4 ±15.8	0.002	0.01
Adiponectin [µg/ml]	11.2 ±7.0	15.3 ±7.7	16.6 ±11.8	0.005	NS

P^1 – baseline compared with 1 year, P^2 – 1 year compared with 4 years, NAP – not applicable, NS – not significant.

±8.3 vs. 3.5 ±2.5; p = 0.001) and ND patients (4.38 ±2.7 vs. 2.90 ±1.7; p = 0.001). After 4 years a significant decline in insulin resistance was noted in ND patients (p = 0.05), but not in DM patients. Analogous changes were observed for insulin concentrations (Tables II, III). After 1 year there was a negative correlation between %EWL and insulin resistance, glucose and insulin levels. After 4 years all correlations except for glucose remained inversely related.

Effect of body weight reduction on adipokine levels

Adiponectin levels significantly increased (11.2 ±7.0 vs. 15.3 ±7.8 µg/ml; p = 0.005) and leptin levels decreased (38.7 ±17.0 vs. 27.9 ±17.8 ng/ml; p = 0.002) 1 year after LAGB in ND patients. In DM patients leptin levels decreased significantly (37.0 ±16.5 vs. 25.1 ±14.1 ng/ml; p = 0.01), but the rise of adiponectin levels was not significant (8.8 ±6.8 vs. 13.0 ±11.9 µg/ml; p > 0.05). After 4 years adiponectin levels increased in both groups, but the difference was not significant; however, leptin levels significantly decreased only in the ND group (p = 0.01).

Effect of glucose metabolism status and insulin resistance on adipokine levels

A correlation between %EWL and adiponectin secretion was observed after 1 and 4 years of follow-up in both groups. Throughout the study period,

Table III. Comparison of anthropometric and laboratory characteristics in diabetic patients before, 1 and 4 years after LAGB

Variable	Before (n = 37)	After 1 year (n = 27)	After 4 years (n = 24)	P^1-value	P^2-value
BMI [kg/m^2]	48.7 ±8.1	41.9 ±9.4	37.1 ±8.1	0.003	0.05
%EWL	NAP	28.6 ±18.3	38.8 ±24.5	–	NS
Glucose [mmol/l]	7.9 ±2.8	6.1 ±1.5	5.9 ±2.4	0.005	NS
HbA_{1c} (%)	7.0 ±1.5	5.9 ±0.7	6.1 ±1.1	0.001	NS
HOMA-IR	9.7 ±8.3	3.5 ±2.5	3.1 ±2.6	0.001	NS
Insulin [mU/l]	26.5 ±18.3	12.4 ±8.0	11.0 ±6.6	0.005	NS
Leptin [ng/ml]	37.0 ±16.5	25.1 ±14.1	22.4 ±18.0	0.01	NS
Adiponectin [µg/ml]	8.8 ±6.8	13.0 ±11.9	11.7 ±7.9	NS	NS

P^1 – baseline compared with 1 year, p^2 – 1 year compared with 4 years, NAP – not applicable, NS – not significant.

a strong positive correlation was observed between %EWL and leptin concentrations.

After 1 year we found a negative correlation in ND patients between adiponectin and insulin levels (r = –0.31; p = 0.03), insulin resistance correlated with adiponectin levels and these correlations persisted during the 4-year follow-up period.

In diabetic patients, there was a statistically significant negative correlation between adiponectin and preoperative HbA_{1c} levels (r = –0.46; p < 0.02); however, this association was lost after 1 year. Despite this non-uniform adiponectin secretion in different follow-up periods a strong negative correlation between adiponectin and insulin levels was noted.

Discussion

Our data showed favorable effects on glucose metabolism in DM patients 1 year after LAGB, which remained similar during the 4 years of follow-up.

There are insufficient data regarding the change of insulin resistance and adiponectin levels after LAGB in diabetic and ND patients. We found that insulin resistance and glucose metabolism in diabetic patients are mostly affected during the first year. No further improvement in insulin resistance and glucose levels was observed after 4 years. In contrast, ND patients demonstrated a persistent decline of insulin resistance during 4 years of follow-up. Preoperative HOMA-IR index and insulin levels were significantly higher in DM patients; however, after 1 year they substantially decreased and were not statistically different from the results of ND patients. The significantly higher fasting plasma glucose and HbA_{1c} values postoperatively in diabetic patients could be explained by reduced β-cell function.

Previous studies demonstrated that adiponectin levels are reduced in diabetic patients [11]. In our study, there were no significant differences in preoperative adiponectin levels between ND and DM patients. This finding indicates that morbid obesity could be associated with marked alteration in adiponectin secretion in ND patients, and this alteration is ameliorated by weight loss.

Previous studies found that weight loss after bariatric surgery results in a reduction of leptin and increase of adiponectin levels in ND or mixed populations [12, 13]; however, the data comparing the effect of weight loss on adipokine levels in diabetic and ND patients are limited. The results of our study indicate that adiponectin secretion in ND patients is mostly affected during the first year after LAGB. We also observed increased levels of adiponectin in DM patients, but the difference was not significant. The further rise in adiponectin levels during 4 years of follow-up was not significant.

Insulin resistance appears to be the major common finding in individuals with obesity, glucose intolerance or T2DM. Previous hyperinsulinemic euglycemic clamp studies demonstrated that adiponectin levels are suppressed in both DM and ND subjects [14]. Both *in vitro* and *in vivo* studies have demonstrated that insulin itself may lead to down-regulation of adiponectin secretion from fat cells [15, 16]. Several studies have reported that insulin-sensitizing agent-induced improved insulin resistance and reduced insulin levels markedly increased adiponectin concentrations [16, 17]. In our study, DM individuals were not treated with insulin-sensitizing agents.

We believe that weight loss-induced improvement of insulin resistance and glucose metabolism in DM patients is more complex since insulin resistance and insulin secretion improved during the first year, but it was not followed by a significant increase in adiponectin levels. Consistent with our results, several studies suggest that adiponectin concentrations are more closely related to differences in insulin resistance than obesity [18, 19].

Obesity is clearly linked to insulin resistance, hyperglycemia, and T2DM; thus weight reduction is associated with the improvement in glucose metabolism. The remission and improvement rates of T2DM closely depend on the criteria used [20]. In 2009, a consensus group from the American Diabetes Association (ADA) developed a standardized definition of remission in T2DM that can be used in clinical studies [21]. Complete remission was defined as glycated hemoglobin (A_{1c}) < 6% and fasting glucose < 5.6 mmol/l, and partial remission as A_{1c} < 6.5% and fasting glucose 5.6–6.9 mmol/l, both lasting ≥ 1 year following bariatric surgery in the absence of medical therapy. Prolonged remission was defined as complete remission lasting ≥ 5 years. In 2011, the International Diabetes Federation became the second organization to introduce criteria defining the improvement and optimization of the metabolic state in patients with T2DM [22].

Comparable to previous reports [13, 23, 24], we found a significant reduction of insulin resistance

and HbA_{1c} levels in DM and ND patients. After 1 year remission of diabetes was observed in 62% of the patients. The remission rate remained unchanged during 4 years. These results confirm the highly beneficial effect of LAGB in subjects with T2DM on weight reduction and glucose metabolism, as also reported by other researchers [25].

The reported rate of improvement or resolution of type 2 diabetes following bariatric surgery in the short term ranges between 47% and 98%, while a shorter duration of diabetes, closer follow-up, and better glycemic control before surgery are associated with better results [26–28]. Based on our data, we suggest that the most significant metabolic changes in glucose and adipokine levels are registered within 1 year after LAGB.

The 4 years of follow-up revealed stabilization rather than a significant improvement in metabolic indices in both DM and ND patients because the continuing decrease in BMI during the 4 years was not followed by a significant decrease in glucose and HbA_{1c} levels. This could be explained by diminished β-cell ability to secrete adequate amounts of insulin.

Our data suggest that %EWL is an important contributor to adiponectin levels, especially in the long term. Adiponectin could be an important factor affecting insulin secretion because the changes of %EWL, insulin levels, and insulin resistance after 4 years were related to adiponectin levels in both groups. The most significant effect on adiponectin levels was achieved during the first year, and this effect was more pronounced in ND patients. We also found a smaller rise in adiponectin levels in the DM group after 4 years. The correlation between EWL and adiponectin levels was also noted by others in T2DM patients 2 years after bariatric surgery [29].

Several case-controlled studies involving morbidly obese diabetic patients have demonstrated an impressive and sustained improvement in metabolic control or even remission of T2DM [30]. In addition, bariatric surgery can effectively prevent progression from impaired glucose tolerance to diabetes in severely obese individuals. However, these studies are difficult to compare, because of inconsistent methodologies and differences in the definitions of T2DM improvement and resolution criteria.

A meta-analysis by Buchwald *et al.* which included 103 studies reporting on the remission of T2DM [30] reported the overall remission rate of 78.1% at least 2 years after bariatric surgery. After 2 years 62% of patients remained in remission. Weight loss and diabetes resolution was greatest for patients undergoing biliopancreatic diversion and duodenal switch, followed by gastric bypass and LAGB [30]. However, there were significant limitations to this review, and the results have to be interpreted with caution. First, the majority of studies included were retrospective, with the inherent biases. Second, the follow-up was poorly described. Finally, remission criteria were poorly defined and largely based on clinical reporting, rather than biochemical outcomes.

Controversy exists regarding the sustainability of bariatric surgery-induced remission of T2DM. In the Swedish Obese Subjects study, 72% of the patients recovered from T2DM 1 year after surgery, but after 10 years this was reduced to 36%. Our study demonstrated a remission rate of 62% for a period as long as 4 years. However, data regarding gradual recurrence of diabetes over time raise questions and concerns about the durability of these effects [31]. Our study suggests that different factors including EWL, insulin, insulin resistance, leptin and adiponectin levels are involved in glucose metabolism in DM and ND patients. Given the above-mentioned metabolic effects, our study suggests that LAGB can result in favorable T2DM remission rates and effectively prevent progression to diabetes in morbidly obese individuals.

This study was limited by its single site design and a relatively low sample size; however, our results will supplement existing data regarding metabolic changes after LAGB.

Conclusions

The most significant metabolic changes were observed during the first year after LAGB. Four years of follow-up revealed stabilization rather than significant improvement of glycemic control and adipokine levels in both DM and ND patients. Significant weight loss after LAGB is associated with an increase in adiponectin secretion in non-diabetic morbidly obese patients. In diabetic patients, LAGB results in a significant reduction in blood glucose and insulin resistance, with an increase in adiponectin levels. Adiponectin levels negatively correlated with insulin resistance in both DM and ND patients. The association between leptin levels and insulin resistance is more complex and depends on the degree of obesity.

Conflict of interest

The authors declare no conflict of interest.

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