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Multifactorial assessment of the effectiveness of surgical treatment for obesity

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Objective – to create a model for choosing the most effective method of surgical treatment of obesity.

Materials and methods. The study was conducted at the Department of General Surgery No 2, Bogomolets National Medical University. The study group included 53 patients who consented to the bariatric procedure. The control group consisted of 59 patients. The study group underwent bariatric interventions: laparoscopic gastric bypass (37.7 %), laparoscopic sleeve gastrectomy (32.2 %), and 30.1 % underwent the installation of an intragastric balloon, followed by gastric bypass and outcome assessment after 12 months. The control group received conservative treatment for obesity. All patients underwent routine general clinical examinations, genotyping via the Fast Real-Time PCR System in TaqMan medium, and stool analysis using polymerase chain reaction to determine the parameters of the intestinal microbiome.

Results. Statistical data processing showed that the chance of achieving an optimal outcome is highest in patients with a detected SNP MC4R, an unsatisfactory initial intestinal microbiota pattern, and an extensive family history of obesity, as well as those who underwent laparoscopic gastric bypass.

Conclusions. Laparoscopic gastric bypass is the preferred surgical technique for obesity treatment, yielding an optimal outcome. The presence of an unsatisfactory initial intestinal microbiota pattern, the detection of SNP MC4R polymorphism, and a family history of obesity influence the effectiveness of surgical treatment. The chance of achieving an optimal outcome is 3.6 times higher in patients with a detected SNP MC4R polymorphism.

Keywords
treatment, polymorphisms, obesity, bariatric surgery.

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Obesity is characterized by an excessive accumulation of adipose tissue in the human body, leading to the occurrence of many comorbidities and a decline in quality of life. Obesity increases the risk of diabetes, metabolic syndrome, arterial hypertension, ischemic heart disease, and acute cerebrovascular accidents. Obesity is associated with gallstone disease, colorectal cancer, non-alcoholic fatty liver disease, hiatal hernia, osteoarthritis, etc. Consequently, enhancing the effectiveness of obesity treatment is relevant.

Bariatric surgery is becoming more prevalent globally as an effective and safe treatment option for obesity. The IFSO 8th Global Registry Report [5] indicates that, in 2023, there were 480,970 bariatric operations performed worldwide. The most common metabolic interventions included sleeve gastrectomy (60.4 %), Roux-en-Y gastric bypass (29.5 %), minigastric bypass (4.3 %), and other operations (5.8 %).

Some scientific studies evaluated changes in the intestinal microbiota of individuals depending on their body weight and response [12] to bariatric interventions. The reseachers also noted a correlation between obesity and polymorphisms in specific genes.

Jianhua Zhao et al. used a global population gene study (GWAS) to analyze the genetic material of 2,760 individuals with class III obesity, revealing polymorphisms in FTO, TMEM18, NRXN3, MC4R, SEC16B, GNPDA2, TNNI3K, QPCTL, and BDNF in 1,697 (61.4 %) of the individuals, indicating a relationship between obesity and the human genome [15]. S. Z. Lutz et al. determined the correlation between the presence of the HSD11B1 gene (responsible for encoding the activator of 11β-hydroxysteroid dehydrogenase, a regulator of cellular fatty acid metabolism) in the genome of obesity-associated single-nucleotide

polymorphisms (SNPs) rs2235543, rs12565406, and rs4844880 and non-alcoholic fatty liver disease in obese individuals [11]. M. Bandstein et al. identified seven single-nucleotide polymorphisms (PTBP2, NUDT3, TFAP2B, ZNF608, MAP2K5, GNPDA2, and MTCH2) associated with obesity in 238 patients undergoing laparoscopic gastric bypass. They discovered that patients who had any of the single-nucleotide polymorphisms had an 11 % greater percentage of excess weight loss (EWL) compared to those lacking these SNPs in all genomes [3].

Consequently, there exists a correlation between obesity, regardless of gender and race, and changes in intestinal microbiota patterns, as well as gene polymorphisms, namely SNP rs571312 of the MC4R gene and SNP rs3810291 of the TMEM160 gene.

Currently, a significant challenge in bariatric surgery is the creation of a decision-making model that enables the selection of the most successful surgical approach for obesity treatment in each case based on specific criteria.

Objective – to create a model for identifying the most effective method for the surgical treatment of obesity based on the analysis of intestinal microbiome parameters and genetic markers associated with obesity.

Materials and methods

The monocentric prospective observational cohort study was conducted at the Department of General Surgery No 2, Bogomolets National Medical University.

The study included 112 patients (see Table 1 for their clinical characteristics). All patients met the IFSO criteria and required surgical treatment: BMI ≥35 kg/m^2 regardless of comorbidities or BMI 30.00–34.99 kg/m^2 with comorbid conditions. All patients in the study were offered surgical treatment. The study group included 53 patients who consented to bariatric surgery. The control group consisted of 59 patients who refused surgical treatment and instead received conservative therapy. The findings were evaluated one year after the start of treatment. The study group underwent the following bariatric interventions: laparoscopic gastric bypass – 20 patients (37.7 %), laparoscopic sleeve gastrectomy – 17 patients (32.2 %), and 16 patients (30.1 %) with super-obesity who underwent two-stage surgical treatment, namely the installation of an intragastric balloon for 6 months as the first stage of the two-stage treatment, followed by gastric bypass within 14 days after balloon removal and outcome assessment 12 months after the two-stage treatment initiation [1]. The control group consisted of 59 obese patients who were treated conservatively, including diet therapy, psychological support sessions, lifestyle adjustments, and moderate physical activity.

At the beginning of treatment, both groups were prescribed anthropometric assessments, standard general clinical evaluations, genotyping via the Allelic Discrimination system using the Fast Real-Time PCR System (Applied Biosystems™, Life Technologies, USA) in TaqMan media, and stool analysis by PCR to determine quantitative and qualitative indicators of the intestinal microbiome.

The assessment of treatment effectiveness was conducted using the following multifactorial criteria:

1) Percentage of EWL. The American Society for Metabolic and Bariatric Surgery defines effective surgical treatment of obesity as achieving a EWL of no less than 50 % within 12 months postoperatively.

2) The intestinal microbiota patterns, specifically the *Firmicutes/Bacterioidetes* ratio (FBR) and *Bacterioidetes/Faecalibacterium* ratio (BFaR), represent the ratios of the dominant families of microorganisms that colonize the intestinal mucosa. The average normal values for the indicated colonies in Europe are 1–5 for FBR and 0.01–100.0 for BFaR [8].

Table 1. **Clinical characteristics of study patients**

Indicator	All patients (n = 112)	Study group (n = 53)	Control group (n = 59)	p
Age, years	48.2 ± 9.2 (27–68)	47.7 ± 9.1 (23–68)	48.9 ± 9.5 (29–67)	0.286*
Body mass, kg	144.8 ± 15.7 (110.1–210.2)	148.0 ± 18.4 (110.1–210.2)	141.8 ± 12.2 (117.2–172.2)	0.085*
Height, cm	166 ± 13 (150–188)	165 ± 12 (152–188)	166 ± 13 (150–185)	0.818
Initial BMI, kg/m^2	45.1 ± 6.1 (35.2–75.3)	48.6 ± 7.4 (35.2–75.3)	41.6 ± 3.1 (35.5–50.5)	0.256*
Ideal body mass, kg	62.2 ± 7.2 (51.5–74.5)	62.6 ± 7.1 (52.8–73.3)	61.2 ± 6.8 (51.1–74.5)	0.362*
Excess weight, kg	100.2 ± 19.0 (65.9–144.6)	101.5 ± 22.3 (70.5–144.6)	99.8 ± 18.5 (62.3–132.7)	0.321*

Note. A comparison of data between the study and control groups.
* In one or both groups, the data distribution differed from normal; the analysis was performed using the Wilcoxon T-test.

3) The presence or absence of genetic markers associated with obesity includes polymorphisms SNP rs571312 of the MC4R gene and SNP rs3810291 of the TMEM160 gene.
4) Comorbidity of diabetes.
5) Patient age.
6) Patient gender.
7) Family history of obesity.
8) Bad habits (alcohol, smoking).

Results

The average BMI of patients in the study group before surgery was 48.6 ± 20.1 kg/m^2. The average BMI among patients in the control group before treatment was 43.6 ± 16.0 kg/m^2. After surgery, the average BMI in the study group decreased to 29.5 ± 5.4 kg/m^2, while in patients in the control group, it was 40.2 ± 13.8 kg/m^2 (Table 2).

The study group exhibited an average EWL of 59.21 % ± 23 % after 12 months of observation. The maximum EWL observed in the study group was 77.2 %, while the minimum EWL was 49.9 %. The control group exhibited a significantly lower average EWL of 9.92 % ± 7.25 %. The EWL range in the control group was 19.45 % to 2.2 %. The average EWL in patients undergoing bariatric surgery with various techniques differed. Patients who underwent gastric bypass using the Roux technique demonstrated the highest average EWL, at 69.71 % ± 20.0 %. In contrast, those who underwent sleeve gastrectomy had an average EWL of 51.57 % ± 5.9 %, while patients after two-stage surgical treatment achieved an average EWL of 51.7 % ± 7.92 %.

Analysis of the FBR and BFaR in the study group revealed an average FBR of 94.5 before surgical treatment. Only three patients in this group (5.67 %) had FBR values within the reference range before treatment. The average BFaR in the study group was 1708.5, with a significant range of minimum and maximum values, specifically 50000 and 0.0003, respectively. Before surgical treatment, BFaR was within reference values for two patients (3.77 %).

The intestinal FBR in the control group was 52.5 ± 91.1 on average before treatment. Two patients in this group (3.38 %) had average FBRs that varied within the reference values before treatment initiation. The average BFaR before treatment was 579.1. Reference values of BFaR before treatment were not detected.

Analysis of intestinal microbiota patterns revealed the following changes 12 months after surgery. The average FBR after surgical intervention for obesity was 2.84 ± 6.4, with a range of maximum and minimum values of 7.19 and 0.79, respectively. The indicators attained reference values in 50 patients (94.33 % of the cohort). Three patients (5.67 %) exhibited no positive changes in FBR indicators, resulting in insufficient effectiveness of surgical treatment, with an average EWL of 49.52 % ± 0.6. The average BFaR indicator in patients under treatment after 12 months was 58.4, with the maximum and minimum values recorded at 121 and 0.256, respectively. In 49 patients (92.4 % of the cohort), the indicators attained reference values. Four patients (7.6 %) did not have intestinal microbiota markers return to reference values, resulting in insufficient effectiveness of surgical treatment, with an average EWL of 49.33 % ± 1.1.

In the control group, the average FBR indicator after treatment was 6.1 ± 22.2, with a range of 0.2 to 22.4. Ten patients (16.9 %) exhibited results within the reference values from the onset of treatment. The average BFaR indicators in treated patients were 130.2, with reference values achieved in 11 patients (18.6 %) (Table 3).

The distribution of results was determined by the presence of polymorphisms in the studied genes.

Table 2. **BMI dynamics in both groups depending on the treatment method, kg/m^2**

Treatment method	Before treatment	After treatment	p
RYGB	47.8 ± 10.1 (35.2–75.3)	28.5 ± 6.2 (26.2–30.1)	< 0.001
Sleeve gastrectomy	42.2 ± 7.4 (35.4–48.6)	30.1 ± 5.5 (29.2–31.0)	< 0.001
Intragastric balloon implantation + gastric bypass	52.2 ± 6.4 (50.1–54.4)	28.3 ± 6.0 (26.1–30.5)	< 0.001
Study group (total)	48.6 ± 20.1 (35.2–75.3)	29.5 ± 5.4 (26.1–31.0)	< 0.001
Control group	43.6 ± 16.0 (35.5–50.5)	40.2 ± 13.8 (33.4–47.0)	0.06

Note. Intragastric balloon implantation + gastric bypass – placement of an intragastric balloon as the first stage of treatment for patients with super-obesity, and performing gastric bypass 6 months after the start of treatment.

Table 3. **Microbiome status depending on the treatment method, % of references**

Treatment method	*Firmicutes/Bacterioidetes*			*Bacterioidetes/Faecalibacterium*		
	Before treatment	After treatment	p	Before treatment	After treatment	p
RYGB	5.00	95.00	< 0.001*	10.00	95.00	< 0.001*
Sleeve gastrectomy	0.00	94.22	< 0.001*	5.82	94.28	< 0.001*
Intragastric balloon implantation + gastric bypass	6.25	87.50	< 0.001*	0.00	81.25	< 0.001*
Study group (total)	5.67	94.33	< 0.001*	3.77	92.40	< 0.001*
Control group	3.38	16.90	0.06	0	18.60	0.07*

Note. * In one or both groups, the data distribution differs from normal. A comparison was performed using the Wilcoxon T-test. *

The analyzed single-nucleotide polymorphisms were identified in 23.2 % (n = 26) of all patients included in the study (n = 112), while 76.8 % (n = 86) did not have SNP rs571312 MC4R and SNP rs3810291 TMEM 160 in the studied samples. The distribution of single- nucleotide polymorphisms among patient groups is presented as follows. The rs571312 MC4R polymorphism was detected more often in the study group compared to the control group (p = 0.007), while the rs3810291 TMEM 160 polymorphism was also more prevalent in the study group (p < 0.01). The presence of both polymorphisms was identified only in the study group, accounting for 7.3 % (n = 3) (Table 4).

The study group consisted of three subgroups depending on the chosen surgical treatment method and the presence of genetic markers associated with obesity: 20 patients underwent laparoscopic gastric bypass (nMC4R = 8, nNMEM160 = 3), 17 patients underwent laparoscopic sleeve gastrectomy (nMC4R = 2, nNMEM160 = 1), and 16 patients received two-stage treatment involving intragastric balloon placement followed by laparoscopic gastric bypass after 6 months (nMC4R = 3, nNMEM160 = 1). Among these subgroups, the highest treatment efficiency in terms of EWL was observed in patients who underwent laparoscopic gastric bypass, achieving 69.7 %. Patients who underwent two-stage treatment had a EWL of 55.7 %, while those operated on by sleeve gastrectomy had the lowest EWL at 52.5 %.

In a significant cohort of patients undergoing surgery for obesity, initial assessments of intestinal microbiome patterns revealed unsatisfactory results. Specifically, the FBR was within reference values for only three patients (5.67 %), while the average BFaR met reference values in only two patients (3.77 % of the cohort) before surgery.

Table 4. **SNPs distribution in both groups**

SNP	Study group (n = 53)	Control group (n = 59)
rs571312 MC4R	10 (18.8 %)	8 (13.5 %)
rs3810291 TMEM 160	5 (9.4 %)	3 (5.1 %)
Both SNPs	3* (5.6 %)	0
No SNPs	38 (71.7 %)	48 (81.4 %)

Note.* n = 3 among patients in whom both polymorphisms were detected (n = 26)

Statistical analysis

The results of univariate logistic regression yielded a statistical model indicating that individual criteria can influence the chance of achieving an optimal outcome (EWL ≥ 65): the presence of the SNP MC4R genotype – OR 3.6 (95 %CI 1.45–5.65; p < 0.0001); unsatisfactory initial pattern of intestinal microbiota – OR 1.32 (95 %CI 2.11–6.15; p < 0.0001); family history of obesity – OR 1.8 (95 %CI 1.1–1.26; p < 0.0001); other criteria do not have a statistically significant effect on the chance of achieving an optimal outcome, as shown in Table 5.

The quality of the model, as indicated by the AUC values, was good (> 0.7) for SNP MC4R at 0.81 (p < 0.001), an unsatisfactory initial pattern of intestinal microbiota at 0.73 (p = 0.003), and a family history of obesity at 0.76 (p < 0.001). Other indicators yielded AUC values below the acceptable threshold, as shown in Table 6.

Discussion

Analysis of the obtained data revealed that the best outcomes in terms of EWL were achieved in patients who underwent laparoscopic gastric bypass surgery – 69.7 % (n = 20). Within this subgroup, the SNP MC4R polymorphism was most

Table 5. **Statictical analysis results**

Parameter	Indicators	Model odds ratio (95 % CI)	p*
SNP MC4R	2.88 ± 0.48	3.60 (1.45–5.65)	< 0.0001
SNP TMEM160	0.50 ± 0.76	1.10 (2.12–6.15)	0.003
Both SNPs	0.26 ± 0.10	7.00 (2.53–19.3)	0.002
Unsatisfactory initial pattern of intestinal microbiota	1.32 ± 0.17	3.1 (2.11–6.15)	< 0.0001
Diabetus mellitus	0.15 ± 0.10	10.10 (3.16–41.0)	0.02
Age	0.38 ± 0.07	0.69 (0.77–1.36)	0.0001
Sex	0.31 ± 0.02	1.19 (0.25–1.57)	0.82
Family obesity	1.92 ± 0.74	1.80 (1.10–1.26)	< 0.0001
Bad habits	0.12 ± 0.03	0.49 (0.52–0.98)	0.009

Note. * Significance level of the difference between the mean and mean values from 0.

Table 6. **ROC analysis of the obtained model**

Parameter	AUC	Sensitivity, %	Specificity, %	Optimal border	p
SNP MC4R	0.81	65.0	98.0	0	< 0.001
SNP TMEM160	0.52	43.0	86.0	0	< 0.001
Both SNPs	0.48	50	77.5	0.5	0.002
Unsatisfactory initial pattern of intestinal microbiota	0.73	72.2	96.0	0	< 0.001
Diabetus mellitus	0.6	22.0	91.0	0	0.046
Age	0.49	50.0	81.0	14.0	0.002
Sex	0.5	11.0	60.0	0	0.838
Family obesity	0.76	69.0	88.0	0.5	< 0.001
Bad habits	0.55	37.0	75.0	0	0.437

often detected (nMC4R = 5), compared to patients who underwent sleeve gastrectomy (n = 17, nMC4R = 2), and those who received two-stage treatment (n = 16, nMC4R = 3). Statistical data processing showed that the chance of obtaining optimal outcomes is highest in patients meeting specific criteria for surgical treatment: the presence of SNP MC4R, unsatisfactory initial intestinal microbiota patterns, and an extensive family history of obesity. Given that the majority of these patients underwent laparoscopic gastric bypass surgery for obesity, it can be inferred that this surgical technique is a preferred treatment option for patients meeting the specified criteria. This hypothesis is confirmed by A. C. Gomes [7].

Multivariate analysis demonstrates that the selected criteria, including the detected SNP TMEM160, the presence of both gene polymorphisms, diabetes, age, gender, and bad habits, do not have a significant impact on achieving better surgical outcomes in patients with obesity.

Conclusions

An unsatisfactory initial pattern of intestinal microbiota, the presence of the SNP MC4R polymorphism, and a family history of obesity influence the effectiveness of surgical treatment as measured by EWL ($p < 0.0001$). Other criteria have little effect on the surgical outcomes as measured by EWL.

The chance of achieving an optimal outcome with EWL (i 65 %) is 3.6 times higher (95 %CI 1.45–5.65; $p < 0.0001$) in patients with a detected SNP MC4R polymorphism; 1.32 times higher (95 %CI 2.11–6.15; $p < 0.0001$) in patients with an unsatisfactory initial pattern of intestinal microbiota; and 1.8 times higher (95 %CI 1.1–1.26; $p < 0.0001$) in patients with an extensive family history of obesity.

Laparoscopic gastric bypass is the preferred surgical technique for obesity treatment to achieve an optimal EWL outcome (i 65 %) in patients with the MC4R SNP polymorphism, an unsatisfactory initial pattern of intestinal microbiota, and an extensive family history of obesity.

Declaration of interests

The authors declare that they have no conflicts of interest.

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Authors contributions

Ioffe OY: conception and critical revision of the manuscript; Kobzar PA: conception, design, data collection, analysis, and interpretation.

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Мультифакторна оцінка ефективності хірургічного лікування ожиріння

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Мета — створення моделі для вибору найефективнішого методу хірургічного лікування ожиріння.

Матеріали та методи. Дослідження проведено на базі кафедри загальної хірургії № 2 Національного медичного університету імені О. О. Богомольця. Досліджуваній групі пацієнтів (n = 53) виконували баріатричні втручання: лапароскопічне шлункове шунтування (37,7 %), лапароскопічну рукавну резекцію шлунка (32,2 %), установлення внутрішньошлункового балона із шунтуванням шлунка (30,1 %). Результат оцінювали через 12 міс. Контрольна група – 59 пацієнтів з ожирінням, яких лікували консервативно. Усім пацієнтам виконували рутинні загальноклінічні обстеження, генотипування з використанням системи Fast Real-Time PCR System у середовищі TaqMan, аналіз калу за допомогою полімеразної ланцюгової реакції для визначення параметрів кишкового мікробіому.

Результати. Статистична обробка даних виявила, що шанс отримати ідеальний результат найвищий у пацієнтів із поліморфізмом SNP MC4R, які мають незадовільний патерн кишкової мікробіоти, обтяжений сімейний анамнез щодо ожиріння та яким виконано лапароскопічне шлункове шунтування.

Висновки. Лапароскопічне шунтування шлунка є оптимальним методом хірургічного лікування ожиріння для досягнення ідеального результату. Наявність незадовільного початкового патерну кишкової мікробіоти, виявлення поліморфізму SNP MC4R та ожиріння в членів родини впливають на ефективність хірургічного лікування. Шанс досягнення ідеального результату в 3,6 разу вищий у пацієнтів із поліморфізмом SNP MC4R.

Ключові слова: лікування, поліморфізми, ожиріння, баріатрична хірургія.

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