



## Changes in the Incretin Levels After Gastric Bypass

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**Abstract:** Most researchers support the important role of incretins, particularly glucagon-like peptide-1 in improving metabolic control in patients with type 2 diabetes after bariatric operations, mostly involving shunting. A positive effect of bariatric surgery for type 2 diabetes is known from numerous publications on the results of surgical treatment of morbid obesity and in this review we try to analyze the mechanisms of this effect.

**Key words:** morbid obesity, type 2 diabetes, bariatric surgery, incretins.

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Obesity is the chronic disease characterized by the excessive accumulation of adipose tissue in the body, which causes health threat, and is the main risk factor for the number of other chronic diseases, including type 2 diabetes mellitus (DM2) and cardiovascular diseases (CVD) [3].

In 1950, the obesity was included in the International Classification of Diseases (ICD) and, given the prevalence of obesity in the XXI century, the term “globesity” appeared in the literature, emphasizing the global significance of the problem, but the obesity epidemic remained virtually unnoticed for more than three decades [4]. Its impact on the level of chronic diseases, quality of life and the health economy is strongly felt all over the world, both in high- and low-income countries. The increased body mass index (BMI) is a risk factor for non-communicable diseases, such as diabetes, cardiovascular diseases and musculoskeletal system disorders, which leads to the sharp decrease in the quality and duration of life, by about 5-20 years, depending on the severity of the condition and concomitant diseases. In 2013, the high BMI caused more than 4 million deaths worldwide [5]. According to WHO, in 2016, >1.9 billion adults over the age of 18 had the excess weight (the same data are indicated in the report for 2020), of which over 650 million suffered from obesity. The prevalence of the excess weight and obesity

worldwide has roughly doubled since 1980, with the result that more than one-third of the world's population is now classified as people with excess weight or obesity. Kelly et al. calculated that 57.8% of the world's population will have the excess weight or obesity by 2030 if current trends continue.

Over the past few decades, there have been significant changes in the trends of obesity treatment

The decision to start weight loss should be based on the assessment of the person's medical need for weight loss, as well as on the patient's desire and behavioral adequacy in weight loss. These factors, along with body mass index (BMI), give the initial idea of which interventions are likely to be most appropriate for the given person.

Lifestyle changes, drug therapy and bariatric metabolic surgery are three methods of treating obesity.

Intensive lifestyle intervention and drug therapy have a relatively low risk, but their effectiveness in weight loss is modest, especially in patients with morbid obesity [6]. Although surgery is associated with the greater risk, it provides for more significant and long-term weight loss and corresponding improvement in comorbidity and long-term survival. Bariatric surgery, recently recognized as one of the methods of combating obesity, has become one of the important areas of modern surgery in short period of time. This is due to the progressively increasing number of patients suffering from morbid obesity. The interest in bariatric surgery is also increasing because today there are no effective drugs for the conservative treatment of morbid obesity and a good result is the decrease in body weight by 5-10%. For the patients with morbid obesity this result is ineffective one.

In addition to the significant effect of weight loss, bariatric and metabolic surgical procedures are associated with other favorable metabolic outcomes, including resolution or improvement of type 2 diabetes, hypertension, dyslipidemia, metabolic syndrome and overall survival. These improvements may be the result of weight loss or factors independent of weight loss

Attention to these effects was attracted by the fact that after gastric bypass surgery, a very rapid normalization of blood glucose levels was noted. It is impossible to explain this fact by a sharp restriction of caloric intake, since it takes place after all bariatric interventions. Meta-analysis of 136 studies on bariatric surgery, including 22,094 patients, confirmed complete remission of DM2 (preservation of normoglycemia after the withdrawal of all hypoglycemic drugs) in 84% of patients after gastric bypass on Ru, compared with 48% after regulated gastric banding (RGB) [2]. The important aspect of bariatric surgery is the improvement of carbohydrate metabolism, most of which lead to the complete remission of diabetes. Similar kind of favorable effects can be achieved with the help of the FPB and GB in various modifications, currently referred to as metabolic surgery. These differences are explained precisely by the different dynamics of gastrointestinal hormones level. It is known that gastrointestinal cells secrete biologically active substances in response to food stimulation. Some of these substances, called incretins, have the effect on glucose-dependent insulin secretion. These hormones are secreted by the mucosa endocrine cells of the distal small intestine after stimulation by food. The main incretins are: ileum L-cells secreted hormone – glucagon-like peptide-1 (GLP-1) and jejunum K-cells secreted hormone - glucose-dependent insulintropic peptide (GIP). Unlike the cells of the endocrine glands, these cells are not united in a glandular structure, but are located among other cells of the mucous layer. GLP-1 and GIP, as already noted, stimulate glucose-dependent insulin secretion, and also have a cytoprotective effect. In particular, the ability to increase differentiation and proliferation of pancreatic  $\beta$ -cells and inhibit their apoptosis has been proven for them in vitro. The important feature of these

hormones action is the dependence of their effect on the secretion of insulin and glucagon on the of glucose level in the blood – at the glucose level higher than basal one, these hormones enhance insulin production and inhibit the production of glucagon. With the decrease in glucose levels below the lower limit of the norm, they cease to stimulate insulin secretion, and glucagon secretion increases. GIP and GLP-1 are secreted in response to food intake, and fats and carbohydrates have the maximum stimulating effect. Secretion of incretins begins on average 10 to 15 minutes after meal, has two-phase character, reaches a maximum in 30-60 minutes and returns to the basal level in 2-3 hours. The half-life of GLP1 is less than 2 minutes, GIP is 5-7 minutes, rapid inactivation of cretins occurs under the influence of the DPP-4 enzyme and other endopeptidases [1, 7,8, 12, 13, 14]. The secretion of incretins is influenced by the direct contact of food with enteroendocrine cells (including its nutrient composition), the rate of food intake into the intestine and the rate of its absorption, as well as central and neurohumoral stimuli.

**Materials and methods:** The study included 22 patients with type 2 diabetes who were operated by using gastric bypass method. There were 16 female patients and 6 male patients. The average age was  $43.6 \pm 1.13$ , BMI is  $37.9 \pm 0.59$ , the average duration of type 2 diabetes is  $3.2 \pm 0.17$ . Venous blood was received before and 3 months after gastric bypass, on the empty stomach and 30 minutes after against the background of the load with 75 g of glucose. The levels of incretins (GLP-1, GIP) and glucagon were studied.

**Results of the study:** The state of incretin levels against the background of the conducted test with 75 grams of glucose showed the initially reduced level of GLP-1, both on empty stomach and 30 minutes after load. 3 months after gastric bypass, the level of GLP-1 significantly increased 30 minutes after load, i.e., the increase in GLP-1 secretion after bypass bariatric surgery occurred mainly postprandially. The data obtained by us are consistent with the results of Russian and foreign authors who registered the increase in the basal concentration of GLP-1 [16, 9, 20] after bariatric bypass surgery, although there are studies that have not revealed any changes [11, 15, 18]. As for the dynamics of the postprandial GLP-1 level, the vast majority of authors demonstrate its increase after bariatric bypass surgery against the background of glucose loading [11, 9, 11, 15, 20, 21] and the absence of its increase after restrictive procedures [10, 17, 19, 20].

GIP levels had similar dynamics, but unlike GLP-1, GIP levels significantly increased both on empty stomach and after load.

The level of glucagon on empty stomach increased significantly 3 months after surgery, but the paradox is that initially the level of glucagon increased 30 minutes after the load, and decreased 3 months after surgery.

**Indicators of incretin and glucagon levels in patients with obesity and type 2 diabetes mellitus before and after the load.**

	Initially	In 3 months
GLP1, 0	$1,52 \pm 0,09^{**}$	$2,13 \pm 0,14^{**}$
GLP1, 30 min	$2,53 \pm 0,20^{**}$	$12,39 \pm 0,32^{**}$
GIP, 0	$142,82 \pm 4,97^{**}$	$499,41 \pm 50,53^{**}$

GIP, 30 min	268,73±25,12**	1069,23±66,27**
Glucagon, 0	124,33±11,52*	161,38±10,52*
Glucagon, 30 min	213,09±14,25**	89,72±4,57**

**Note:** in all observation groups there are significant differences before and after treatment. \* -  $P < 0.05$ , \*\* -  $P < 0.01$ .

The data obtained indicate the restoration of the incretins physiological secretion and significantly positive effect on glucagon, which in turn leads to the improvement in the condition of not only  $\alpha$ -cells of the pancreas, but  $\beta$ -cells as well.

**Conclusion:** The study of incretin levels (GLP 1, GIP) in patients with type 2 diabetes after GB showed a significant increase ( $p < 0.01$ ) 3 months after GB on empty stomach and 30 minutes after glucose loading. Glucagon levels in the blood during the loading test, despite a significant increase in fasting indicators, had a significant decrease ( $p < 0.01$ ) during the loading test 3 months after surgery.

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