

# Effectiveness of stage by stage bariatric interventions for regression of comorbidity at obese class III patients

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## ABSTRACT

**Introduction.** Currently obesity is considered as a chronic, relapsing, multifactorial neurobehavioral disease, in which an increase in body fat contributes to the dysfunction of adipose tissue and the biomechanical effect of adipose tissue on surrounding tissue with development of metabolic and psychosocial health effects. It has been proven that bariatric surgery significantly reduces the level of pro-inflammatory senility-associated secretory proteins (SASPs), weight reduction increases telomeres length and declines their oxidative degradation (lowering of oxidative stress in telomeres), miR10a\_5p, which is post-regulated with increasing of biological age, decreased after surgery, what suggests that bariatric surgery abated the premature aging phenotype. It is of big interest to evaluate comorbidity conditions in people with obese class III after the intervention of intragastric balloons (IGB) and laparoscopic sleeve gastrectomy (LSG), which are lead to weight loss. **Methods.** A total of 40 patients (32 female and 8 male aged 19–55 years) were considered for the study. Comorbidity was assessed by the structure and severity of diseases associated with obesity according to the recommendations of Nedogoda (2016). Cardiometabolic disease staging scale of Guo (2015) was used to assess the metabolic health. Endovisual surgery-LSG was performed (n=40) on a laparoscopic set and instruments of Karl Storz, GMBH & CoKG (Germany). The spherical intragastric balloon (IGB) was installed according to the manufacturer's method (BIB™ System Intragastric Balloon from Allergan Inc. USA) using a GIF-1T20 Olympus gastrointestinal fibroscope (Japan). **Results.** Evaluation of the obesity phenotype, a completely metabolically healthy phenotype was not detected in any case. Nowadays, the opinion about the usefulness of the clinical concept of the metabolic syndrome (MS) is disputed, because it has not been convincingly proven its predictive value exceeds that for individual components. **Conclusion.** Obese class III is associated with dyslipidemia/hypertriglyceridemia in 85%; with type 2 diabetes mellitus (DM2)/prediabetes in 50%; with arterial hypertension (AH) in 45%; and with non-alcoholic fatty liver disease (NAFLD) in 35% of cases. Therefore, two-stage treatment by IGB and LSG make it possible to improve the performance on the Cardiometabolic disease staging scale, achieving zero cardiometabolic risk in 35% of patients, and in rest of patients move to a lower stage.

## Original Article

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## INTRODUCTION

Currently, on the recommendation of the American Society for Metabolic & Bariatric Surgery Updates (2014–2015), obesity is considered as a "chronic, relapsing, multifactorial neurobehavioral disease, in which an increase in body fat contributes to the dysfunction of adipose tissue and the biomechanical effect of adipose tissue on surrounding tissue with development of metabolic and psychosocial health effects [1, 2]. The cost of medical care for people with obesity is significantly higher than for people with normal weight. So, for people with obese class I the cost of medical care is 14% more compared to those of normal weight, then for persons with obese class III - the cost is 77.1% more; comorbid pathology in obesity has a strong influence on these data [3].

Comorbidity - a combination of pathological conditions that worsen the patient's prognosis - the risk of death from competing diseases, the Charlson index allows to quantify this risk. According to a study that included 514,350 individuals [3], the Charlson Comorbidity Index (CCI) in non-obese individuals was 1.84; with overweight - 2.04; with obese class I - 2.29; class II - 2.7; class III - 3.06, respectively. The spectrum of CCI diseases includes ischemic heart disease, myocardial infarction, cerebrovascular diseases, peripheral vascular diseases, connective tissue diseases, chronic lung diseases, ulcers, chronic liver diseases, dementia, diabetes, hemiplegia, kidney diseases, tumors, leukemia, lymphoma, metastatic tumors, and immunodeficiency syndrome [4].

Diseases, traditionally associated with obesity, are arterial hypertension (AH), depression, type 2 diabetes mellitus (DM2), non-alcoholic fatty liver disease (NAFLD), sleep apnea [5–8]. Comorbidity with obesity also

includes a pro-inflammatory status, a phenotype of premature aging, including secretion of senility-associated secretory proteins (SASP) and telomere length reduction. Micro-RNA - non-coding molecules are able to modify the post-transcriptional processes causing a metabolically unhealthy condition [9].

It has been proven, that bariatric surgery significantly reduces the level of pro-inflammatory SASPs, weight reduction increases telomeres length and declines their oxidative degradation (lowering of oxidative stress in telomeres), miR10a\_5p, which is post-regulated with increasing of biological age, decreased after surgery, what suggests that bariatric surgery abated the premature aging phenotype. Randomized trials have shown that excessive weight loss after laparoscopic sleeve gastrectomy (LSG) after 5 years is 61.1%; after shunting operations (Roux-en-Y bypass) - 68.3% (the differences are not significant), while the LSG is advantageous in terms of frequency of gastric reflux after surgery, showing 25%, whereas after shunting operations - 60.4%; the number of reoperations after LSG and shunting operations was 15.8% and 22.1%, respectively [10, 11]. According to Salminen et al. [12]'s data, in 5 years after LSG, weight loss was 49%, remission of DM2 and AH was achieved in 37% and 29% of cases, respectively, hypolipidemic therapy was stopped in 47% of patients.

Treatment with intragastric balloons (IGB) as a method of reducing excessive body mass, that does not require invasive surgery, has become widespread. The method is endoscopic, and opens up the possibilities of minimally invasive correction of obesity and serves as an alternative to diet therapy and medical preparation of patients for bariatric surgery [13]. The mechanisms of action of the IGB are can be explained as following: to decrease in the gastric reservoir due to the volume of the balloon, the achievement of early satiation during the meal, as well as slowing down the evacuation of food from the stomach.

Recent data suggests, that weight loss causes reduction of the risk of comorbidities, where the proportion of patients is 52-92% for AH, 82% - is for cardiovascular diseases (CVD) and bronchial asthma; 63% - is for dyslipidemia; in 82% of cases there is a decrease in the degree of hepatitis, in 20% - the degree of fibrosis in NAFLD is declined; 83% of patients achieved remission of DM2, in 95% patients lowered congestion in the venous vessels of the lower extremities; in 55% - depression is eliminated, and ultimately, in 95% of patients the quality of life is improved [14]. In consideration of above-given data, it is of interest to evaluate comorbid conditions in people with obese class III after the intervention of IGB and LSG, which are lead to weight loss.

## MATERIAL AND METHODS

The objective of the research was 40 patients (32 female and 8 male) aged 19–55 years ( $34.7 \pm 2.5$  years) hospitalized in the State Institution "Republic Specialized Scientific-Practical Medical Center of Surgery named after acad. V.Vahidov" in 2016-2019. All patients were obese class III. The class of obesity was assessed by WOG (2011), which provides for the Asian type. Criteria for Asians are next: lowered weight ( $<18.5$  kg/m<sup>2</sup>), normal weight (18.5-22.99 kg/m<sup>2</sup>), overweight (23-24.99 kg/m<sup>2</sup>), obese class I (25-29.99 kg/m<sup>2</sup>), obese class II (30-34.99 kg/m<sup>2</sup>), obese class III (35-59.99 kg/m<sup>2</sup>) [15]. The metabolic unhealthy phenotype of obesity is considered to be an increase in waist circumference (WC) of more than 102 cm in male and 88cm in female, an increase in blood C-reactive protein (CRP) more than 3 mg/l; glucose - more than 5.6 mmol/l; triglycerides (TG) - more than 1.7 mmol/l; a decline in high-density lipoprotein (HDL) less than 1.04 in men and 1.30 mmol/l in women; elevation of blood pressure (BP) more than 130/85 mm Hg.

Comorbidity was assessed by the structure and severity of diseases associated with obesity according to the recommendations of Nedogoda [15]. Cardiometabolic Disease Staging scale [16] was used to assess the metabolic health [4]. Endovisual surgery - LSG was performed on a laparoscopic set and instruments of Karl Storz, GMBH & CoKG (Germany), using the Harmonic G11 ultrasonic scalpel (Johnson & Johnson, USA), Forse Triad energy platform with Liga Sure technology (USA), endoscopic stapling-transection devices of company Ethicon Endo Surgery (Johnson & Johnson, USA). This intervention is a restrictive bariatric surgical procedure. The technique of operation is consisted in resection most of the stomach, located along the greater curvature (curvature major) with preservation of the cardiac sphincter and pylorus and the formation of a narrow gastric tube with a volume of 60-150 ml, located along the lesser curvature (curvature minor). LSG was performed in 40 patients.

The spherical intragastric balloon (IGB) was installed according to the manufacturer's method (BIB™ System Intragastric Balloon from Allergan Inc. USA) using a GIF-1T20 Olympus gastrointestinal fibroscope (Japan) under intravenous potentiation with the addition of a local anesthesia of pharynx with solution of Lidocaini 10% in spray. After filling the balloon with an adequate volume of liquid and removing the connecting tube-catheter, endoscopic monitoring of its position and hermetic properties was performed. The duration of

the IGB entire procedure was 10-15 minutes. The intervention was performed with the participation of an endoscopist, a surgeon, an anesthesiologist and an anesthesiological nurse. Patients were observed in 2-3 days, in order to prevent complications associated with the possible intolerance of patients to the presence of a balloon in the stomach. For the entire period of treatment, proton pump inhibitors (pantaprazole) were prescribed, which contributed to a decrease in gastric secretion. Removal of the balloon was carried out after 6 months.

C-reactive protein concentration, serum lipid profile: total cholesterol (CH), triglycerides (TG), HDL, very low density lipoprotein cholesterol (VLDL), and glucose, uric acid (UA) , were determined on an automatic biochemical analyzer "VITROS-350" ("Ortho Clinical Diagnostics", USA). The atherogenic index (AI) was calculated using the Klimov's formula:  $AI = (cholesterol-HDL)/HDL$ .

### Ethical approval

The review board and ethics committee of RSCS named after acad. V.Vakhidov approved the study protocol and informed consents were taken from all the participants.

## RESULTS

We had divided all patients in 2 groups: the 1-st group consists of 34 patients with one stage treatment - only by LSG; the second group consists of 6 patients, which treated by IGB installation on 6 month (the 1-st step of treatment) and then LSG (the 2-nd step of treatment). Mean body mass index was  $51.2 \pm 2.3$  at the 1-st group and  $62.2 \pm 1.3$  kg/m<sup>2</sup> at the 2-nd group patients. Evaluation of the obesity phenotype, a completely metabolically healthy phenotype was not detected in any case, since in all patients, waist circumference exceeded 88 cm in female and 102 cm in male. At the same time, 6 patients of the 1-st group had glucose levels below 5.6 mmol/l; at 5 patients of the 1-st group and 1 patient of the 2-nd group TG concentration was below 1.7 mmol/l; the level of HDL is over 1.3 in 5 women from 1-st group, blood pressure was lower than 130/85 at 18 patients (14 patients from 1-st group and 4 patients from 2-nd group). These data show the unequal occurrence of components of the metabolic syndrome (MS) in obese people.

**Table 1.** Diseases associated with obesity and their stage 6 months after LSG (by Nedogoda scale)

Items	Diseases	0 stage (absent)	1 stage	2 stage	0 stage (absent)	1 stage	2 stage
		Before LSG			After LSG		
DM2/prediabetes		20 (50%)	18(45%)	2(5%)	30(75%)	6(15%)	4(10%)
AH		22(55%)	-	18(45%)	34(85%)	2(5%)	4(10%)
hypertriglyceridemia/dyslipidemia		6(15%)	26(65%)	8(20%)	22(55%)	12(30%)	6(15%)
Sleep apnea syndrome		40(100%)	-	-	40(100%)	-	-
NAFLD		26(65%)	14(35%)	-	32(80%)	8(20%)	-
Polycystic ovaries syndrome		40(100%)	-	-	40(100%)	-	-
Fibrillation of atrium		40(100%)	-	-	40(100%)	-	-
Osteoarthritis		40(100%)	-	-	40(100%)	-	-
GERD		38(95%)	2(5%)	-	38(95%)	2(5%)	-
Hypodynamic lifestyle		-	28(70%)	12(30%)	26(65%)	8(20%)	6(15%)
Depression		30(75%)	10(25%)	-	38(95%)	2(5%)	-

AH= arterial hypertension, DM2= type 2 diabetes mellitus, NAFLD=non-alcoholic fatty liver disease, GERD= gastroesophageal reflux disease, LSG= laparoscopic sleeve gastrectomy.

Nowadays, the opinion about the usefulness of the clinical concept of the MS is disputed, because it has not been convincingly proven its predictive value exceeds that for individual components; it could be more informative to indicate everyone component separate, moreover, since all the criteria for diagnosing MS suggest the presence of three components, and, in fact, we are talking about various options for combining obesity with elevated blood pressure, dyslipidemia, hypertriglyceridemia, and impaired glucose tolerance [14, 16, 17]. Evaluation of diseases, associated with obesity, at patients of 2-nd group (n=6) showed that AH (2 stage according Nedogoda scale) was found at 4 patients; hypertriglyceridemia/dyslipidemia – at 5 patients (at 2 patients - the 2 stage, at 3 patients – the 1 stage according Nedogoda scale); at 3 patients was prediabetes (1 stage according Nedogoda scale), at 5 patients – depression. All patients of the 2-nd group had high anesthesiological risk, LSG was contraindicated for them. So, IGB was installed to these patients. It was very

effective to weight loss and cardiometabolic risk reduction. After 6 month IGB was removed with good result: body mass index (BMI) reduced from  $62.2 \pm 1.3$  kg/m<sup>2</sup> to  $50.1-52.4$  kg/m<sup>2</sup>, hypertriglyceridemia/dyslipidemia reduced at 5 patients to 0 stage; AH reduced at 4 patients (to 1 stage at 3 patients and to 0 stage at 1 patient); at 2 patients fasting glucose level became normal (0 stage); at 4 patients reduced depression (0 stage). After IGB removing patients of the 2<sup>nd</sup> group were underwent LSG (2-nd step of treatment).

For evaluation effectiveness of LSG we have united patients of the 1-st and the 2-nd groups (n=40). Evaluation of comorbidity before LSG showed that AH was the most frequent – at 18 patients (45%), NAFLD 1-2 degree - 14 (35%). In addition, in 11 (28%) cases was found cholecystitis without stones, gastritis - in 5 (13%) cases, goiter - in 6 (15%) cases, ventral hernia - in 1 (3%) case, IHD and DM2 - in 1 patient (3%). After LSG, there was a significant decrease in the number of patients with DM2/prediabetes, AH, hypertriglyceridemia/dyslipidemia (Table 1).

## DISCUSSION

Discussion of this data confirms that our results reflects common trend. So, according to Song et al. [4] obesity strongly increases the risk of developing hypertension (RR = 2.33); complicated DM2 (RR=2.22); uncomplicated DM2 (RR=1.85); IHD (RR=1.58); chronic liver disease (RR = 1.3); cerebrovascular diseases (RR=1.08); meanwhile, the overall risk for all diseases in people with BMI over 30 kg/m<sup>2</sup> is quite high (RR = 2.22) [4].

It is known, that the class of obesity greatly influences the growth of comorbidity of AH, DM2 and chronic liver diseases; whereas the incidence of IHD, cerebrovascular diseases, depression does not increase significantly depending on the increase in BMI, being approximately less than 8-10% in normal-weight and 10-15% in people with obese class III, while the incidence of AH in people with normal weight/overweight is about the same and is about 18%, and in persons with obese class III - more than 50%; chronic liver diseases in overweight people occur in 18%, and in obese class III - in 35% of cases, for DM2, these numbers are 16-18% in overweight and 45% in obese class III [4].

Of particular interest is NAFLD — a systemic disorder, which associated with various chronic conditions, including obesity, diabetes, kidney disease, and cardiovascular diseases [15]; some authors supposed that NAFLD – is a hepatic manifestation of the MS [18]. The frequency of NAFLD has increased over the past 30 years in direct correlation with an increase in sugar consumption (sugar-containing beverages, cakes) and the development of obesity [19]. Liver lipogenesis is an insulin and glucose-dependent process that is controlled by transcription factors. At the presence of insulin resistance (IR), the formation of lipids from glucose in the liver is enhanced by the transcription factor SREBP-1c, and its targets are the enzymes of the synthesis of fatty acids (FA) – palmitoil-synthase, acetyl-CoA-carboxylase, stearoyl-CoA desaturase [20].

Our results indicate a significant regression of diseases associated with obesity, as well as a reduction in the factors responsible for the metabolic unhealthy phenotype of obesity. In addition, there was a positive dynamics of a significant decrease in the level of UA from  $359 \pm 18$  to  $283 \pm 9$   $\mu\text{mol/l}$  (the difference with the initial data was 21.2%,  $P < 0.05$ ) and the CRP from  $15.5 \pm 0.2$  to  $5.0 \pm 0.5$  mg/l (the difference with the initial data - 66.7%,  $P < 0.05$ ).

Discussing the pathogenetic role of UA in obesity, we note that UA has a pro-inflammatory effect and enhances lipogenesis, and is closely associated with the development of NAFLD [21]. The pro-inflammatory effect of UA is realized through the activation of NFkB, stimulation of NLRP3 by inflammasomes, activation of NADPH-mitochondrial (MCH) oxidase, which increases the accumulation of reactive oxygen species (ROS). It is known that two enzymes are sensitive to ROS in mitochondria — enoyl-CoA hydratase (an enzyme of fatty acid beta-oxidation) and aconitase — an enzyme of the Krebs cycle [22]. Oxidative modification of aconitase and enoyl-CoA hydratase leads to their inactivation, resulting in an increase in citrate, its release into the cytosol and increased lipogenesis. Synthesis of UA is associated with generation of ROS, which initiate oxidative stress (OS) both in mitochondria and in the endoplasmic reticulum (EPR), inducing inflammation and fibrosis, as well as insulin resistance. OS in MCH and EPR of hepatocytes lead to activation of the sterol-regulatory element that binds the transcription factor beta (SREBP-1c), followed by stimulation of lipogenesis through the activation of acetyl-Coa-carboxylase [22, 23]. Clinical studies have shown that the degree of liver fibrosis according to biopsy is higher in patients with high concentration of UA [12]. Meta-analysis confirmed that the frequency of NAFLD increases by 3% with an increase in UA by 1 mg/dL [20]. It is possible, that the decrease in UA levels that we detected in our patients also contributes to the regression of comorbidity in the bariatric treatment of obesity.

In the majority of clinical recommendations, a good target effect from the point of health is considered to be a weight reduction of 3-10% within 6 months and its subsequent stabilization. With a BMI of more than 35

kg/m<sup>2</sup> and the presence of comorbid pathology, a weight reduction target is of more than 10%, and with a BMI of  $\geq 40$  kg/m<sup>2</sup> by 20-25% (AAACE/ACE, 2014) [1]. As our results, after limiting the amount of ingested food by reducing the volume of the stomach after IGB installation weight loss was 17.7%, after LSG – 19.5% from the baseline, respectively. At the patients of the 2-nd group after 2 steps of treatment (IGB installation and LSG) weight loss was 33.8% from baseline level. IGB was established for 6 months as a preoperative preparation to reduce perioperative risk, followed by LSG. Improving the metabolic profile in patients after treatment reflects the average numbers of anthropometry and laboratory tests (Table 2).

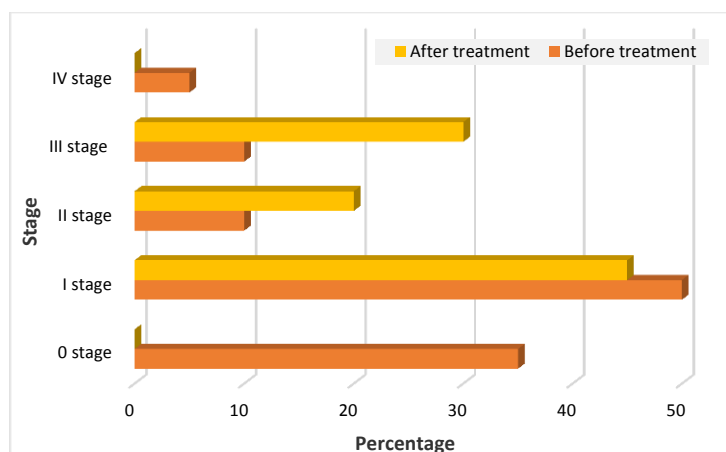
**Table 2:** Characteristics of lipid profile, pro-inflammation cytokines 6 month after LSG

Patients group	Control group, n=10	Before LSG, n=40	After LSG (6 month), n=40
WC, cm	76±1.0	130.6±2.5*	120.3 ±2.1*,**
BMI, kg/m <sup>2</sup>	23.4±0.3	51.2±2.3*	41.2±1.4**
Fasting glucose, mmol/l	4.7±0.1	6.05±0.21*	5.58±0.04*,**
TG, mmol/l	0.93±0.05	1.56±0.18*	0.99±0.11**
VLDL, mmol/l	0.44±0.11	1.14±0.06*	0.61±0.13**
CH, mmol/l	4.4±0.1	5.1±0.3*	4.07±0.26**
HDL, mmol/l	1.34±0.03	0.99±0.05*	1.07±0.06*,**
Atherogenic index	2.3±0.2	4.2±0.2*	2.8±0.1*,**

Note: \* - significant relative to control,  $p < 0.05$ ; \*\* - significant relative to baseline characteristics. LSG= laparoscopic sleeve gastrectomy, WC=waist circumference, BMI=body mass index, CH=total cholesterol, TG=triglycerides, VLDL=very low density lipoprotein cholesterol, HDL=high-density lipoprotein,

In patients after LSG the lipid profile, fasting glucose level did not differ significantly from the control group ( $P > 0.05$ ), indicating that LSG is effective in the first 6 months after the intervention. When choosing the method of operation of patients with obese class III, such factors as BMI, cardiopulmonary diseases and other factors that increase the risk of abdominal operations come to the fore. IGB can be effectively used as a preoperative preparation in individuals with extremely high body mass as the first stage of weight loss before LSG.

Regarding the results, we note that, according to randomized trials, caloric restriction of food allows achieving sustainable weight loss, and even with subsequent weight gain, the positive effect of weight loss on pro-inflammatory markers and biochemical parameters persists permanently [24]. According to Shelest et al. [23], it is obesity that makes a significant contribution to the increase in pro-inflammatory cytokines and adipocytokines. These authors have shown that in patients with AH in combination with obesity, there was a significant increase in leptin and decrease in adiponectin on the background of a significant increase in IL-6 and IL-10; in hypertension without obesity, these parameters did not change significantly relative to control ( $P > 0.05$ ) [25]. As our observation study showed, all patients after bariatric intervention have improved metabolic health, assessment with Cardiometabolic Disease Staging scale by Guo [16] showed that zero (0) stage, when there are no risk factors, was observed in 14 (35%) patients (before treatment - none); Stage 1 (2 risk factors) - in 20 (50%) patients versus 18 before treatment; Stage 2 (3 or more risk factors) - in 4 patients versus 8 before treatment; Stage 3 (3 factors + prediabetes) - in 4 versus 12 before treatment; Stage 4 (DM2, CHD, etc.) - in 2 patients (Figure 1).



**Figure 1.** Regression of cardiometabolic risk stages in the dynamics of bariatric treatment (% of patients).



## CONCLUSION

Obese class III is associated with dyslipidemia/hypertriglyceridemia in 85%; with DM2/prediabetes - in 50%, with AH in - 45%; and with NAFLD - in 35% of cases. IGB as the 1-st step of treatment allow to achieve a reduction in BMI by on 17,7% of the baseline, and regression of comorbidity. Two step treatment – IGB and then LSG caused reduction of weight on 33,8% in 12 month after starting of treatment. LSG caused reduction of comorbidity: prediabetes decreases by 2 times, AH - by 3 times; dyslipidemia – 1,9 times; reduction of NAFLD – 1,8 times in 6 months after the intervention. Two stage treatment by IGB and LSG make it possible to improve the performance on the Cardiometabolic Disease Staging scale, achieving zero cardiometabolic risk in 35% of patients, and in rest of patients - move to a lower stage. Reduction in weight and comorbidity because of LSG and IGB combined with a significant reduction in UA and SRP.

## DECLARATIONS

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### Authors' Contributions

All authors contributed equally to this work.

### Competing interests

The authors declare that they have no competing interests.

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