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# TYPE 2 DIABETES MELLITUS REMISSION AND ITS PREDICTION AFTER TWO-STAGE SURGICAL TREATMENT OF PATIENTS WITH MORBID OBESITY

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## ABSTRACT

**Introduction:** Morbid obesity (MO) has a significant impact on mortality, health and quality of life of patients. Type 2 diabetes mellitus (T2DM) is a common comorbidity in patients with MO.

**The aim** is to study T2DM remission and to develop a prediction model for T2DM remission after two-stage surgical treatment of patients with MO.

**Materials and methods:** The study included 97 patients with MO. The mean BMI was 68.08 (95% CI: 66.45 - 69.71) kg/m2. 70 (72,2%) patients with MO were diagnosed with T2DM. The first stage of treatment for the main group (n=60) included the IGB placement, for the control group (n=37) - conservative therapy. In the second stage of treatment the patients underwent bariatric surgery. The study addresses such indicators as BMI, percentage of weight loss, percentage of excess weight loss, ASA physical status class, fasting glucose level, HbA1c, C-peptide.

**Results:** Two-stage treatment of morbidly obese patients with T2DM promotes complete T2DM remission in 68.1% of patients. The risk prediction model for failure to achieve complete T2DM remission 12 months after LRYGB based on a baseline C-peptide level has a high predictive value, AUC = 0.84 (95% CI: 0.69-0.93), OR = 0.23 ( 95% CI: 0.08-0.67).

**Conclusions:** Two-stage treatment of patients with MO promotes improvement of carbohydrate metabolism indicators. With a C-peptide level > 3.7 ng/ml, prediction of complete T2DM remission 12 months after Laparoscopic Roux-en-Y Gastric Bypass is favorable.

**KEY WORDS:** Morbid Obesity, Bariatric Surgery, Type 2 Diabetes Mellitus

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## INTRODUCTION

About 13% of adult population in the world suffer from obesity [1]. Being aware of the risks that the patients face, doctors pay special attention to the problem of morbid obesity (MO) in patients with a body mass index (BMI) ≥ 40 kg/m2 [2]. MO has a significant impact on mortality, health status and quality of life of these patients, which determines the relevance of this problem [3]. In particular, the presence of excess body weight leads to a substantial increase in the incidence of type 2 diabetes mellitus (T2DM) [4].

Since the causes of obesity are multifactorial, the solution to this problem should be multidisciplinary [5]. At the same time proper consideration should be given to lifestyle and dietary modifications, changes in physical activity, behavioral counseling, and pharmacotherapy [3]. However, the patients, who do not respond to the indicated conservative treatment, require bariatric surgery [6].

The 2nd Diabetes Surgery Summit (DSS-II) adopted a series of recommendations for bariatric surgery in patients with T2DM based on evidence-based medicine. Thus, metabolic surgery is recommended for patients with T2DM and BMI ≥ 40 kg/m2 and for individuals with BMI 35.0-39.9 kg/m2 when hyperglycemia can't be adequately controlled by lifestyle and relevant medical therapy [7]. However, patients with MO that is strongly associated with T2DM have a high surgical and anesthetic risk [8,9]. In order to reduce it and make bariatric surgery appropriate and beneficial, two-stage treatment of these patients is used: the first stage - the placement of an intragastric balloon (IGB) before surgery, the second stage - bariatric surgery itself [10].

## THE AIM

The aim of the research is to study the onset of T2DM remission and to develop a prediction model for T2DM remission after two-stage surgical treatment of patients with MO.

## MATERIALS AND METHODS

The study included 97 patients with MO - 45 (46.4%) men and 52 (53.6%) women. The mean weight of 97 patients was 191.63 (95% CI: 186.75 - 196.51) kg, BMI 68.08 (95% CI: 66.45 - 69.71) kg/m2. The surgical and anesthetic risk on the ASA PS scale was 3.27 (95% CI: 3.18-3.36). 70 (72,2%) patients with MO were diagnosed with T2DM. This diagnosis was supported by the reference to the criteria recommended by the American Diabetes Association (2018) [11]. T2DM was diagnosed in 46 (76.7%) patients assigned to the main group and in 24 (64.9%) patients assigned to the control group.

The treatment was carried out in 2 stages. The first stage of treatment for the main group (n=60) included the IGB placement, for the control group (n=37) - conservative therapy. There was no statistically significant difference (p>0.05) in the gender, age and clinical parameters for both groups of patients. In the second stage of treatment the patients of both groups underwent surgical procedure for the MO management. The duration of the study included 6 months of the follow-up period for all patients after the first stage of treatment and 12 months - after the second stage. 61 (62.9%) patients completed the two-stage treatment, including the preparatory stage and bariatric surgery.

Clinical and laboratory methods of investigation were used to monitor fasting glucose levels, glycosylated hemoglobin HbA1c, and C-peptide throughout the study. BMI, weight loss (%WL) and excess weight loss (%EWL) were calculated. The surgical and anesthetic risk was assessed on the scale presented by the American Society of Anesthesiologists as ASA Physical Status Classification System 2014 (ASA PS) [12].

The conservative treatment of obese patients incorporated a complex of measures aimed at lifestyle modifications, including dietary changes, physical activity and behavioral therapy. Pharmacotherapy of co-morbidities was administered individually in each case. The endoluminal treatment of patients in the main group was conducted by the placement of IGB, namely the ORBERA ™ Intragastric Balloon System produced by Apollo Endosurgery, Inc. The surgical procedure, which was used in the presence of T2DM, included the Laparoscopic Roux-en-Y Gastric Bypass (LRYGB) according to the Fobi-Capella technique. In the absence of T2DM and positive outcomes of the treatment with IGB, restrictive bariatric surgery was performed - Laparoscopic Adjustable Gastric Banding (LAGB) (until 2013) and Laparoscopic Sleeve Gastrectomy (LSG) [10].

Statistical analysis was conducted using IBM SPSS Statistics Base (version 22). A value of $p<0.05$ was considered statistically significant. Quantitative data are expressed as mean and with 95% confidence interval (CI). To analyze the relationship between the risk of failure to achieve complete remission of T2DM and a set of factors, single-factor logistic regression models were constructed and analyzed. The strength of the relationship between each factor and the risk of failure to achieve complete remission of T2DM was estimated by the odds ratio (OR) with 95% CI calculated. In order to compare the quality of prediction of the risk of failure to achieve complete remission of T2DM based on the selected significant factors, Receiver Operating Characteristic (ROC) curve construction and analysis were used. Optimization of the decision threshold was realized with the help of the Youden Index test.

The research was carried out in compliance with the modern principles of bioethics. The design of this study was approved by the commission on bioethical expertise and ethics of scientific research at the National Medical University named after O.O. Bogomolets, the research does not present an increased risk for the subjects of the study and was implemented in view of existing bioethical norms and scientific standards for conducting clinical trials involving patients. All patients signed a written informed consent form.

## RESULTS

After the first stage of treatment the patients of the main group had the mean %WL 14.86 (95% CI: 13.87 - 15.85)%, %EWL - 22.46 (95% CI: 20.93 - 24.0) %. The patients of the control group had the mean %WL 1.39 (95% CI: -0.52 - 3.30)%, %EWL - 1.87 (95% CI: -1.22 - 4.96)%. In the main group, after the first stage of treatment, partial remission of T2DM, which was defined based on the ADA criteria (2009), was seen in 3 patients. In the control group, none of the patients achieved either partial or complete remission of T2DM.

61 patients with MO, who completed the first stage of treatment with a decrease in the initial level of surgical and anesthetic risk for ASA PS and/or clinical improvement of co-morbidities, and, therefore, had no contraindications for bariatric surgery, and gave informed written consent, underwent bariatric surgery: 51 (83.6%) patients underwent LRYGB, 9 (14.8%) - LAGB, 1 (1.6%) - LSG.

12 months after surgery, the mean BMI decreased from 58.02 (95% CI: 56.16 - 59.88) kg/m2 to 38.53 (95% CI: 37.39 - 39.67) kg/m2 ($p<0.001$). The mean %EWL was 55.27 (95% CI: 53.32 - 57.23)%, with 47 (77.0%) patients having %EWL ≥ 50%. Before surgery, the level of glycosylated hemoglobin (HbA1c) was 6.70 (95% CI: 6.44 - 6.96)%, 12 months after surgery - 5.49 (95% CI: 5.26 - 5.71 ) % ($p<0.001$). Before surgery, the mean C-peptide level was 3.77 (95% CI: 3.30-4.23) ng/ml, after surgery it reduced to 2.47 (95% CI: 2.18 - 2.75) ng/ml ($p <0.001$).

44 (72.1%) patients were diagnosed with T2DM. Before surgery, the mean level of fasting glucose was 8.64 (95% CI: 8.30 - 8.97) mmol/L, glycosylated hemoglobin (HbA1c) - 7.18 (95% CI: 6.97 - 7.39)%. 12 months after surgery, the mean levels of fasting glucose and glycosylated hemoglobin (HbA1c) decreased to 6.23 (95% CI: 5.79 - 6.68) mmol/L and 5.67 (95% CI: 5, 38 - 5.95)% respectively, in both cases $p<0.001$. Before surgery, a C-peptide level in morbidly obese patients with T2DM was 4.16 (95% CI: 3.70 - 4.63) ng/ml, and after surgery, it statistically significantly decreased to 2.64 (95% CI: 2.27 - 3.01) ng/ml ($p<0.001$).

Complete remission of T2DM, which was defined based on the ADA criteria (2009), was observed in 29 (65.9%) patients 12 months after the second stage of treatment that included LRYGB. The study investigated the effect bariatric surgery had on the onset of complete remission of T2DM in patients with MO 12 months after LRYGB, which was defined based on the ADA criteria (2009) [13].

To analyze the relationship between the risk of failure to achieve complete remission of T2DM and a set of factors, single-factor logistic regression models were constructed and analyzed. A set of factors included 10 variables that were observed: gender, age, height, body weight, BMI, excess body weight, C-peptide level, glycosylated hemoglobin level (HbA1c), fasting glucose level, assessment on the DiaRem scale before surgery. The primary endpoint was a prediction of the probability of complete remission of

**Table I.** Analysis of single-factor logistic regression models for predicting the risk of failure to achieve complete remission of T2DM in patients with MO 12 months after surgery.

| Factor | Area under the ROC curve model, AUC (95% CI) | Odds Ratio, OR (95% CI) | Level of significance of difference between OR and 0, p |
|---|---|---|---|
| Gender | 0.58 (0.42–0.72) | 0.54 (0.15–1.96) | 0.35 |
| Age | 0.51 (0.35–0.66) | 1.01 (0.94–1.09) | 0.79 |
| Height | 0.53 (0.37–0.68) | 0.97 (0.91–1.04) | 0.42 |
| Body weight | 0.60 (0.44–0.75) | 1.00 (0.97–1.03) | 0.89 |
| BMI | 0.58 (0.42–0.72) | 1.04 (0.95–1.13) | 0.45 |
| Excess body weight | 0.52 (0.37–0.68) | 1.00 (0.97–1.04) | 0.84 |
| C-peptide level | 0.84 (0.69–0.93) | 0.23 (0.08–0.67) | 0.007 |
| HbA1c level | 0.74 (0.59–0.86) | 3.97 (1.34–11.8) | 0.01 |
| Fasting glucose level | 0.73 (0.58–0.85) | 2.32 (1.17–4.60) | 0.02 |
| Assessment on the DiaRem scale | 0.71 (0.55–0.84) | 1.27 (1.04–1.55) | 0.02 |

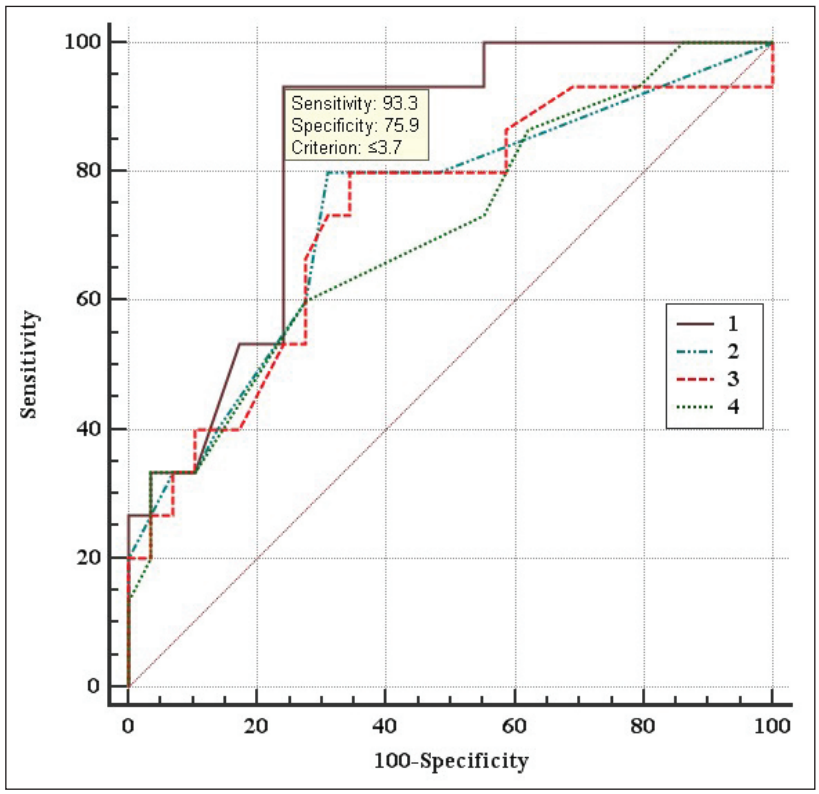


**Figure 1.** Receiver Operating Characteristic (ROC) curves for the risk prediction tests for failure to achieve remission 12 months after surgery: 1 – C-peptide level, 2 – glycosylated hemoglobin HbA1c level, 3 – fasting glucose level, 4 – assessment on the DiaRem scale.

T2DM 12 months after surgery, Y = 0 in case of remission and Y = 1 in case of failure to achieve remission. The analysis was carried out based on the findings of the follow-up period that included 44 patients with MO, who underwent LRYGB, with 29 (65.9%) achieving complete remission of T2DM 12 months after surgery and 15 (34.1%) patients failing to achieve the same result within the indicated period. Table I shows the results of single-factor analysis.

The conclusion can be made about the presence of a link ($p < 0,05$) between the risk of failure to achieve complete remission of T2DM 12 months after surgery and the value of the C-peptide index (risk reduction with an increase in the index, OR <1 at $p = 0.007$), the value of glycosylated hemoglobin HbA1c level (increased risk with an increase in the index, OR> 1 at $p = 0.01$), the value of fasting glucose level (increased risk with an increase in the index, OR> 1 at $p = 0.02$), the value of the assessment on the DiaRem scale (increased risk with an increase in the indicator, OR> 1 at $p = 0.02$).

No link was found between gender, age, height, body weight, BMI, excess body weight and the risk of failure to achieve complete remission of T2DM 12 months after

surgery (the area under the ROC curve does not differ from 0.5 and the OR score does not differ from 1 at p> 0.05). In order to compare the quality of prediction of the risk of failure to achieve complete remission of T2DM based on the selected significant factors, Receiver Operating Characteristic (ROC) curve analysis was used for these four tests (Figure 1).

The analysis shows a high predictive value of the risk prediction test for failure to achieve complete remission of T2DM 12 months after surgery for a C-peptide level, AUC = 0.84 (95% CI: 0.69-0.93), which indicates a "very good" quality of the model). When the level of C-peptide increases to 1 ng / ml, the chances of failure to achieve remission decrease (p = 0.007) by 4 times, OR = 0.23 (95% CI: 0.08-0.67). For the other three significant factors, the predictive characteristics are worse.

A selection of the optimal threshold for the risk prediction test for failure to achieve complete remission of T2DM 12 months after surgery was based on the initial level of C-peptide and carried out with the help of the Youden Index test optimization, the critical threshold for C-peptide = 3.7 ng/ml. With a C-peptide level ≤ 3.7 ng/ml, a high probability of failure to achieve complete remission of T2DM is expected after 12 months following surgery, with a C-peptide level > 3.7 ng/ml prediction is favourable.

When selecting the optimal test threshold, its sensitivity is 93.3 (95% CI:68.1 - 99.8)%, specificity - 75.9 (95% CI: 56.5 - 89.7)%, positive predictive value PPV = 66.7 (95% CI: 50.8 - 79.5)%, negative predictive value NPV = 95.7 (95% CI: 76.6 - 99.3)%. Thus, if the C-peptide level is > 3.7 ng/ml, then it is possible to predict the achievement of complete remission of T2DM and in 95.7% of cases this remission will actually be achieved 12 months after bariatric surgery.

In the analysis of C-peptide, it was noted that 12 months after surgical treatment of MO in the subgroup of patients with a C-peptide value > 3.7 ng/ml, complete remission of T2DM was observed in 22 (75.9%) patients, with a C-peptide value ≤ 3.7 ng/ml - in 7 (24.1%) patients.

## DISCUSSION

The patients with the mean BMI of 68.08 (95% CI: 66.45 - 69.71) kg/m2 were characterized not only as morbidly obese, but also as extremely overweight (BMI ≥ 50 kg/m2). In this case, the presence of co-morbidities, first of all, T2DM is an essential clinical problem. These patients have a high surgical and anesthetic risk, which makes bariatric surgery significantly complicated or even impossible. The two-stage treatment used in this study is consistent with the current views of the American Society of Metabolic and Bariatric Surgery (ASMBS, 2017) on the treatment of patients with MO and high surgical and anesthetic risks [6]. The two-stage treatment of patients with MO, which included the IGB placement during the first stage, showed its efficacy both in terms of anthropometry and analysis of T2DM as comorbidity.

An overview of the first stage of treatment suggests that IGB is effective in improving carbohydrate metabolism in patients with MO. It impacts the relevant indicators of carbohydrate metabolism, probably due to the reduction in adipose tissue. The dynamics of the C-peptide level did not become statistically significant in both groups of patients, since the use of IGB does not have any action on the incretin effect. In general, the first stage of treatment in patients with MO is not enough to solve the clinical problem of T2DM. At the same time, the improvement of important indicators of carbohydrate metabolism is one of the essential factors in reducing surgical and anesthetic risks.

In the second stage of treatment, morbidly obese patients with T2DM underwent LRYGB, a surgical procedure that was more preferable than restrictive interventions such as gastric volume reduction and bypass, during which a significant part of the small intestine is excluded from the digestion, as well as combined interventions including both procedures. Gastric bypass combines mechanisms of restriction and malabsorption and, in addition, it has a direct effect on the achievement of T2DM remission by reducing the production of anti-incretins and accelerating the passage of food in the distal part of the small intestine that stimulates the release of glucagon-like polypeptide-1. Consequently, the type of bariatric surgery in patients with MO should be selected taking into account T2DM that is a commonly present co-morbidity. The dynamics of the laboratory indicators that were investigated showed positive outcomes of LRYGB in terms of the key indicators of carbohydrate metabolism.

The aforementioned dynamics of carbohydrate metabolism and C-peptide in patients after LRYGB give evidence of equal importance of adipokinin and other mechanisms related to secretory activity of the duodenum [14]. It is widely known that due to the exclusion of the duodenum and the proximal part of the small intestine from digestion, the production of anti-incretin factors in the duodenum decreases and the production of glucagon-like peptide GLP-1 and glucose-dependent insulinotropic peptide GIP in the small intestine increases, which contributes to the normalization of insulin levels [15,16,17].

## CONCLUSIONS

T2DM is a common co-morbidity in patients with MO, which emphasizes the medical and social significance of the problem.

Two-stage treatment of morbidly obese patients with T2DM promotes complete remission of T2DM in 68.1% of patients. The first stage of treatment should include the use of IGB for 6 months, and the second stage of treatment should be realized through bariatric surgery.

The risk prediction model for failure to achieve complete remission of T2DM 12 months after LRYGB that is based on the preoperative level of C-peptide has a high predictive value, AUC = 0.84 (95% CI: 0.69-0.93), OR = 0.23 (95% CI: 0.08-0.67). With a C-peptide level ≤ 3.7 ng/ml, a high probability of failure to achieve complete remission of T2DM is expected after 12 months after surgery, with a C-peptide level > 3.7 ng/ml prediction is favourable. The sensitivity of the test is 93.3% (95% CI: 68.1 - 99.8), specificity - 75.9% (95% CI: 56.5 - 89.7), PPV = 66.7% (95% CI: 50 , 8 - 79.5)%, NPV = 95.7% (95% CI: 76.6 - 99.3)%.

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**Authors' contributions:**
*According to the order of the Authorship.*

**Conflict of interest:**
*The Authors declare no conflict of interest.*

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