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Circulating biomarker profile changes in obese patients undergoing bariatric surgery

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Abstract

Bariatric surgery (BS) remains the most effective treatment for morbid obesity (MO). It's relevant to identify biomarkers for predicting the outcome of BS in patients with MO. The aim of the study was to determine the dynamical change in the biomarker levels in patients undergoing BS and apparently healthy donors. Serum and plasma samples were obtained from 66 patients, of which 26 patients with MO (aged 26–72 years) underwent BS, and 40 healthy donors, at the age of 56 ± 10.3 years. Patient samples were obtained the day before BS (first group), 3–7 months after BS (second group), and 7 or more months after BS (third group). Analyte concentrations were determined by multiplex immunoassay on the xMAP platform (Luminex). Spearman's rank correlation was used. The nature of analyte variability was described by building multiple regression models. In the patients compared with healthy controls, differences in the levels of resistin, PAI1, MCP1, GLP1, leptin, FGF23, adiponectin, adipsin were observed. In patients after BS, the levels of resistin, ANGPTL6, FGF21, and leptin changed. In patients over 55 years old compared with younger patients, differences for total ANGPTL4, amylin, and pancreatic polypeptide were observed. Differences in levels of glucagon, resistin, GLP1 and leptin were noted between men and women. The dynamics of the levels of adipokines and incretins indicates biochemical changes in patients after BS compared with healthy persons.

Keywords: obesity, biomarkers, bariatric surgery, weight loss, body weight

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Introduction

Morbid obesity — exceeding the body mass index (BMI) ratio of 35 kg/m^2 — is one of the most important medical and social problems of our time (Ko and Delmonico, 2008). Morbid obesity is a consequence of adipose tissue dysfunction, in which there is an increase in the levels of pro-inflammatory adipokines, incretins and a decrease in anti-inflammatory adipokines. There are three main ways to treat MO: psychotherapy, including behavioral therapy, changing the patient's diet, pharmacotherapy, and bariatric surgery (BS). The most effective way in the long term, and with much evidence in evidence-based medicine, is BS (Sjöström, 2013; Jakobsen et al., 2018; Kvalem et al., 2015), which has been shown to alleviate metabolic disorders of MO, such as type 2 diabetes mellitus. Several types of BS are used nowadays.

Intragastric balloon placement (IGB) is a minimally invasive procedure for patients with a BMI over 50 kg/m^2 to reduce body weight to an optimal level. It is assumed that the intragastric balloon controls hunger and gastric emptying, patients

have changes in the secretion of cholecystokinin, pancreatic polypeptide, leptin (Mathus-Vliegen and de Groot, 2013; Mathus-Vliegen and Eichenberger, 2014). Although IGB shows good results on patient weight loss, the effect remains only for a short time and other techniques should be used to maintain weight (Kim et al., 2016).

Laparoscopic adjustable gastric banding (LAGD) — procedure that restricts a little portion of the stomach (15–50 mL) for oral intake; gastroplasty — longitudinal resection of the stomach converting the lesser curvature of the stomach into a narrow tube; gastric plication — reversible procedure that involves the application of several rows of stiches resulting in the formation of a narrow tube from the greater curvature of the stomach. In the 30 years since its invention (1993), LAGD has become a standard operation in bariatric surgery (Furbetta, Cervelli, and Furbetta, 2020). At the same time, the widespread and frequent use of LAGD has allowed a large body of data to accumulate, and we now know that 50–60 % of patients maintain sustained weight loss for 20 years after surgery (Furbetta et al., 2019).

Gastric bypass (GB) — procedure of creating a small upper pouch with a volume of 20–50 mL connected to the proximal or distal region of the jejunum with a Y-shaped anastomosis. Numerous recent studies suggest that bile acid metabolic pathways are "disrupted" after GB (Kuipers and Groen, 2014). Bile acids, whose synthesis is altered after surgery, are signaling molecules in several homeostatic processes: glucose metabolism, lipid regulation, and insulin synthesis (Patti et al., 2009; Li and Chiang, 2014). Several studies in recent years indicate that after surgery (GB), fibroblast growth factor-19 (FGF19) synthesis is altered through activation of the Farnesoid X Receptor. Higher levels of FGF19 production, through bile acid regulation, help maintain normal weight after surgery, and some evidence suggests that intravenous administration of FGF19 normalizes weight without surgery (Fu et al., 2004; Neuschwander-Tetri et al., 2015; Jain et al., 2018)

Biliopancreatic diversion (BPD) — procedure of imposing two anastomoses between the gastric tube, the jejunum and the biliopancreatic limb through which the gastric juices are passed to the region of the jejunal-ileal anastomosis. In recent years, more and more articles have appeared criticizing BPD as an outdated surgical procedure that leads to more side effects and less sustainable weight loss (Gagner, 2019; Papadia et al., 2023).

The dynamics of most biomarkers in patients with MO after BS remains unknown. In addition, the predictive biomarkers of metabolic conditions and prognosis after BS for patients with MO and diabetes mellitus (DM) have not yet been determined (O'Rourke et al., 2019). The majority of the published studies involves a small number of major biochemical markers as well as employs different analytical techniques making it difficult to compare the results. Few studies have been published on the dynamics of biomarkers after BS. The development of this field of work by involving a large number of patients and expanding the range of measured parameters is one of the promising ways of studying the physiological changes after BS. Such studies will allow the qualitative improvement of the MO therapy effectiveness and the accuracy of BS prognosis.

Since BS is a new field of research in Russia, there are almost no studies of the features of changes in biochemical status after bariatric intervention in the Russian population. The conduction of large-scale studies of biochemical parameters is undoubtedly problematic without the help of biobanks that ensure the collection and storage of not only biological material but also medical history.

The aim of this study was to examine the dynamical change in the circulating biomarker levels in patients undergoing BS in order to determine the major biochemical changes in patients with MO before and after BS.

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Materials and methods

Study design

Blood plasma and serum samples from patients who had previously undergone BS as well as apparently healthy donors acting as a control group were obtained from the biobank of City Hospital no. 40.

Study participants

The study included biological material (serum, blood plasma) obtained from 66 patients (30 women and 36 men) aged 38–83 years (44.5 ± 24.4 years). A mandatory inclusion criterion was the presence of a signed informed consent form. History of cancer was an exclusion criterion. The experimental groups were comprised of 26 patients with MO (17 women, 9 men), BMI 43.4 ± 10.7 kg/m^2, aged 26–72 years (47.0 ± 12.7 years) who had undergone BS (5 patients had undergone GB surgery and 21 patients had undergone GP). The samples were taken the day before surgery (the first experimental group, n = 26), 3−7 months after BS (the second experimental group, n = 26), 7 or more months after BS (the third experimental group, n = 21). The control group was represented by 40 donors (13 women and 27 men, BMI < 30 kg/m^2, aged 56.0 ± 10.3 years).

Inclusion criteria

Inclusion criteria for participation in the study:

1. Previously conducted BS;
2. No oncological diseases;
3. An informed consent form signed by the donor for the storage of their biological material in the bio-

bank and its subsequent use for any type of biomedical research;
4. Patient blood plasma or serum samples taken before and 3–18 months after BS available in the biobank of City Hospital no. 40.

Inclusion criteria of the control group:
1. BMI < 30.0 kg/m^2;
2. No oncological diseases, cardiovascular pathology or metabolic disorders;
3. An informed consent form signed by the donor for the storage of their biological material in the biobank and its subsequent use for any type of biomedical research;
4. Donor blood plasma or serum samples available in the biobank of City Hospital no. 40.

Conditions

All studies were conducted in City Hospital no. 40.

Outcome registration methods

The concentrations of protein biomarkers in blood plasma and serum were determined by multiplex immunofluorescence analysis using the MILLIPLEX MAP panel (Merck, Millipore). The reagent panels used in the study are listed in Table 1.

Frozen serum and plasma samples were used. Sample preparation and analysis were conducted according to the user protocol.

Statistical data processing

Version 4.0.2 of the R programming language and tidyverse, lubridate, car, Hmisc, corrplot packages from CRAN repository (https://www.R-project.org) were used for statistical analysis and graphical presentation of the results. The results were presented with the median of data as well as the first and third quartiles (ME (Q1; Q3)). The Shapiro-Wilk test was used to assess the normality of distribution. Spearman's rank correlation was used to determine the association between two unrelated values in the data set (in case of statistical significance $p < 0{,}05$). The nature of analyte variability was described by building multiple regression models with categorical variables where the values of analyte concentration in each sample served as an independent variable, and the patient group (one of the three experimental groups or the control group), gender and age acted as dependent variables. The patients were divided into three groups depending on their age: under 45 years old, 45–55 years old and over 55 years old. Akaike Information Criterion was used to select the model with the highest predictive power (Venables and Ripley, 2013).

Table 1. Reagent panels used in the study

CAT number	Analytes included in the panel	Full name
HLPPMAG-57K	ANGPTL3	Angiopoietin-like protein 3
	ANGPTL4	Angiopoietin-like protein 4
	ANGPTL6	Angiopoietin-like protein 6
	FABP1 (L)	Fatty acid-binding protein 1
	FGF19	Fibroblast growth factor 19
	FGF21	Fibroblast growth factor 21
	FGF23	Fibroblast growth factor 23
HADK1MAG-61K	Adiponectin	Adiponectin
	Adipsin	Adipsin (complement factor D)
	Total PAI-1	Plasminogen activator inhibitor 1 (total)
	Resistin	Resistin
HMHEMAG-34K	Total Amylin (IAPP)	Total Amylin
	C-peptide	C-peptide
	Ghrelin	Ghrelin
	GIP	Gastric inhibitory polypeptide
	GLP1 total	Glucagon-like peptide-1 (total)
	Glucagon	Glucagon
	IL6	Interleukin 6
	Leptin	Leptin
	MCP1 (CCL2)	Monocyte chemoattractant protein 1 (C-C motif chemokine ligand 2)
	Pancreatic peptide (PP)	Pancreatic peptide
	PYY	Peptide YY (peptide tyrosine tyrosine)
	TNFα	Tumor necrosis factor alpha

Results

Multiple changes in the concentrations of circulating biomarkers were discovered in patients with MO after BS via regression model (Tables 2, 3). Furthermore, the biomarkers with significantly different levels in patients with MO and healthy controls were identified. In addition to the discovered intergroup differences, the biomarkers, whose levels were influenced by the age and gender of the patients, were identified (Tables 2, 3).

The patients in the control group and those under the age of 55 prior to their BS showed a higher level of

Table 2. The dependence of the analyte concentrations on gender of patients and healthy persons

Biomarker	Control group	Experimental groups		
		Group 1 (before BS)	Group 2 (3–7 months after BS)	Group 3 (7 and more months after BS)
Adiponectin, mg/L	12090.0 (80.3; 20000.0)	1496.9[a] (86.5; 10572.5)	12000.0 (156.9; 20277.5)	13435.0 (179.1; 20000.0)
Resistin, mg/L	84.7 (32.1; 1690.0)	2824.5[a] (1231.8; 4060.8)	423.1[b] (31.8; 3386.0)	2438.0 (33.1; 5587.0)
Resistin, mg/L (♀)	54.3 (26.5; 93.0)	2401.0*,[a] (39.5; 3682.0)	70.5[b] (28.3; 2640.8)	2018.0 (33.1; 5685.0)
Resistin, mg/L (♂)	149.6 (33.4; 1703.0)	3887.0*,[a] (2666.0; 6867.0)	3020.5[b] (88.2; 3816.5)	4738.0 (33.1; 5293.0)
Adipsin, mg/L	4509.0 (23.9; 10067.5)	92.3[a] (34.5; 1645.3)	650.6[a] (48.6; 3167.0)	132.8[a] (48.8; 2327.2)
Total PAI1, mg/L	90.8 (47.0; 4925.5)	8439.0[a] (2898.0; 13202.5)	3527.0 (30.0; 11432.5)	4464.0 (29.8; 12902.5)
ANGPLT3, mg/L	6.8 (5.0; 11.8)	5.3 (3.6; 8.9)	7.2 (5.5; 8.9)	6.8 (4.9; 9.7)
ANGPLT4, mg/L	202.1 (94.7; 307.7)	247.5 (159.2; 308.8)	312.7 (282.7; 395.8)	261.6 (203.1; 303.5)
ANGPLT6, mg/L	113.2 (50.3; 228.1)	281.1 (72.6; 730.1)	706.8[a] (417.7; 880.2)	577.5[a] (255.3; 967.4)
ANGPLT6, mg/L (♀)	100.3 (70.6; 153.6)	331.7 (113.6; 612.9)	823.4[b] (642.4; 980.4)	652.5 (421.6; 1025.0)
ANGPLT6, mg/L (♂)	144.7 (46.5; 247.5)	135.6 (70.9; 737.8)	465,9 (305.7; 754.8)	108.9 (58.5; 340.5)
FABP1, ng/L	255.2 (0.0; 1047.0)	1325.0 (570.8; 2449.0)	970.0 (0.0; 1853.5)	749.5 (398.1; 2902.0)
FGF19, ng/L	0.0 (0.0; 119.2)	0.0 (0.0; 8.4)	0.0 (0.0; 8.4)	0.0 (0.0; 0.0)
FGF21, ng/L	180.6 (60.3; 578.7)	283.4 (144.2; 661.8)	671.1 (381.3; 893.8)	611.8[a,b] (306.2; 977.8)
FGF23, ng/L	0.0 (0.0; 54.3)	0.0[a] (0.0; 0.0)	0.0[a] (0.0; 0.0)	0.0[a] (0.0; 0.0)
Total amylin, ng/L	7.3 (4.6; 13.6)	7.5 (5.6; 12.7)	9.6 (7.1; 11.9)	7.7 (6.6; 9.0)
C-peptide, ng/L	633.0 (54.1; 1296.0)	286.4 (109.5; 367.7)	396.4 (241.0; 727.2)	296.1 (210.3; 447.9)
C-peptide, ng/L (♀)	570.8 (74.7; 1150.0)	352.6[a] (173.6; 576.3)	516.8[a] (330.0; 753.0)	300.1[a] (249.4; 451.7)
C-peptide, ng/L (♂)	767.2 (27.7; 1301.5)	140.8 (100.0; 209.7)	283.1 (94.1;468.5)	292.1 (177.1; 376.8)
Ghrelin, ng/L	5.6 (0.6; 11.1)	8.4 (3.8; 22.0)	6.5 (4.5; 9.5)	5.1 (1.5; 6.6)
GIP, ng/L	40.7 (23.0; 63.9)	35.5 (26.2; 61.6)	61.0 (47.2; 76.0)	66.2 (43.3; 91.2)
Total GLP1, ng/L	106.4 (86.8; 151.8)	137.2[a] (102.5; 185.2)	144.4[a] (76.8; 205.4)	134.6 (88.9; 152.6)
Total GLP1, ng/L (♀)	90.5* (74.9; 153.4)	137.1*,[a] (96.2; 154.2)	114.8[a] (73.3; 195.6)	126.8 (84.4; 151.7)
Total GLP1, ng/L (♂)	109.9* (97.7; 149.3)	178.8*,[a] (122.3; 202.9)	176.5[a] (142.4; 214.7)	142.4 (111.6; 152.9)

End of the Table 2

Biomarker	Control group	Experimental groups		
		Group 1 (before BS)	Group 2 (3–7 months after BS)	Group 3 (7 and more months after BS)
Glucagon, ng/L	28.9 (7.6; 53.7)	23.6 (5.4; 44.8)	26.1 (10.5; 52.0)	27.1 (0.0; 56.0)
Glucagon, ng/L (♀)	15.0* (0.0; 33.8)	21.1* (5.4; 38.5)	19.5 (1.4; 33.5)	29.0 (0.0; 57.5)
Glucagon, ng/L (♂)	40.3* (11.2; 57.5)	38.0* (5.4; 82.1)	49.0 (26.2; 64.3)	13.1 (0.0; 43.7)
IL6, ng/L	0.0 (0.0; 1.6)	0.6 (0.0; 5.9)	0.4 (0.0; 6.0)	0.2 (0.0; 3.2)
Leptin, ng/L	3617.0 (1474.5; 5806.5)	15465.0[a] (7360.8; 21855.0)	7853.5[b] (2901.8; 11680.0)	5855.5[b] (3615.5; 9451.0)
Leptin, ng/L (♀)	5741.0* (4840.0; 9330.0)	19260.0*,[a] (14460.0; 27020.0)	8695.0[b] (5697.8; 14725.0)	7568.0[b] (5307.0; 13130.0)
Leptin, ng/L (♂)	2396.0* (877.1; 4796.0)	5901.0*,[a] (3360.0; 13720.0)	2773.0[b] (1282.2; 7796.2)	1971.0[b] (1371.0; 2438.0)
MCP1, ng/L	176.5 (117.8; 277.4)	114.4[a] (75.2; 217.6)	88.2[a,b] (69.5; 114.3)	89.5[a] (77.8; 118.2)
PP, ng/L	48.0 (36.7; 77.6)	47.8 (37.8; 108.8)	45.0 (22.0; 84.2)	48.7 (35.0; 103.0)
PYY, ng/L	46.9 (0.0; 66.0)	37.5 (0.0; 55.4)	40.7 (0.0; 67.5)	38.6 (12.9; 70.1)
TNFα, ng/L	4.0 (1.8; 6.4)	2.0 (1.3; 2.7)	2.2 (1.7; 3.6)	1.9 (1.2; 3.5)
TNFα, ng/L (♀)	3.4 (3.0; 4.4)	2.0[a] (1.3; 2.8)	1.9[a] (1.4; 3.1)	1.9[a] (1.2; 3.3)
TNFα, ng/L (♂)	4.5 (1.5; 6.8)	1.8 (1.3; 2.2)	3.0 (2.1; 4.1)	1.3 (1.2; 3.9)

Data are presented with median and interquartile range. * — differences between male and female patients ($p < 0.05$), [a] — differences from the control group ($p < 0.05$), [b] — differences from the experimental group 1 ($p < 0.05$).

ANGPTL4 compared to the patients over 55 years of age (Table 3). No statistically significant differences in ANGPTL3 levels were observed between patients from different groups as well as depending on gender and age. No differences for this analyte were found between the experimental and control groups, as well as between men and women within these groups (Table 2). There was an increase in ANGPTL6 levels in female patients with MO after BS in the second experimental group ($p = 0.0005$) followed by a decrease to levels statistically indistinguishable from the initial values (Table 2). At the same time, differences were observed in female patients from the second ($p = 0.000001$) and third ($p = 0.0009$) experimental groups compared to the patients from the control group (Table 2). However, analyte concentrations did not differ statistically between females from the first experimental group and the control group. Men did not show such alterations in ANGPTL6 concentrations.

Patients from the third experimental group (7 or more months after BS) showed a higher level of FGF21 compared to the control ($p = 0.028$) and first ($p = 0.025$) experimental groups (Table 2). In our study the level of FGF23 was statistically lower in patients before and after BS (experimental groups 1–3) compared to the control group ($p = 0.042$; $p = 0.033$ and $p = 0.036$, respectively) (Table 2). No statistically significant differences in FGF19 levels were observed between patients from different groups as well as depending on gender and age. However, no changes in the levels of FGF23 concentrations were observed in patients from the experimental groups.

Higher levels of resistin were observed in patients from the first experimental group (before BS) compared to the control group ($p = 2.63 \times 10^{-6}$). A decrease in resistin level was observed 3–7 months after BS compared to the preoperative level ($p = 0.005$). In addition, significant differences in resistin levels associated with gender were observed among the patients from the first experimental group with resistin levels being lower in female patients ($p = 0.005$) (Table 2).

Table 3. The dependence of the analyte concentrations on the age of patients and healthy persons

Biomarker (age group)	Control group	Experimental groups		
		Group 1 (before BS)	Group 2 (3–7 months after BS)	Group 3 (7 and more months after BS)
ANGPLT4, mg/L (< 45 years old)	257.2 (231.8; 707.7)	128.0 (82.3; 283.1)	164.6 (108.3; 256.6)	248.4 (184.1; 315.7)
ANGPLT4, mg/L (45–55 years old)	247.6 (216.8; 333.8)	203.0* (109.2; 276.0)	394.8* (303.6; 426.2)	300.0* (238.6; 327.1)
ANGPLT4, mg/L (> 55 years old)	302.5 (287.7; 324.6)	321.4* (303.5; 368.5)	203.1* (76.4; 283.9)	239.9* (191.8; 262.3)
Total amylin, ng/L (< 45 years old)	11.4 (7.3; 14.2)	4.1 (1.5; 8.5)	10.9 (5.0; 15.0)	6.7 (5.0; 10.2)
Total amylin, ng/L (45–55 years old)	7.3 (6.5; 10.5)	10.8* (8.4; 15.9)	10.2* (6.8; 12.0)	9.8 (8.3; 12.2)
Total amylin, ng/L (> 55 years old)	8.8 (7.2; 10.1)	6.8* (6.6; 7.7)	7.1* (5.0; 7.9)	8.8 (8.1; 27.5)
PP, ng/L (< 45 years old)	38.2 (34.2; 53.1)	50.1 (37.0; 63.1)	55.0 (41.6; 163.8)	41.8 (26.8; 78.0)
PP, ng/L (45–55 years old)	44.8 (39.0; 85.8)	69.3* (61.5; 127.6)	43.6* (16.0; 84.2)	38.0* (25.8; 79.0)
PP, ng/L (> 55 years old)	58.8 (39.7; 128.5)	15.6* (11.1; 40.4)	84.3* (51.8; 109.7)	53.1* (40.0; 97.2)

Data are presented with median and interquartile range. * — differences between patients of different age groups ($p < 0.05$).

This study showed an increase in adiponectin levels after BS. Its concentration was significantly lower ($p = 0.013$) in patients from the first experimental group (before BS) than in the healthy controls (Table 2). No differences in adiponectin levels between patients after BS (experimental groups 2 and 3) and members of the control group were determined.

Higher adipsin levels were observed in the control group compared to the experimental groups 1–3 ($p = 0.031$; 0.008 and 0.014, respectively) (Table 2).

We observed a higher ($p = 0.003$) level of total PAI1 in patients from the experimental group before BS compared to the control group (Table 2).

The first experimental group (before BS) presented higher levels of leptin compared to the control group ($p = 0.0003$). The levels of leptin after BS decreased to the preoperative level. This decrease was observed both in the second ($p = 0.0099$) and third ($p = 0.0115$) experimental groups (Table 2).

We identified significant gender-based differences in the serum concentrations of leptin, glucagon and total GLP1 in all the experimental groups. Females showed a significantly higher level of leptin ($p = 8.89 \times 10^{-5}$) and a decrease in the levels of glucagon and GLP1 ($p = 0.008$ and $p = 0.05$, respectively) (Table 2). The levels of total GLP1 were higher in the first and second experimental groups than in the control group ($p = 0.026$ and $p = 0.010$, respectively). The levels of GLP1 7 months after BS were statistically indistinguishable from the control group.

Lower levels of MCP1 were established in the experimental group before BS compared to the control group ($p = 0.044$), as well as a tendency towards their decrease in the postoperative period ($p = 0.039$) relative to the initial values (Table 2).

Our study showed lower levels of TNFα and C-peptide ($p < 0.01$ and $p < 0.05$, respectively) in female patients from the experimental groups both before and after BS compared to the control group. At the same time, there was no change in the levels of these analytes after BS (Table 2). This pattern was not observed in male patients.

Higher levels of total amylin and pancreatic polypeptide were demonstrated in patients over 55 years of age compared to younger individuals ($p = 0.026$ and $p = 0.003$, respectively) (Table 3).

Discussion

The family of angiopoietin-like proteins (ANGPTL) includes eight proteins that differ by their function. All members of this family are structurally similar to angiopoietin; however, they do not bind to angiopoietin receptors and are considered orphan ligands. Only three of these proteins — ANGPTL3, 4 and 6 — are found in the systemic circulation and can affect glucose and lipid metabolism, as well as energy homeostasis (Cinkajzlova et al., 2017). However, the exact role of these proteins remains unclear. Similar to the results observed in our

study, researchers from the Institute of Medical Biochemistry and Laboratory Diagnostics at Charles University (Prague, Czech Republic) noted the initial levels of ANGPTL6 did not differ between patients with MO and type 2 diabetes mellitus (T2DM), and those from the control group (Cinkajzlova et al., 2017). Also, the researchers noted a similar pattern for the profile of serum ANGPTL6, as well as its mRNA expression in tissues. The primary increase in the level of ANGPTL6 was followed by a decrease to control levels 12 months after BS in 13 patients with MO (BMI > 40.0 kg/m^2) and T2DM, and 23 patients with MO but without diabetes on a low-calorie diet. Thus, the change in ANGPTL6 levels can be associated with the process of weight loss, regardless of the cause for nutritional deficiency. In a 2022 study, plasma ANGPTL3 and ANGPTL4 concentration levels were shown to change after surgery: ANGPTL4 decreases after surgery, while ANGPTL3 concentration increases, but only after BPD (Bini et. al., 2022). The reduction in ANGPTL4 concentration is explained by a decrease in body fat mass and an improvement in the body's sensitivity to insulin, which regulates ANGPTL4 synthesis through ChREBP activation (Kersten et al., 2000; Bini et. al., 2021). In our study, we also found a decrease in ANGPTL4 concentration after BS, but only in patients older than 55 years.

The family of fibroblast growth factors (FGF) includes 23 proteins that are involved in the regulation of a wide variety of biological functions. Unlike most members of this family, FGF19, 21 and 23 (along with FGF11–14) do not have a pro-proliferative effect. To date, it has been shown that FGF19 functions as a regulator of bile acid and cholesterol synthesis. FGF21 participates in the regulation of glucose and lipid metabolism, while FGF23 is predominantly involved in the physiological regulation of renal phosphate and vitamin D metabolism (Ezzat and Asa, 2005). Similar to the results observed in our study, Fjedborg et al. also observed a lower level of FGF21 ($p < 0.001$) in 31 patients after GB. Moreover, its level correlated with the content of fat in the liver ($r = 0.40$, $p < 0.05$) (Fjeldborg, Pedersen, Møller, and Richelsena, 2017). Nevertheless, a study by Woelnerhanssen et al. did not reveal any changes in FGF21 levels over time in 23 patients with MO after GP and GB (Woelnerhanssen et al., 2011). In a study conducted in Denmark, researchers tested the hypothesis that bariatric surgery affects circulating FGF21 concentrations, based on the earlier assumption that FGF21 influences the subjective evaluation (positive) of taste from eating foods high in sugar (Nielsen et al., 2021). Although they confirmed the negative correlation between biomarker concentration and hedonic evaluation of foods (albeit with a high p-value), they could find no evidence for a postoperative change in FGF21 concentration. The evidence for the effects of bariatric surgery on patients with diabetes is still mixed, for example, a research group from Taiwan found a significant decrease in FGF21 concentration levels after surgery, but more pronounced in diabetic patients, although even if the patient did not have diabetes, regression showed a significant decrease in FGF21 concentration (Yen et al., 2020).

There are few studies on the effect of BS on resistin levels and they do not allow definitive conclusions to be drawn. Some researchers also reported a postoperative decrease in resistin levels while others did not discover any significant alterations in pre- and postoperative values (Adami, Scopinaro and Cordera, 2016; Kelly et al., 2016). A paper by scientists from İstanbul University studied the effect of BS on obesity-related peptides. Although the paper has a rather small sample, the significance of statistical tests is high enough to be trustworthy. The conclusion regarding resistin in the publication is as follows: resistin concentration is significantly higher in obese patients than in patients from the control group (healthy), but it begins to decrease after BS, with the level reducing 6 months after surgery ($Me = 5.68$) to the level of concentration in patients from the control group ($Me = 4.95$) (Arica et al., 2018).

Our results showing an increase in adiponectin levels after BS are fully consistent with numerous studies on adiponectin profile both in patients with MO and those in the process of weight loss (both as a result of diet and after BS) (Adami, Scopinaro and Cordera, 2016; Kelly et al., 2016; Sams et al., 2016). The decrease in adiponectin levels in these studies correlated with a reduced risk of cardiovascular complications and a decrease in insulin resistance in patients with T2DM. At this point, the issue of increased adiponectin levels is not controversial; for example, one meta-analysis shows that 54 studies have seen an increase in concentrations of this hormone after BS (Askarpour et al., 2020).

We observed the higher adipsin levels in the control group versus the experimental groups 1–3. However, Vasilenko et al. reported higher levels of adipsin in obese patients compared to those with normal body weight (Vasilenko et al., 2017). A similar correlation is also found in other studies, although, as in our study, the p-value of these statistical tests is often quite large — often above 0.01, as in our case (Lejawa et al., 2021; Milek et al., 2022). Our data contradict the results of Vasilenko et al. but are generally consistent with the conclusions by Flier et al. drawn from the results of experiments on animal models. There was a significant decrease in the amount of circulating adipsin in rodents with genetically determined obesity as well obesity induced by glutamate injections. Albeit to a much lesser extent, this effect was also reported in animals whose obesity had been caused by excessive calorie intake (Flier, Cook, Usher, and Spiegelman, 1987).

Our data showing the higher level of total PAI1 in patients from the experimental group before BS are con-

sistent with the results of the researchers from Istanbul University (Turkey) showing higher PAI1 levels in serum samples from 37 obese patients (aged 60.6 ± 8.9 years, BMI 31.4 ± 3.9 kg/m^2) compared to the control group (n = 20, aged 54.85 ± 7.3 years, BMI 27.7 ± 4.2 kg/m^2) (Gazioglu, Akan, Atalar, and Erten, 2015). The study by Elci et al. reported higher serum levels of PAI1, asymmetric dimethylarginine, C-reactive protein, homocysteine, vascular endothelial growth factor (VEGF) and ANGPTL6 in 30 obese female patients with polycystic ovary syndrome (aged 22.6 ± 3.4 years, BMI 31.57 ± 1.59 kg/m^2) compared to the control group (n = 30) (Elci et al., 2017). These results combined with our data indicate that elevated PAI1 levels may reflect the presence of dyslipidemia, atherosclerosis and obesity. Decreases in body weight and severity of listed conditions also lead to the normalization of PAI1 levels. A similar effect is observed in the study of P. J. Hohensinner and a team of scientists: the level of PAI1 concentration decreased in patients after BS even 2 years after surgery (Hohensinner et al., 2018). The researchers attribute the decrease in protein concentration to the fact that the disappearance of adipose tissue also leads to the reduction of senescent cells accumulated in them. At the same time, an increase in telomere length was found, which was possible due to the fact that blood was taken so long after the surgery (Formichi et al., 2014).

Researchers from the University of Minnesota (USA) also reported a decrease in serum leptin and IL6 levels in 39 teenage patients with MO (mean age 16.5 ± 1.6 years, BMI 52.8 ± 9.6 kg/m^2) 12 months after GB and GP. It is reasonable to suggest that after BS, lower levels of leptin, IL6 and higher levels of adiponectin contribute to a potential decrease in the risk of T2DM and cardiovascular diseases and indicate the success of BS (Adami, Scopinaro and Cordera, 2016; Kelly et al., 2016). Decreased serum leptin concentrations are not found only in young patients, the already mentioned meta-analysis stipulates that decreased concentrations were recorded in 17 studies on 2751 patients, and the researchers stated differences between the groups separated by gender, age, and type of surgery (Askarpour et al., 2020).

Contrarily to our data showing that the levels of GLP1 7 months after BS were statistically indistinguishable from the control group, Jiang et al. reported an increase in GLP1 levels in 20 patients with MO and T2DM 1, 3, 6, 9 and 12 months after laparoscopic IGB. Moreover, GLP1 was negatively correlated with fasting glucose, insulin, glycosylated hemoglobin and C-peptide (Jiang et al., 2010).

Our results showing the decreasing levels of MCP1 in the experimental group before BS are consistent with the data from the University of Copenhagen (Denmark) that showed a decrease in MCP1 levels ($p < 0.0001$) with weight loss due to GB (1 week, 3 months and 1 year after BS) while there was no change in the levels of YKL40 ($p \geq 0.120$) (Thomsen et al., 2013). Several studies have also found the opposite data, MCP1 was higher in patients without MO (Sachan et al., 2020; Abulmeaty et al., 2023).

In addition, Sams et al. studied the effect of laparoscopic GB and IGB on cytokine levels (TNFα, MCP1, adiponectin) in serum and adipose tissue from 25 patients 2 weeks and 6 months after BS. The researchers noted a tendency towards a decrease in MCP1 levels after surgery, whereas the levels of adiponectin in serum and adipose tissue increased already 2 weeks after BS, while the levels of TNFα remained stable (Sams et al., 2016).

The changes of the levels of TNFα in our patients are consistent with the results by Viana et al. that showed a significant decrease in serum IL6 and TNFα concentrations one year after BS ($p < 0.05$) (Viana et al., 2013). The observed dynamics of TNFα may indicate a decrease in inflammation and oxidative stress due to the lowered levels of reactive oxygen species, nitric oxide, prostaglandins and lipid peroxidation as a result of BS.

Conclusions

We studied the dynamics of the circulating biomarker levels in patients undergoing BS in order to determine the main biochemical changes in MO patients before and after BS. The discovered changes indicate the presence of significant shifts in the balance of adipokines, incretins and hormones associated with the formation of eating behavior. Moreover, the observed changes did not depend on the type of BS and were demonstrated both in patients who had undergone GP and in those who had had a more drastic reconstruction of the gastrointestinal tract such as GB. Thus, no change in biomarker levels was observed that could be associated with the malabsorptive effect after GB.

The majority of circulating biomarkers, which differed between the patient groups according to the regression model, belongs to the biomarkers of obesity and associated pathology — T2DM and metabolic syndrome. These include resistin, adiponectin, PAI1, leptin and MCP1. Other studies also demonstrate that these proteins are linked to obesity and comorbid conditions.

Another group of important analytes can be attributed to the biomarkers of the active fat loss phase since the peak of their level deviation from the baseline occurs during the first months after BS. At the same time, the return to initial values is typical for these biomarkers 7 or more months after surgery when the weight loss process usually slows down. This group of analytes involves ANGPTL6, GLP1 and adipsin.

The observed differences in the total levels and dynamics of ANGPTL6, resistin, C-peptide, GLP1, tumor necrosis factor, leptin and glucagon between female and male patients indicate gender-based differences in the

mechanisms of weight loss. Subsequent studies should take these differences into account and include the main spectrum of sex steroid hormones in the list of studied analytes. This may help clarify the relationship between the functioning of the endocrine system and the synthesis of adipokines and incretins in patients with MO.

The determined features of serum ANGPLT4, total amylin and pancreatic peptide concentrations indicate the necessity to exclude patients over 55 years of age from future studies in order to minimize the age factor.

No such study has previously been conducted among the residents of the North-West region. The biological material of the study participants as well as apparently healthy donors was collected, stored and characterized in the biobank of City Hospital no. 40 from 2015 to 2019. The collection of biological material continues in order to expand the number of patients in the experimental group as well as to form a most representative control group. Further research will involve not only increasing the number of study participants, but also expanding the range of the analyzed factors. One of the research directions will be the identification of links between the changes in the biochemical profile and physiological parameters, which will allow most accurate determination of the molecular mechanisms that are shifted as a result of BS.

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