Impact of laparoscopic sleeve gastrectomy on body mass index, ghrelin, insulin and lipid levels in 100 obese patients

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Abstract

Introduction: A high percentage of patients benefit from bariatric procedures in terms of metabolic effect and substantial body mass reduction. These procedures improve glucose metabolism leading to the amelioration or complete resolution of type 2 diabetes, reduction of insulin resistance and alleviation of metabolic syndrome effects.

Aim: To assess the impact of laparoscopic sleeve gastrectomy (LSG) on the plasma levels of ghrelin, insulin, glucose, triglycerides, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) fractions as well as aspartate and alanine transaminases in patients with obesity.

Material and methods: One hundred patients who underwent laparoscopic sleeve gastrectomy in our centre between 2005 and 2009 were included in the study. Among them were 48 males with an average age of 47.93 ± 9.24 years and 52 females with an average age of 44.19 ± 9.33 years. Percentage excess weight loss (%EWL), percentage excess body mass index (BMI) loss (%EBL), ghrelin, insulin, glucose, triglycerides, cholesterol, HDL, LDL, alanine transferase (ALT), and asparagine transferase (AST) were measured preoperatively and on the 7th day then 1, 3 and 6 months after the surgery.

Results: Statistically significant reduction in postoperative BMI, plasma levels of glucose and insulin as well as the homeostatic model assessment insulin resistance (HOMA IR) score was noted in comparison to the preoperative values. The ghrelin levels decreased. Lipid profile, AST and ALT levels varied depending on the particular time points.

Conclusions: Laparoscopic sleeve gastrectomy reduces body mass and leads to the decrease of concentration of ghrelin in plasma as well as to the improvement of metabolism of insulin, glucose, cholesterol and triglycerides. The above changes alleviated symptoms of metabolic syndrome and obesity related co-morbidities.

Key words: obesity, sleeve gastrectomy, ghrelin, insulin, glucose and lipid homeostasis, metabolic syndrome.

Introduction

Obesity is defined as the result of a chronic imbalance between the supply of energy and its expenditure on environmental, genetic or hormonal functions. This surplus of energy then manifests as an excessive aggregation of fat tissue and leads to many serious, co-existing disorders [1, 2]. Because obesity is reaching the magnitude of a pandemic, obesity related co-morbidities such as type 2 diabetes, arterial hypertension, cardiovascular disorders, dyslipidaemias, obstructive sleep apnoea, osteoarthritis, liver lipidosis, depression or gastrointestinal tract cancer are seen in a new light. Besides the health costs, worldwide psycho-social and socio-economic effects of obesity seem to be very important as well. It is noteworthy that since 1997 obesity has been listed
on the WHO social diseases register. The number of obese patients in the world is increasing constantly, and what is particularly striking is the massive increase that has occurred in the last two decades. There were 1600 million overweight and 400 million obese people (aged over fifteen) worldwide in 2005. In Poland, 1% of the population have a body mass index (BMI) of over 40 kg/m², which represents over 300,000 people [3].

Orexigenic and anorexigenic hormones influence the regulation of energy balance. The only known orexigenic hormone is ghrelin, a polypeptide product of X/A cells belonging to the APUD (amine precursor uptake and decarboxylation) system. Not all mechanisms regulating ghrelin excretion have been discovered so far. Its maximal concentration is observed in the gastric fundus and decreases in the caudal direction. Its concentration decreases with a positive energy balance and increases in negative energy balance conditions (e.g. anorexia) [4].

Metabolic syndrome is a significant clinical problem directly linked to obesity. Metabolic syndrome is a complex of multiple risk factors predisposing to the development of diabetes mellitus and cardiovascular disorders; and as such it has become a part of follow-up examinations in patients after bariatric procedures. The diagnosis of metabolic syndrome is usually based on one of several clinical classifications, with WHO classification and ATP III (Adult Treatment Panel III) being the most commonly used. Most of the classifications assess one of the metabolic parameters constituting the syndrome, and studies assessing more parameters are in the minority. Nevertheless, the benefits of bariatric surgery are clearly visible in these studies [5, 6].

Surgical techniques for obesity management continue to gain broader implementation possibilities. Nowadays, gastric sleeve resection is performed mainly laparoscopically. Despite late introduction as a treatment modality, it is gaining popularity not only as the first step in the staged treatment of superobese patients from high-risk groups but mainly as an isolated, definitive bariatric procedure [7]. Its increasing popularity among bariatric surgeons and patients’ acceptance of its impact on body mass reduction started in 2003. Sleeve gastrectomy (GS) was first described in 1988 as a part of the duodenal switch procedure [8] and in 1993 as an independent one-stage procedure [9]. The number of laparoscopic sleeve gastrectomies continues to increase both in Europe and North America. There was an increase from 0% to 4% in the USA and Canada and a 7% increase in Europe during the period of 2003-2008. Laparoscopic sleeve gastrectomy (LSG) started to be performed in Poland in 2005, and one can observe a constant increase in the number of procedures from year to year [3].

Aim

The aim of this study is to assess the influence of laparoscopic sleeve gastrectomy on the plasma levels of ghrelin, insulin, triglycerides (TG), total cholesterol and HDL and LDL, asparagine transferase (AST) and alanine transferase (ALT) in obese subjects.

Material and methods

The study population consisted of a hundred (n = 100) obese patients subjected to bariatric surgery (laparoscopic sleeve gastrectomy) in the 1st Department of General and Endocrinological Surgery at the Medical University of Białystok from 2005 to 2009. All patients were followed for 6 months after their surgery. There were 48 male patients, mean age 47.93 ± 9.24 years old; and 52 female patients, mean age 44.19 ± 9.33 years old in the group. The mean pre-operative body mass index (BMI) was 52.15 ± 8.5 kg/m², and the mean body mass was 151.2 ± 25.19 kg. Pre-operative patients’ characteristics are shown in Table I.

The co-morbidities of obesity we assessed were: type 2 diabetes mellitus (T2DM), arterial hypertension (AHT) and obstructive sleep apnoea (OSA). Pre-operatively T2DM was present in 39 patients (39%), AHT in 56 patients (56%) and OSA in 31 patients (31%).

All study subjects fulfilled criteria to be eligible for the bariatric procedure. To exclude any upper GI pathology we performed multiple examinations including abdominal ultrasound scans (abdominal USS) and upper GI endoscopy. All patients had endocrine, dietetic and psychological consultations, and women also had gynaecological examinations. All bariatric procedures were performed laparoscopically in a standardized fashion with the use of 5 trocars. Following introduction of all trocars, a thorough inspection of the abdominal cavity and in particular of the stomach was performed. Crow’s foot was identified. The greater omentum was dissected using a harmonic scalpel or LigaSure device close to the

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stomach wall and medially to the gastropiploic ves-
sels. The omentum was dissected up to the left
diaphragmatic crus and down to leave 4-6 cm dis-
tance from the pylorus. The first stapler separated
the greater curve of the stomach in the direction of
the crow’s foot and the following staplers were
applied in the direction of the angle of His. If any
bleeding from the staple line occurred it was cau-
terised using electrocoagulation or a haemosta-
tic suture was applied. Stomach width was reduced to
that of a narrow tube and the leak-proof test was
performed in each case. A drain was left along the
dissection line.

Patients were discharged home on the 2nd or 3rd
postoperative day. Advice was given on a semisolid
and low-calorie diet with low Na+ for the first
2 weeks, followed by a low-fat and low-calorie diet
with monthly follow-up visits. Blood samples were
taken before the operation, 7 days after the opera-
tion and 1, 3 and 6 months after the operation. Clot-
ted samples were centrifuged to separate out blood
plasma. Fasting levels of ghrelin, insulin, glucose,
total cholesterol and HDL and LDL, triglycerides, ALT,
AST, urea and uric acid were measured. Ghrelin was
measured using the Human Ghrelin (TOTAL) RIA KIT
(Merck Millipore). Based on the laboratory test
results, the percentage of excess weight loss (%EWL)
and percentage excess BMI loss (%EBL) were calcu-
lated according to the guidelines from 2007 [10].
Homeostatic model assessment insulin resistance
(HOMA IR) was calculated according to the formula:
HOMA-IR = [(fasting insulin [µU/ml] × fasting glu-
cose [mmol/l])/22.5] [11].

Statistical analysis

Statistical analysis was performed using Statisti-
ca 6.0 software for Windows. All values were pre-
sented as the mean ± standard deviation (± SD). The
Mann-Whitney test was used to assess the differ-
ces between values before and after the opera-
tion. A value of \( p < 0.05 \) was considered to be statis-
tically significant.

Results

During the 6-month follow-up we observed a sta-
tistically significant reduction of BMI, and significant-
ly increased %EWL and %EBL. Statistically significant
reduction of BMI was observed 1 month after surgery
\( (45.81 ±7.71 \text{ kg/m}^2) \) when compared to BMI before
surgery \( (52.15 ±8.5 \text{ kg/m}^2) \). Three and 6 months after
the surgery we also observed a significant reduction
of BMI in these patients \( (42.72 ±6.86 \text{ kg/m}^2; 37.98
±4.97 \text{ kg/m}^2) \). Seven days after surgery the mean val-
ue of BMI \( (48.23 ±8.16 \text{ kg/m}^2) \) also lowered, though it
did not reach statistical significance. The evolution of
BMI changes in time is shown in Table II. During
the follow-up period we noted both excess weight
loss (EWL) and excess body mass index loss (EBL).
On the 7th postoperative day %EWL was 13.57 ±2.92
\( (p < 0.05) \), after the 1st month %EWL was 22.04 ±3.95
\( (p < 0.001) \), after 3 months 32.5 ±4.73 \( (p < 0.0001) \)
and after 6 months %EWL was 48.98 ±6.58
\( (p < 0.00001) \). %EBL on the 7th postoperative day
was 14.97 ±3.45 \( (p = NS) \), after the 1st month it was 24.43
±5.09 \( (p < 0.01) \), after 3 months it was 36.04 ±6.48
\( (p < 0.0001) \), and after 6 months %EBL was 52.1
±7.28 \( (p < 0.0001) \). Changes of %EWL and %EBL are
shown in Figures 1 A and 1 B.

Statistically significant changes of ghrelin levels
were particularly noticeable. Preoperative ghrelin level
of 491.49 ±176.27 decreased to 410.17 ±91.56 at the 7th
postoperative day. During the observation period, fur-
ther decrease in ghrelin levels was observed. After the
1st month it decreased to 395.57 ±58.76, 3 months

| Parameter            | LSG n = 100 |
|----------------------|-------------|
| Gender female/male [%] | 52/48      |
| Age female/male [years] | 44.19 ±9.33/47.93 ±9.24 |
| Weight [kg]           | 151.2 ±25.19 |
| BMI [kg/m²]           | 52.15 ±8.5  |
| Ghrelin [pg/ml]       | 491.49 ±176.27 |
| Insulin [µU/l]        | 42.9 ±28.82 |
| Glucose [mg/dl]       | 147.7 ±61.64 |
| Total cholesterol [mg/dl] | 213.08 ±19.68 |
| Triglycerides [mg/dl] | 166.3 ±35.31 |
| LDL [mg/dl]           | 138.44 ±35.31 |
| HDL [mg/dl]           | 42.48 ±11.19 |
| ALT [UI/l]            | 29.47 ±11.52 |
| AST [UI/l]            | 25.5 ±12.35 |
| Uric acid [mg/dl]     | 5.78 ±1.73  |
| Urea [mg/dl]          | 32.22 ±7.77  |
after surgery to 380.01 ±60.78, and 6 months after surgery to 389.08 ±33.01. These results are summarized in Table II.

The mean fasting insulin level in plasma also decreased significantly when compared to the preoperative level of 42.9 ±28.82. It decreased almost by half (21.4 ±18.86) at the 7th postoperative day, and it decreased even further at each point of the observation: 19.31 ±16.24 at 1 month, 16.69 ±13.55 at 3 months, and 16.01 ±8.41 at 6 months after surgery.

All changes of fasting glucose (Glc) levels in plasma were statistically significant. The mean preoperative level of 147.7 ±61.64 decreased to 112.79 ±26.56 seven days after surgery. A tendency for further reduction of Glc levels was present during the remaining observation time. The mean Glc level decreased to 103.87 ±12.06 at 1 month after surgery, 101.53 ±10.5 after 3 months and 98.42 ±7 after 6 months. Figures 2 A and 2 B show positive correlations between the changes of Glc levels and BMI reduction as well as insulin levels and BMI reduction.

Based on the levels of insulin and Glc, the calculation of HOMA IR gave statistically significant and interesting results. Before surgery HOMA IR had a value of 12.22 ±13.4. At the 7th postoperative day it decreased to 5.11 ±4.09, and after the 1st month to 4.02 ±3.2. Three months after surgery the mean HOMA IR increased to 4.22 ±3.48, to drop to 3.52 ±2.52 after the next 3 months.

Reduction of TG levels was statistically significant at 1 (122.64 ±28.54), 3 (118.43 ±20.46) and 6 months after surgery (116.45 ±36.01) compared with

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**Figure 1.** Changes of %EWL (A) and %EBL (B) at the 7th postoperative day and 1, 3, 6 months following LSG

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**Figure 2.** Correlation between BMI and glucose plasma levels (A) and between BMI and insulin plasma level (B) following LSG procedure
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**Table II. Changes in BMI, plasma ghrelin, insulin, glucose, total cholesterol, HDL, LDL, triglycerides, AST, ALT levels and HOMA IR score on the 7th day, 1st, 3rd and 6th month post LSG**

| Parameter | Prior to surgery | 7th day | 1 month | 3 months | 6 months |
|-----------|-----------------|---------|---------|----------|---------|
| BMI       | 52.15 ±8.5      | 48.38 ±6.5* | 45.81 ±7.71* | 42.72 ±6.86* | 37.98 ±4.97* | <0.00001 |
| Ghrelin   | 491.49 ±176.27 | 410.17 ±91.56* | 395.57 ±58.76* | 380.01 ±60.78* | 389.08 ±33.01* | <0.05 |
| Insulin   | 42.9 ±28.82     | 21.4 ±18.86* | 19.31 ±16.24* | 16.69 ±13.55* | 16.01 ±8.41* | <0.05 |
| Glucose   | 147.7 ±61.64    | 112.79 ±26.56* | 103.87 ±12.06* | 101.53 ±10.5* | 98.42 ±7.8* | <0.05 |
| HOMA IR   | 12.2 ±13.4      | 4.2 ±2.2* | <0.001 | <0.0001 | <0.0001 |
| Total cholesterol | 213.48 ±193.68 | 214.48 ±107.47 | 206.14 ±109.74 | 210.55 ±28.95 | 185.6 ±11.36 | <0.0001 |
| HDL       | 42.48 ±11.19    | 26.2 ±26.56* | 21.4 ±18.86* | 19.31 ±16.24* | 16.69 ±13.55* | <0.05 |
| LDL       | 12.2 ±13.4      | 5.1 ±1.8* | <0.05 | <0.001 | <0.001 |
| Triglycerides | 166.3 ±51.64 | 151.57 ±22.36 | 122.64 ±28.54* | 118.43 ±20.46* | 116.45 ±36.01* | <0.01 |
| AST       | 29.47 ±11.52    | 35.78 ±12.22 | 31.05 ±13.98 | 36.47 ±10.25 | 39.5 ±16.87 | <0.05 |
| ALT       | 29.47 ±11.52    | 35.78 ±12.22 | 31.05 ±13.98 | 36.47 ±10.25 | 39.5 ±16.87 | <0.05 |

*Statistical significance, NS – not significant (p value > 0.05)
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31 affected patients. The results of co-morbidities improvement are summarized in Table III.

**Discussion**

The most important factors leading to obesity are irrational nutritional habits [12]. Surgical management of obesity is currently the most effective in treating causes of obesity, its symptoms and systemic effects such as AHT, T2DM, cardiovascular disorders, dyslipidaemias, OSA, hepatic steatosis, gastroesophageal reflux disease (GERD), generalised oedema, depressive syndromes, osteoarthritis and neoplasms (including gastrointestinal neoplasms) [13]. The results of surgery are especially noticeable because other treatment modalities with different pharmacological options do not satisfy the expectations of patients.

Obesity is a disorder that has been quite extensively examined in North America and Europe. However, with increasing frequency new studies indicate the rising rates of obesity in developing countries, and even in countries that were considered undeveloped economically so far. That trend is also visible in Poland, which accelerates the development of bariatric services in our country [3, 14]. Each bariatric procedure leads to some extent of weight loss [15]. Although the sleeve gastrectomy is one of the most recently introduced bariatric procedures and the availability of published outcomes is modest, it does not seem to be inferior to other procedures and some authors claim its superiority in terms of BMI reduction [16]. The weight loss after LSG is achieved due to two mechanisms of restriction and hormonal modulation. The presented results of LSG surgery are similar to published results of other bariatric centres worldwide. We proved that the BMI reduction continued for the whole 6-month observation period and was comparable to the results of Armstrong and O’Malley [17] or Karamanakos et al. [18]. Short-term outcomes of LSG are comparable to other techniques, and to laparoscopic adjustable gastric banding (LAGB) outcomes. Nevertheless, the long-term (> 1 year) outcomes are in favour of LSG. These effects are visible at 1, 2, 3 years or even later, though the greatest effect was observed at 1 and 2 years after surgery [19-22].

World literature supports the thesis of reduction of plasma levels of ghrelin using non-surgical management such as a low-energy diet, lifestyle modification or increased physical activity. The effects of bariatric procedures on ghrelin levels are diverse. Some of the procedures increase ghrelin levels, some decrease the levels and others do not influence levels. Laparoscopic sleeve gastrectomy significantly reduces the production of ghrelin in 90% of patients in a durable fashion [23, 24]. It is probably the result of resecting the gastric fundus where the majority of ghrelin production takes place [25]. Age and gender are not proved to have an influence on the plasma levels of this orexigenic hormone. In turn, food intake plays a crucial role in ghrelin plasma secretion. The greatest reduction in plasma levels of ghrelin can be observed as a result of high-carbohydrate meal ingestion, and slightly less reduction is observed following a high-fat meal. Studies on the influence of high-protein meals are inconclusive and contradictory [26, 27]. The relationship between body mass reduction and the plasma levels of ghrelin are very complex as we can frequently observe weight loss despite a reduction in the peripheral levels of ghrelin. In the presented study we could observe the reduction of plasma levels of ghrelin after 7 days, and that continued to decrease after the 1st and 3rd postoperative months. At the end of the observation at 6 months we could observe a slight elevation of the mean ghrelin level reaching the level seen at the end of the first postoperative month.

An important effect of the weight loss is the improved metabolism of glucose and the reduction of insulin resistance and thus the clinical improvement of T2DM. Also other bariatric procedures influence T2DM. The co-existence of obesity with insulin resistance has been studied extensively and is well documented. Silecchia et al. documented resolution of non-insulin-dependent DM (NIDDM) in 69.2% and 76.9% of patients, 12 and 18 months after LSG, and improvement of NIDDM in 15.4% and 15.4% in patients with super morbid obesity [28]. It has been

**Table III. Improvement of T2DM, hypertension and sleep apnoea after LSG in 6-month follow-up**

| Variables          | LSG                       |
|--------------------|---------------------------|
|                    | Prior to surgery | 6 months |
|                    | n   | %   | n   | %   |
| Type 2 diabetes    | 39  | 39  | 21  | 53.84 |
| Hypertension       | 56  | 56  | 26  | 46.28 |
| Sleep apnoea       | 31  | 31  | 16  | 51.61 |

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suggested that the patients with diagnosis of T2DM shorter than 5 years benefit more from the bariatric surgery than those who suffered from T2DM for more than 5 years [29]. Rizzello et al. demonstrated fast insulin tolerance and insulin resistance improvement following LSG that was independent of body mass reduction [30]. In a study comparing outcomes of LAGB and LSG, Frezza et al. noted that LSG provides better glucose control at 1 and 1.5 years after surgery than the LAGB, which seems to be suggestive of an important but not well understood influence of resection of the gastric fundus [31].

In our study, the symptoms of metabolic syndrome improved significantly following LSG. It allowed for the reduction of pharmacological treatment of co-morbidities. Laparoscopic sleeve gastrectomy is comparable to LAGB among other procedures in regards to the reduction of symptoms of T2DM and also to the majority of components of metabolic syndrome. It is particularly visible one year after surgery [32, 33]. Studies comparing LSG with other operative techniques are still rare due to the natural history of LSG. Nevertheless, the available literature indicates that the LSG procedure is comparable to laparoscopic Roux-en-Y gastric bypass (LRYGBP) [34]. Hence, the authors conclude that the small intestine is not a significant part of the glucose homeostasis chain. It has been supported by the comparison of LAGB and LRYGBP, where there was a reduction of insulin resistance in both groups without a significant influence of duodenal and small intestine switch [35]. Thus, it seems that the above improvement is a result of body mass reduction rather than the use of particular operative technique.

Available studies indicate that the greatest benefit of bariatric surgery with regards to the amelioration of components of the metabolic syndrome is seen in patients in the second and third class of obesity. Some of the studies show that the use of LSG provides a similar effect on metabolic syndrome to LRYGBP [36], while some other studies favour LRYGBP [37]. Some authors indicate the effect of weight loss, although the preoperative triglyceridaemia and diabetic status also matter [38]. In some of the longitudinal studies investigators showed that the weight loss following LSG [28] does not always cause significant improvement of metabolic syndrome and its lipid profile [39].

We observed a significant reduction of insulin levels, particularly at the 7th postoperative day and 3 months after surgery. Glucose levels decreased as well. Insulin resistance (expressed as the HOMA IR) decreased significantly 7 days and 1 month after surgery. A smaller effect was seen 6 months after the procedure. The level of triglycerides decreased noticeably 7 days after surgery, decreasing systematically from the first postoperative day through the following 6 months. Total cholesterol level also decreased during the observation.

Chen et al. tried to prove a synergistic correlation between obesity, insulin resistance and ALT levels. They suggest that such a correlation might be much more clinically significant in the diagnosis of insulin resistance than the metabolic syndrome itself [40]. Bariatric surgery has become a treatment of choice in super morbid obesity and as such proved to be the only effective modality controlling weight loss for the long term. Moreover, the majority of patients with the aforementioned co-morbid conditions recovered or achieved an improvement in symptoms. We noted a greater effect of bariatric surgery in patients with a greater number of co-morbidities [41]. Thanks to all above-mentioned effects, LSG is one of the most popular bariatric procedures in our centre [42].

Bariatric techniques and standards are still being developed [43]. But at this stage one can conclude that the evolution of both significantly reduces the risk of complications and patients’ postoperative discomfort [44]. The possibility of applying SG as a stand-alone and definitive treatment with the option of a two-stage procedure constitutes significant progress [45-47].

Adequate consideration should be paid to the recently published technique of LSG combined with simultaneous application of adjustable gastric banding (AGB), not only due to the metabolic benefits [48]. We should think what benefits might come from adding restrictive and malabsorptive techniques. In theory, benefits of such a procedure might not be better than those of each procedure on its own, or there might be a synergistic effect of the procedure. However, it seems that this technique might be more effective because the band would prevent the stomach from dilating, and the sleeve resection and removal of the gastric fundus with cells producing ghrelin would reduce appetite. This however still requires further clinical evaluation. One of the first papers describing glucose homeostasis and body
mass reduction in patients after combined procedures of LSG and LAGB was published recently [49]. The outcomes seem very promising, but due to the small size of the study group and short follow-up time further studies are needed.

Conclusions

The LSG procedure causes noticeable weight loss with BMI reduction and an increase in %EWL and %EBL. It also causes a reduction in ghrelin levels. It improves the metabolism of insulin, glucose and lipids. The achieved body weight loss improves the patient’s quality of life and improves or resolves co-morbidities such as metabolic syndrome. In our opinion one should consider the LSG procedure to be the first line of treatment in super morbid obesity, as it is relatively easy to perform with a low burden of peri-operative morbidity.

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