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Article

Proper Diet without Probiotic Administration May Reduce Depressive Symptoms in Patients after Bariatric Surgery: A Randomized Double-Blind Placebo Controlled Pilot Study

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Abstract: (1) Background: Studies have shown that some patients experience mental deterioration after bariatric surgery; (2) Methods: We examined whether the use of probiotics and improved eating habits can improve the mental health of people after bariatric surgery who suffered from mood disorders. We analyzed patients' mental state, eating habits and microbiota; (3) Results: Depressive symptoms were observed in 45% of 200 bariatric patients. After 5 weeks, we noted an improvement in patients' mental functioning (reduction in BDI and HRSD), but it was not related to the probiotic used. Consumption of vegetables and whole grain cereals increased (DQI-I adequacy), consumption of simple sugars and SFA decreased (moderation DQI-I), and consumption of monounsaturated fatty acids increased it. In the feces of patients after RYGB, there was a significantly higher abundance of Muribaculaceae family, Veillonella and Roseburia, while those after SG had more Christensenellaceae R-7 group, Subdoligranulum, Oscillibacter and UCG-005; (4) Conclusion: The noted differences in the composition of the gut microbiota (RYGB vs SG) may be one of the determinants of the functioning of the gut-brain microbiota axis, although there is currently a need for further research on this topic with a larger group of patients and different probiotic doses.

Keywords: bariatric surgery; sleeve gastrectomy; Roux-en-y gastric bypass; obesity; microbiota; gut-brain axis; beck scale; depression; diet; probiotics

1. Introduction

One of the benefits of bariatric surgery is the improvement of psychosocial status, social relationships, and quality of life [1,2]. Depression and anxiety symptoms decrease in the majority of patients 6-24 months after bariatric procedure. However, they reappear in some patients during 36-60 months even to pre-surgery levels [3]. Studies have shown that compared to preoperative values, 10 years after bariatric surgery (despite successful weight loss), patients' mental status deteriorates, including overall mental health, sense of control, and fear of intimacy [4]. The meta-analyzes

performed suggest that patients undergoing bariatric surgery have a higher risk of self-harm/suicide attempts than the control group, matched in terms of age, gender, and BMI. The authors suggested that this may be related to various pre- and postoperative psychosocial, physiological, and medical factors [5,6].

One of the factors affecting mental state and mood is gut microbiota [7]. The diagnosis of mental disorders (including depression) is associated with the presence of dysbiosis [8]. In our previous study we shown that bariatric surgery affects the gut microbiota, which may play an important role in the development of depressive and gastrointestinal symptoms [9]. Low fiber consumption and increased levels of faecal isobutyric acid may lead to intestinal inflammation. Alterations of the composition or function of the microbiota in depressed patients may be related to inflammation, reduced production of short-chain fatty acids, impaired intestinal barrier integrity, and abnormalities in neurotransmitter, carbohydrate and amino acid metabolism [10]. Psychobiotics are probiotics that have a beneficial effect on mental health [11]. Most systematic reviews and meta-analyses confirm the beneficial effects of psychobiotics on depressive symptoms in healthy people, patients with major depressive disorder (MDD) and people with various concomitant psychiatric and somatic disorders [12,13]. The mechanism of action of psychobiotics is not well understood. It may be related to a reduction in blood levels of kynurenine [14,15], which may have neurotoxic and neurodegenerative effects [16]. Other mechanisms are related to urinary cortisol reduction, anti-inflammatory effects [13,17,18] or increased production of brain-derived neurotrophic factor (BDNF), which correlates with antidepressant activity [19]. Supplementation with *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 strains reduced the level of somatization, anxiety, intensity of depressive behaviors and hostility index, as well as plasma cortisol levels [20].

Nutritional status of the organism is also important for proper psychological functioning. For patients after bariatric surgery, a diet of energy-dense meals with large amounts of vegetables and fruits and a restriction of highly processed products, saturated fatty acids (SFA), and simple sugars is recommended. In addition, the adequate amount of protein in the diet is crucial, with an estimated amount of 60-80 g / day. Dairy products, eggs, fish, lean meat and seeds of legumes are recommended as the main sources of protein. Equally important is the consumption of complex carbohydrates that provide fiber, as well as adequate vitamin and mineral intake [21–24]. Such a diet is known to be optimal for improving the composition of the intestinal microbiota [25,26].

Unfortunately, despite these recommendations, protein, vitamin and mineral deficiencies are diagnosed in many patients after bariatric surgery. The main causes are: insufficient consumption of individual food components, development of food aversion, lack of recommended nutritional supplementation, decreased secretion of hydrochloric acid in the stomach, bypassing a part of the intestine that allows absorption of nutrients, and gastrointestinal concomitants [27]. Also, in patients suffering from depression, the concentration of many micronutrients in the diet is low, as well as omega-3 fatty acids [28]. It is known that vitamin B deficiency contributes to the development of hyperhomocysteinemia (found in some patients after bariatric surgery), which correlates with the development of depression, for example, through the generation of oxidative stress, remodeling of the extracellular matrix of the brain and endothelial dysfunction, and disruption of the integrity of the blood-brain barrier [29]. A low intake of omega-3 fatty acids in the diet combined with a high intake of omega-6 fatty acids (a typical ratio in the Western diet) increases the concentration of lipopolysaccharide (LPS) and LPS-binding protein (LBP) in the blood, increases intestinal permeability, and thus increases the risk of developing depressive disorders [28].

To the best of our current knowledge, there are few scientific studies addressing the relationship between dietary changes, intestinal barrier functioning, and worsening mental status in patients after bariatric surgery. The aim of the study was to evaluate the efficacy of a five week probiotic therapy with multistrain probiotic preparation (Sanprobi Barrier) and the introduction of a balanced diet to improve the mental performance of patients ≥6 months after bariatric surgery who suffered from mood disorders. The multi-strain probiotic, used in the study showed previously both a reduction in depressive symptoms [30,31], and favourable effect on metabolic risk factors. Additionally it

improves integrity of the gut barrier [32–34] and can modify the influence of microbiota on biochemical, physiological and immunological parameters related to obesity and inflammation [35].

2. Materials and Methods

Two hundred patients who had undergone a Roux-en-Y gastric bypass (RYGB) or a sleeve gastrectomy (SG) at least 6 months before, completed the Beck Depression Inventory (a self-rating scale to screen for depression symptoms). Patients with a score of ≥12 points were eligible for the study [36–38]. Of the 90 subjects who scored ≥12 points, 23 subjects had exclusion criteria (taking antibiotics and proton pump inhibitors in the six months before testing), and 29 subjects declined further participation in the project. This allowed the initiation of further studies with a group of 38 patients. During the first study visit, biological material (blood, feces) was collected, and anthropometric measurements and a questionnaire test were performed. Diet was assessed using a food diary for the previous 72 hours.

Patients were randomized and double-blinded into two groups, one of which received a probiotic or placebo for a period of 5 weeks:

- Probiotic: Sanprobi Barrier (Sanprobi), consisting of Bifidobacterium bifidum W23, Bifidobacterium lactis W51, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Levilactobacillus brevis W63, Lactocaseibacillus casei W56, Ligilactobacillus salivarius W24, Lactococcus lactis W19, and Lactococcus lactis W58;
- Placebo: corn starch, maltodextrins, vegetable protein;
- Dosage: 4 capsules (2.5×10^9 CFU)/day (taken with a meal (2 capsules in the morning and 2 capsules in the evening)).

Patients in both groups were educated about the principles of a healthy diet and were given a balanced meal plan tailored to the needs of patients after bariatric surgery [21]. After 5 weeks, patients were invited back for a follow-up visit, and the entire series of trials was repeated (Figure 1).

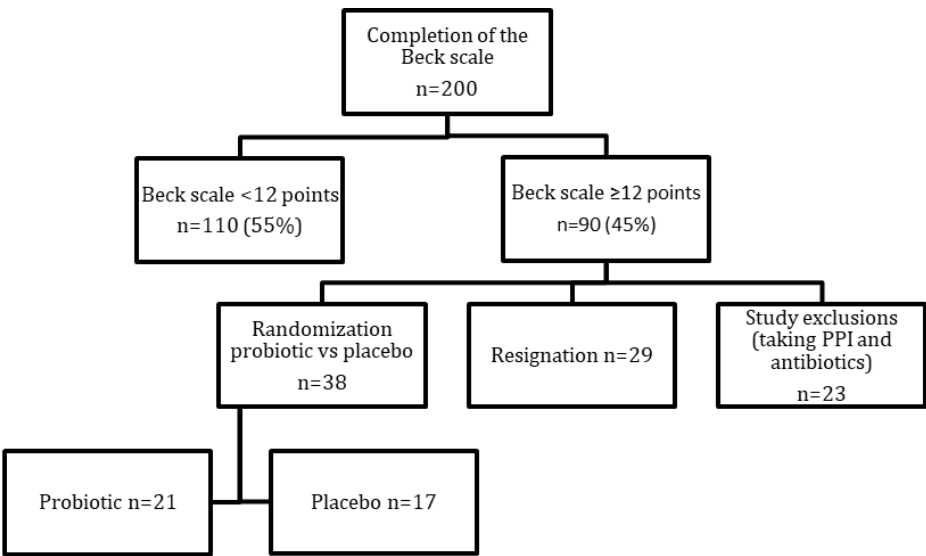


Figure 1. Study design.

Anthropometric examinations

Body composition analysis was performed using a Jawon Medical ioi-353 analyzer (Korea). Body height [cm] was measured using a metric stadiometer. Waist circumference [cm] and hip circumference [cm] were measured using a tape measure.

Survey research - mental state

Beck Depression Inventory (BDI)- a self-assessment questionnaire was used to assess the occurrence and severity of depressive symptoms. The total score ranges from 0 to 63 points, with the higher the score, the higher the severity of depressive symptoms. ≥ 12 points were considered as the presence of depressive symptoms [36–38].

The Athenian Insomnia Scale - is a scale consisting of 8 items that assess falling asleep, waking up at night and in the morning, total sleep time, sleep quality, well-being, psychophysical fitness, and daytime sleepiness. The total score ranged from 0 to 24 points, with a higher score representing poorer sleep quality. A score of ≥ 6 points was considered insomnia [39].

The Hamilton Depression Rating Scale (HDRS) was administered by an experienced psychiatrist. A 21-item version was used in the study, including items on guilt, suicidal ideation, circadian rhythm disturbances, agitation, anxiety, somatic symptoms, and psychomotor retardation. Responses are scored on a scale of 0-4 and 0-2. A score of ≥ 7 points indicates the presence of depression [40,41].

Eating habits assessment

A food frequency questionnaire (FFQ), consisting of a comprehensive list of foods and beverages with response categories indicating usual frequency of consumption over a period of time (never or almost never, once a month or less often, several times a month, several times a week, every day, several times a day) was used.

The consumption log for the last 72 hours was evaluated using the Diet 5D program (Food and Nutrition Institute, Warsaw). Based on the data collected with the above tools, the International Diet Quality Index (DQI-I) was calculated, with a total score ranging from 0 to 100 points. The lower the score, the poorer the quality of the diet used. This indicator consists of four categories:

- Variety - consumption of each food group (fish, meat, eggs, legumes, vegetables, fruits, cereals) and different sources of protein (fish, meat, eggs, legumes, dairy products) (0-20 points).
- Adequacy - assessment of consumption of individual food components that need to be supplied to ensure a healthy diet and prevent malnutrition (vegetables, fruits, cereals, fiber, protein, iron, calcium, vitamin C) (0-40 points)
- Moderation - assessing the consumption of dietary components that may require a reduction in daily intake due to an increased risk of developing chronic diseases (total fat, cholesterol, saturated fatty acids, sodium, low calorie foods) (0-30 points)
- Overall dietary balance-assessment of the ratio of individual macronutrients and fatty acids (0-10 points) [42].

Laboratory tests

Biological material was collected from patients at two time points - visit 1 and control (after 5 weeks). Venous blood was collected in EDTA tubes, centrifuged (3500 rpm for 10 minutes), and then the plasma and morphos fractions were separated in each eppendorf. Stool was collected using a stool sample kit (Kaśzyk, Poland). The biological material was stored at -80°C until laboratory analyses were performed.

Markers of the intestinal barrier integrity

Fecal zonulin levels were determined by enzyme-linked immunosorbent assay (ELISA) (Immundiagnostik AG, Bensheim, Germany) according to the manufacturer's protocol. Absorbance was measured with a spectrophotometer (Sunrise, Tecan) at 450 nm.

The concentration of LPS and occludin in blood serum was determined using an ELISA assay (EIAAB SCIENCE INC, Wuhan, China), and that of LBP was determined using an ELISA assay (FineTest, Wuhan, China) according to the manufacturer's protocols. In each case, absorbance was measured using a spectrophotometer (Sunrise, Tecan) at 450 nm.

Sequencing analysis of bacterial 16S RNA genes

DNA isolation from feces and sequencing of the V3-V4 regions of the 16S rDNA gene were performed using the Illumina MiSeq instrument (Illumina INC, San Diego, CA, USA) at the Institute of Clinical Molecular Biology, of the University of Kiel (Kiel, Germany) according to their own protocol. DNA was isolated using microcentrifuge columns with silica membrane. Extracted DNA was purified using an Agencourt AMPure®XP instrument (Beckman Coulter, Brea, CA, USA). Bacterial 16S RNA analysis was based on amplification of the V3-V4 regions of the 16S rRNA gene and was performed using the Metagenomic Library Construction Kit 16S (V3-V4) for Next Generation Sequencing (Takara Bio Inc., Kusatsu, Japan). Sequencing was performed using the Illumina MiSeq v3 2x250 bp Kit (Illumina Inc., San Diego, CA, USA).

Determination of homocysteine and vitamin D levels in blood serum

The concentration of vitamin D metabolite 25 (OH) was determined by Diagnostyka SA with the automated chemiluminescence immunoassay method (CLIA) using the LIAISON XL device (DiaSorin, Italy). Serum homocysteine concentration was determined by ELISA (Bioassay Technology Laboratory, Shanghai, China) according to the manufacturer's protocol. Absorbance was measured using a spectrophotometer (Sunrise, Tecan) at 450 nm.

16. S rRNA sequence preprocessing

The sequencing was carried out using Illumina paired-end technology, specifically targeting the V3-V4 region of the 16S rRNA gene. To assess the quality of the raw sequencing data, a thorough initial quality screening was conducted using FastQC (version 0.12.1) and MultiQC (version 1.12) tools. Subsequently, all data preprocessing was executed using the QIIME2 software [43]. We used the DADA2 (Divisive Amplicon Denoising Algorithm 2) [44] which is a widely used tool for denoising and quality filtering of amplicon-based sequencing data, such as 16S rRNA gene sequences. DADA2 employs a denoising algorithm to identify and correct errors within the sequencing reads. It models the error rate using the quality scores and uses this information to distinguish true biological variants (amplicon sequence variants, ASVs) from sequencing errors. After quality filtering, trimming, denoising, and chimera removal, DADA2 assigned 5,685 unique ASV to each high-quality sequence and provided estimates of the abundance of each ASV within each sample (including a minimum frequency of 22.0, a 1st quartile at 23,939, a median frequency of 33,121.0, a 3rd quartile at 40,242.5, a maximum frequency of 78,764.0, and an overall mean frequency of 31,861.6). Three samples with the lowest abundance (22, 31, 43) were removed from downstream analysis. Furthermore, taxonomic classification was performed utilizing the QIIME2 implementation of VSEARCH in conjunction with the Silva 138-99 reference dataset of 16S rRNA gene sequences for taxonomic assignment. Prior to classification, an additional step involved filtering low-abundance features - the ASVs with a frequency (total abundance across samples) below 10 were excluded, allowing for a focus on robust and abundant sequences. ASVs assigned to Eukaryota, Archaea, mitochondria, and chloroplasts were excluded from the dataset due to their likely representation of contaminants or non-bacterial sequences. Lastly, the remaining ASVs were collapsed into six taxonomic levels, ranging from genus to phylum, to simplify the dataset for subsequent microbial community analysis, providing a comprehensive and refined dataset for downstream analysis.

Statistical analysis

To compare baseline characteristics of patients, we utilized either the Wilcoxon test or Fisher test. To evaluate differences between treatment groups (Placebo *versus* Probiotic) concerning changes in clinical response variables from baseline to the end of the intervention, including Beck Depression Inventory (BDI), Hamilton Psychiatric Rating Scale for Depression (HRSD), Insomnia scale, and DQI-I (Diet Quality Index – International), we employed a mixed-effect linear model implemented in the lme4 R package (version 1.1-34) [45]. To provide more accurate and reliable estimates of the standard errors and degrees of freedom for the fixed effects (and more reliable P values) we used the Kenward-

Roger approximation, as implemented in the lmerTest R package (version 3.1-3) [46]. To elucidate how changes in predictor variables influenced the response variables, accounting for both fixed and random effects, we used marginal effects in conjunction with predictor effect plots. Marginal effects calculated using the marginaeffects R package (version 0.14.0), provide insight into the average change in the outcome variable for a specific predictor variable while holding all other variables constant, especially in models with multiple predictors, as they allow you to isolate the effect of one predictor variable while keeping others at fixed values. Predictor effect plots are graphical representations that show how the predicted values of the response variable change as a function of one or more predictor variables.

The analysis of gut microbiome data was conducted at baseline, where alpha-diversity measures were compared between groups using a mixed-effect model (as described above), considering the type of surgery. To test for significant differences in the composition of biological communities among groups we applied PERMANOVA (Permutational Multivariate Analysis of Variance) implemented in the vegan R package (2.6-4) using Bray-Curtis dissimilarity metric. Principal Coordinate Analysis (PCoA) was used for reducing the dimensionality of beta-diversity and representing it in two-dimensions.

In the analysis of genus-level data (with a 10% prevalence filtering), differential abundance analysis (DAA) was performed using five different methods: ALDEx2, ANCOMBC2, WilcoxTSS, WilcoxRarefied, and LEfSe. WilcoxTSS and WilcoxRarefied applied the Wilcoxon test to relative abundance data (TSS, total sum scaling) and rarefied data WilcoxRarefied (with sampling depth = 14193), respectively. All statistical analyses were carried out using the R software (version 4.2.3, R Core Team (2022) [47].

3. Results

3.1. Patients characteristics

The characteristics of patients are presented in Table 1. There were no significant differences between the Placebo and Probiotic groups.

Table 1. Characteristics of patients.

	Placebo		Probiotic		P	Q
	n	mean ± sd, n (%)	n	mean ± sd, n (%)		
age	17	44.4 ± 10.4	21	44.9 ± 10.7	0.659	0.843
Beck scale	17	18.2 ± 7.1	21	18.8 ± 8.4	0.952	0.971
Hamilton scale	16	12.9 ± 4.6	17	13.3 ± 4.7	0.971	0.971
Insomnia scale	16	10.5 ± 4.8	17	10.1 ± 3.1	0.612	0.843
Waist circumference (cm)	17	100.6 ± 11.4	21	96.2 ± 12.7	0.277	0.665
WHR	17	0.86 ± 0.07	21	0.85 ± 0.09	0.702	0.843
Weight (kg)	17	93.2 ± 18.8	21	84.8 ± 15.5	0.168	0.589
FFM (kg)	17	59.3 ± 10.0	21	57.1 ± 10.4	0.463	0.788
Fat mass (kg)	17	33.9 ± 11.5	21	29.1 ± 8.2	0.191	0.589
BMI (kg/m²)	17	32.2 ± 5.3	21	30.1 ± 4.5	0.127	0.589
Weight at surgery day (kg)	17	125.9 ± 24.2	21	114.5 ± 16.0	0.167	0.589
Time after surgery (months)	17	41.3 ± 41.8	21	28.4 ± 27.4	0.462	0.788
LBP (ng/ml)	17	551 ± 127	21	643 ± 236	0.127	0.589
LPS (pg/ml)	17	107.9 ± 33.4	21	97.9 ± 36.6	0.252	0.665
Homocysteine (nmol/ml)	17	8.4 ± 10.4	21	8.6 ± 8.8	0.411	0.788
Zonulin (ng/ml)	14	145.7 ± 84.6	15	128.9 ± 63.4	0.777	0.847

Occludin (ng/ml)	17	13.2 ± 3.4	21	14.1 ± 3.6	0.500	0.788
Vitamin D (ng/ml)	17	19.4 ± 7.9	19	20.3 ± 6.5	0.318	0.694
DQI_I (points)	17	46.1 ± 9.7	21	48.6 ± 7.5	0.186	0.589
Variety_DQI_I (points)	17	9.6 ± 4.8	21	10.0 ± 4.9	0.677	0.843
Adequacy_DQI_I (points)	17	22.5 ± 3.6	21	22.7 ± 3.5	0.746	0.847
Moderation_DQI_I (points)	17	13.2 ± 4.8	21	15.3 ± 4.3	0.196	0.589
Overall_balance_DQI_I (points)	17	0.71 ± 1.99	21	0.57 ± 0.93	0.196	0.788
Surgery type (RYGB/SG)	17	4 (23.5)/13 (76.5)	21	12 (57.1) / 9 (42.9)	0.052	0.589

3.2. Psychiatric scales

First, we examined differences between treatments groups (Placebo versus Probiotic) with respect to the average change from baseline to end of intervention in three response variables, i.e. Beck Depression Inventory (BDI), Hamilton Psychiatric Rating Scale for Depression (HRSD), and Insomnia scale while accounting for the type of bariatric surgery (RYGB versus SG, Figure 2).

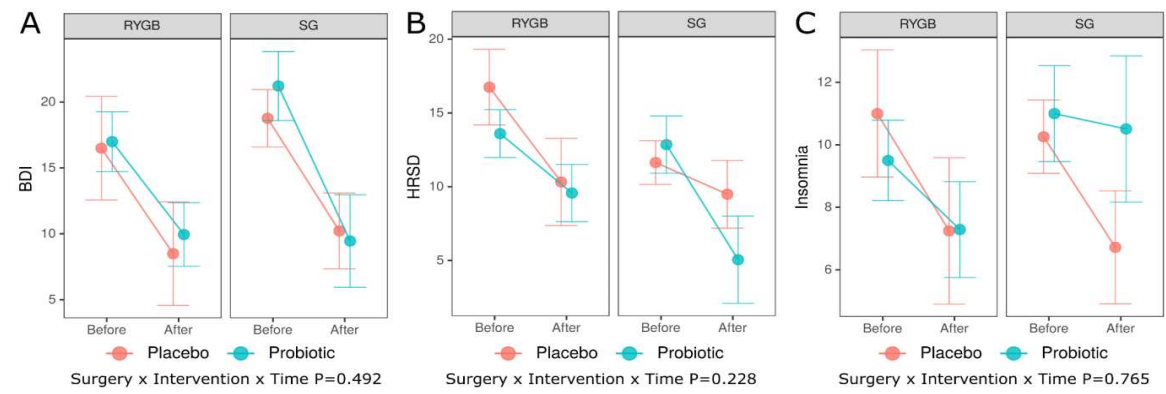


Figure 2. Predictor effect plots summarizing the role of intervention and surgery type on predicted values of the BDI (A), HRSD (B) and Insomnia (C).

P - p value obtained from a general mixed-effects model for the three-way interaction, i.e. type of surgery (RYGB versus SG) by intervention (Placebo versus Probiotic) by time (Before versus After); BDI - Beck Depression Inventory, HRSD - Hamilton Psychiatric Rating Scale for Depression, RYGB – Roux-en-Y Gastric Bypass, SG – Sleeve Gastrectomy

The lack of significant interaction between the type of surgery, intervention and time (P=0.492, P=0.228, P=0.765 for BDI, HRSD and Insomnia, respectively) indicates that the average changes from baseline to end-point were not significantly different. The differences of predicted outcomes from baseline to end-point (Before versus After) - average marginal effects (AME) evaluated for all combinations of the two remaining categorical predictors (type of surgery and intervention) are summarized in Table 2. Although the changes over time were significant in some cases, especially for BDI, pairwise comparisons of these changes between Placebo and Probiotic groups did not reveal any significant differences.

Table 2. Average marginal effects as a difference in predicted outcomes (Before versus After) for all combinations of levels of the categorical predictor (type of surgery and intervention) for psychiatric outcomes.

Outcome	Surgery	Intervention	Est	SE	P	Est _{pairwise}	SE _{pairwise}	P _{pairwise}
BDI	RYGB	Placebo	-8.00	3.49	0.022	-0.95	4.11	0.817
		Probiotic	-7.05	2.17	0.001			
	SG	Placebo	-8.55	2.69	0.002			
		Probiotic	-11.76	3.29	<0.001			
HRSD	RYGB	Placebo	-6.43	3.86	0.096	-2.40	4.59	0.601
		Probiotic	-4.03	2.49	0.106			
	SG	Placebo	-2.15	2.71	0.428			
		Probiotic	-7.80	3.50	0.026			
Insomnia	RYGB	Placebo	-3.76	2.92	0.199	-1.54	3.48	0.658
		Probiotic	-2.21	1.89	0.242			
	SG	Placebo	-3.54	2.09	0.090			
		Probiotic	-0.49	2.68	0.855			

Examined contrasts in all cases - Before versus After (After minus Before), BDI - Beck Depression Inventory, HRSD - Hamilton Psychiatric Rating Scale for Depression, RYGB – Roux-en-Y Gastric Bypass, SG – Sleeve Gastrectomy, Est - estimate of average marginal effect (AME), SE - standard error, P - p value for testing the significance of AME estimates, Est_{pairwise}, SE_{pairwise}, P_{pairwise} - estimates of AME, standard error and p value, respectively, for pairwise comparisons between Placebo and Probiotic group (Placebo minus Probiotic).

3.3. DQI-I and its subscales

In addition to psychiatric outcomes, Diet Quality Index-International (DQI-I) and four subscales, namely variety, adequacy, moderation and overall balance were also examined. Figure 3 and Table 3 shows all DQI-I related outcomes.

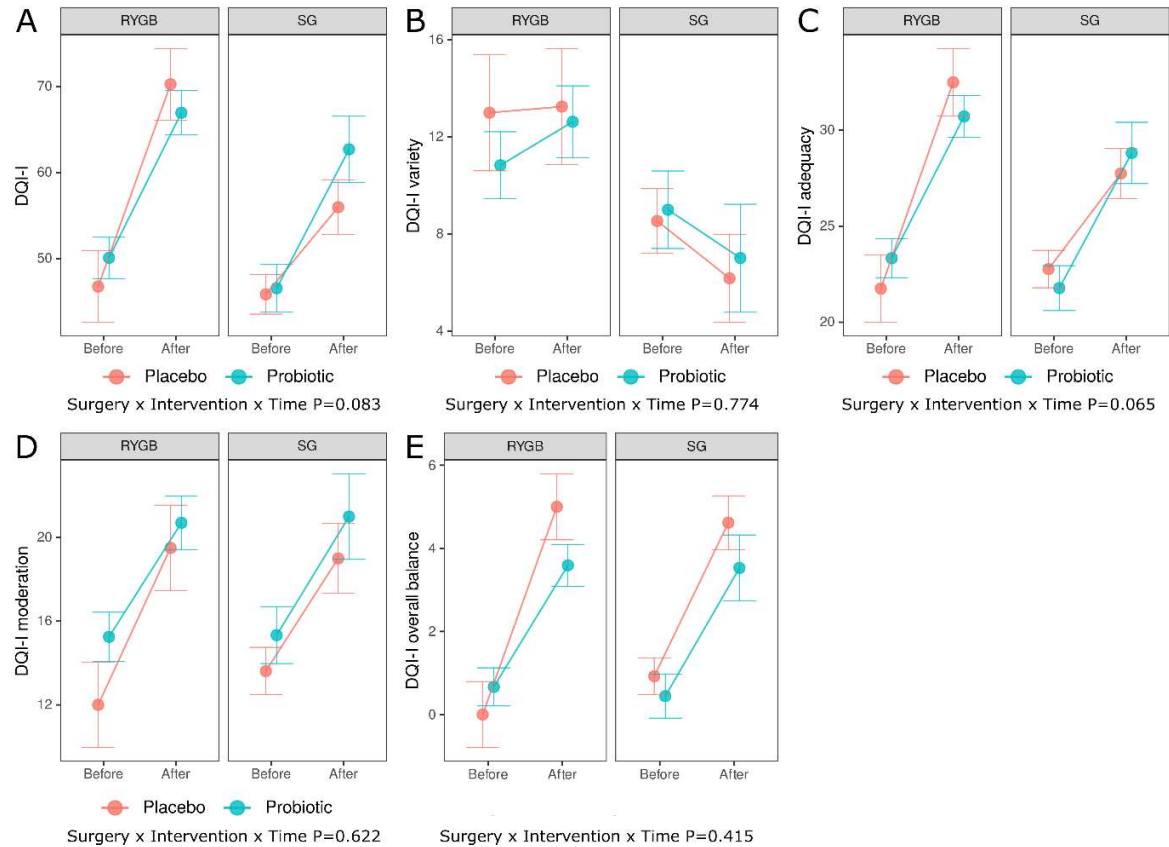


Figure 3. Predictor effect plots summarizing the role of intervention and surgery type on predicted values of the DQI-I (A), DQI-I variety (B), DQI-I adequacy (C), DQI-I moderation (D) and DQI-I overall balance (E), RYGB – Roux-en-Y Gastric Bypass, SG – Sleeve Gastrectomy .

Table 3. Average marginal effects as a difference in predicted outcomes (Before versus After) for all combinations of levels of the categorical predictor (type of surgery and intervention) for DQI-I.

Outcome	Surgery	Intervention	Est	SE	P	Est _{pairwise}	SE _{pairwise}	P _{pairwise}
DQI-I	RYGB	Placebo	23.5	4.12	<0.001	6.64	4.85	0.171
		Probiotic	16.9	2.55	<0.001			
	SG	Placebo	10.1	3.14	0.001	-6.02	4.95	0.224
		Probiotic	16.1	3.83	<0.001			
DQI-I variety	RYGB	Placebo	0.25	2.38	0.916	-1.54	2.80	0.582
		Probiotic	1.79	1.47	0.224			
	SG	Placebo	-2.36	1.81	0.192	-0.37	2.86	0.897
		Probiotic	-1.99	2.21	0.268			
DQI-I adequacy	RYGB	Placebo	10.75	1.64	<0.001	3.37	1.94	0.082
		Probiotic	7.39	1.02	<0.001			
	SG	Placebo	4.98	1.26	<0.001	-2.06	1.99	0.300
		Probiotic	7.04	1.54	<0.001			
DQI-I moderation	RYGB	Placebo	7.50	2.89	0.009	2.05	3.38	0.544
		Probiotic	5.45	1.75	0.002			
	SG	Placebo	5.38	2.02	0.008	-0.28	3.18	0.929
		Probiotic	5.67	2.46	0.021			
DQI-I overall balance	RYGB	Placebo	5.00	1.09	<0.001	2.08	1.27	0.103
		Probiotic	2.92	0.66	<0.001			
	SG	Placebo	3.69	0.77	<0.001	0.61	1.21	0.614
		Probiotic	3.08	0.94	<0.001			

In the next stage, we investigated the effect of body mass change (BMC), in addition to intervention, to see if patients who had experienced a higher loss of body mass between the time of their surgery and the start of the trial had a distinct reaction to the probiotic intervention. BMC in patients receiving placebo and probiotic is shown in Figure 4. In subsequent analyses, we excluded three patients with extreme values (outliers, i.e. -61.7, -61.7 and 7.1 kg).

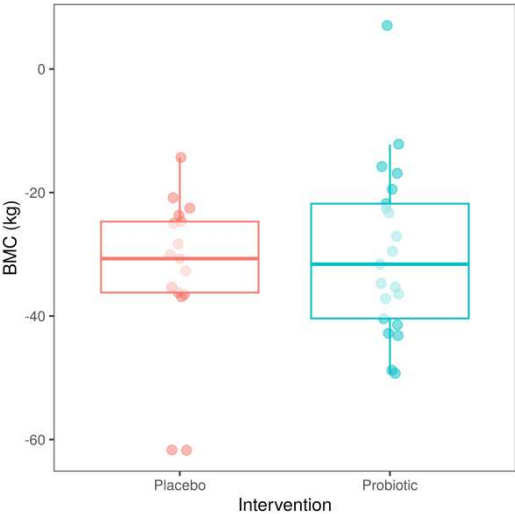


Figure 4. Body mass change (BMC) between the time of patient’s surgery and the start of the study.

The BMC was computed as the difference between the patient's body mass at the start of the study and the patient's body mass at the time of surgery; hence, a decrease is indicated by a negative number, while an increase is indicated by a positive value; BMC did not differ between groups, $P = 0.837$ (Wilcoxon test)

3.4. Gut microbiota

At baseline, alpha diversity did not differ between Placebo and Probiotic groups regardless of the type of bariatric surgery (Figure 7A-D). In contrast, we found a significant difference (PERMANOVA $P=0.020$) in overall taxonomic composition between RYGB versus SG (but not between Placebo and Probiotic, PERMANOVA $P=0.777$) as demonstrated in PCoA of Bray-Curtis distances (Figure 7E) which shows a separation between RYGB and SG. In line with this finding, there were numerous differences in the abundance of individual taxa between these groups and the results of differential abundance analysis (DAA) at the genus level using various methods are shown in Figure 7F. The Venn diagram illustrates a correspondence of 5 DAA methods and reveals that 7 genera: genus belonging to Muribaculaceae family (enriched in the RYGB), Christensenellaceae R-7 group (enriched in the SG), Veillonella (enriched in the RYGB), Subdoligranulum (enriched in the SG), Roseburia (enriched in the RYGB), Oscillibacter (enriched in the SG) and UCG-005 (enriched in the SG) were identified as differentially abundant between RYGB and SG in the ALDEx2, WilcoxTSS and Wilcox. When ANCOMBC2 method was considered, only two of them (genus belonging to Muribaculaceae family, Christensenellaceae R-7 group) remained differentially abundant. The taxa at higher levels of taxonomy were also found to be differentially abundant (Figure S1).

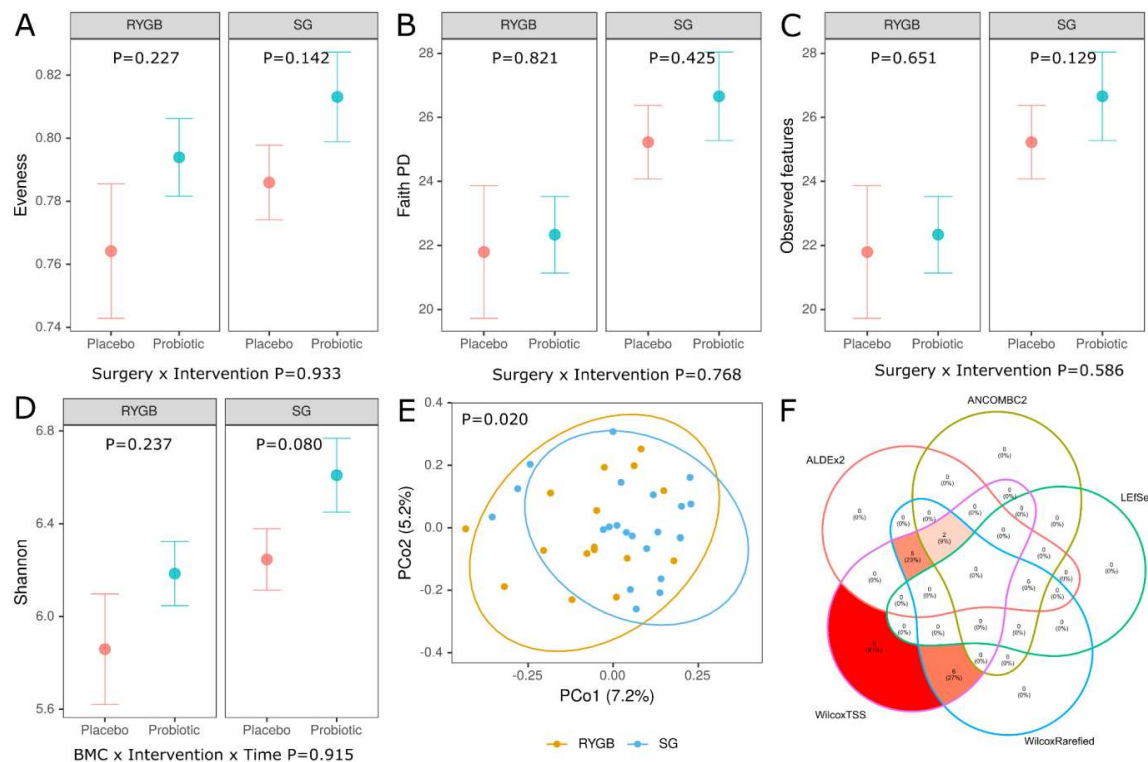


Figure 5. Alpha-diversity, beta-diversity and differential abundance analysis at baseline. Alpha-diversity (A, B, C, D), beta-diversity using Bray-Curtis distance (E) and Venn diagram (F). Below plots in A, B, C and D p values are obtained from a general mixed-effects model for the two-way interaction, i.e. type of surgery (RYGB versus SG) by intervention (Placebo versus Probiotic) while p values in each facet refer to Placebo versus Probiotic comparison in the RYGB and SG group; E - Principal-coordinate analysis (PCoA) ordination plot based on Bray-Curtis distance metrics demonstrating

significant grouping of samples (PERMANOVA $F=1.27$, $P=0.020$ RYGB versus SG); F - Venn diagram comparing 5 methods of differential abundance analysis at the genus level (10% prevalence filtered) (ALDEx2, ANCOMBC2, WilcoxTSS, WilcoxRarefied and LEfSe) [48–50], WilcoxTSS and WilcoxRarefied use Wilcoxon test on relative abundance data (TSS, total sum scaling) or rarefied data (sampling depth=14193), RYGB – Roux-en-Y Gastric Bypass, SG – Sleeve Gastrectomy.

4. Discussion

To the best of our knowledge, the study conducted is the first to address the possibility of reducing the severity of depressive disorders in people after bariatric surgery using diet and probiotic therapy.

Depressive symptoms were observed in 45 % of 200 patients who underwent bariatric surgery. The presence of depressive disorders was also noted in other studies. Alsubaie et al [51] showed that 30.4% of patients suffered from moderate or severe depression and 33% from moderate or severe anxiety disorders after bariatric surgery. In addition, the authors associated the occurrence of depression with young age, postoperative complications, and psychiatric symptoms that occurred 1 to 2 years after surgery [51]. It seems that disturbances in the function of the cerebral and intestinal axes may also have a significant influence on the deterioration of the mental state of patients after bariatric surgery [52].

At present, there are lack of data in the literature examining the relationship between changes in the microbiota and the development of depression after bariatric surgery. Finding such marker bacteria in the future could be a very valuable predictor of the development of depression. In a previous paper, we published results that indicate a role for the gut microbiota and inflammatory processes in the development of depressive disorders in patients after bariatric surgery [9]. Of note the bariatric surgery itself significantly affects the composition of the microbiota [53]. In our study, we noted significant differences in the composition of the gut microbiota of patients undergoing RYGB and SG surgery. In the feces of patients after RYGB, there was a significantly higher abundance of Muribaculaceae family, Veillonella and Roseburia, while those after SG had more Christensenellaceae R-7 group, Subdoligranulum, Oscillibacter and UCG-005. Muribaculaceae produce enzymes that break down complex carbohydrates. In one study conducted in an animal model, the authors suggested that their higher abundance may be related to higher dietary fiber intake [54,55]. Although in another study, Muribaculaceae appear to be positively correlated with body weight and have been linked to the lean phenotype [56]. Interestingly, their numbers are also positively related to depressive and anxiety behaviors [57]. In contrast, the relative abundance of Veillonella was lower in studies involving participants with anxiety and depression [58]. Another study [59] found an association of thirteen microbial taxa, including genera Eggerthella, Subdoligranulum, Coprococcus, Sellimonas, Lachnospiraceae, Hungatella, Ruminococcaceae (UCG002, UCG003 and UCG005), Lachnospiraceae UCG001, Eubacterium ventriosum and Ruminococcusgaurvreauii group, and family Ruminococcaceae with depressive symptoms. These bacteria are known to be involved in the synthesis of glutamate, butyrate, serotonin and gamma amino butyric acid (GABA), which are key neurotransmitters for depression. In addition, the number of Clostridiales also seems to be important for emotional functioning [60]. The number of Clostridiales (including Faecalibacterium, Roseburia, Lachnospira, Anaerostipes) is reduced in many mental disorders, which is associated with disturbances in amino acid and carbohydrate metabolism [60]. It is worth noting that Roseburia is one of the most important butyrate-producing bacteria, which is important for modulating the brain-gut axis [61,62]. The presence of Roseburia has been associated with good cognitive abilities [60,63] and increased insulin sensitivity [64], while insulin resistance is associated with high systemic branched-chain amino acid concentrations [65]. Excess consumption of valine, leucine, and isoleucine may lead to a decrease in brain tryptophan (a precursor of serotonin) concentration and thus to a decrease in brain serotonin concentration [66,67]. When the excess of branched-chain amino acids competes with tryptophan, the transport of this amino acid across the blood-brain barrier is less efficient [67,68]. The authors of one of the papers [60] suggested that the gut microbiota contribute (at least indirectly) to occurrence of mental disorders through low numbers

of *Clostridiales*. This bacterial order, very important for the homeostasis of the organism, plays a significant role in the degradation of branched amino acids and prevents their increased concentration in the bloodstream (which could counteract the decrease in serotonin synthesis in the central nervous system) [60].

In our study, after 5 weeks, we noted an improvement in patients' mental functioning (reduction in BDI and HRSD), but it was not related to the probiotic used (Figure 2). Effect of probiotics after bariatric surgery does not seem very significant. A systematic review by Cook et al [69] also found no effect of probiotics on quality of life and weight loss after bariatric surgery. This may be due to significant changes in the composition of the microbiota after surgery, functional changes (e.g. food passage) of gastrointestinal tract, changes of body weight and dietary habits. The dosage, method and timing of probiotic use are adapted to the anatomically and functionally typical gastrointestinal tract. There are no data on the adhesion and other mechanisms of action of probiotics in the gastrointestinal tract undergoing surgery.

In our study the most important factor that contributed to the reduction in the severity of depressive disorders may have been the dietary intervention. Consumption of vegetables and whole grain cereals increased (DQI-I adequacy), consumption of simple sugars and SFA decreased (moderation DQI-I), and consumption of monounsaturated fatty acids derived mainly from olive oil increased (overall balance DQI-I). A Western-style diet, characterized by the consumption of highly processed products with a high content of sugars and saturated fatty acids and, at the same time, a low consumption of vegetables, fruits and fiber, favors the development of microbiota disorders [70]. This type of diet predisposes to low microbiological diversity, increased intestinal barrier permeability, endotoxemia, and chronic low-intensity inflammation, which can contribute to the development of many diseases [7,70]. In addition, a diet with a high glycemic load increases the risk of developing mood disorders, fatigue, and severity of depression symptoms compared with diets based on a low glycemic load (especially in overweight or obese people) [71]. On the other hand, a diet rich in fruits, vegetables, nuts, legumes, and whole grains seems to have a beneficial effect on psychophysical performance [72]. This type of diet has been shown to be associated with a lower risk of MDD and anxiety disorders than in people following the Western diet [73]. In addition, the introduction of a Mediterranean diet has been associated with an improvement in depression symptoms in patients suffering from MDD with low diet quality [74].

The original composition of the microbiota may be important for the functioning of the intestinal barrier and the effectiveness of its sealing. It seems that RYGB has a greater impact on the gut microbiota than restrictive surgery [69]. This could be due to the fact that the anatomical changes induced by the RYGB procedure reduce the absorptive surface of the intestine and also result in the stomach being exposed to higher amounts of gastric acid. In addition, the passage of food through the gastrointestinal tract is accelerated, and the increased pH in the intestine alters its redox potential, which affects the increase in the number of aerobic and facultative aerobic microorganisms, i.e. *Proteobacteria* [75].

In our study, we noted no significant differences in parameters assessing intestinal barrier integrity (LPS, LBP, zonulin, occludin) between the group taking the probiotic and the placebo. However, in the study by Clemente-Postigo et al [75], showed that the concentration of LPS and LBP in the blood depended on the bariatric surgery performed and the previous blood glucose level of the patient. LPS and LBP concentrations decreased significantly (compared with preoperative values) on the ninetieth day after SG surgery. In contrast, LBP levels increased on the 15th day after bile duct exclusion and returned to preoperative levels on the 90th day after surgery. The values increased again on the 90th day after surgery [76]. In turn, Yang et al [77] showed that LBP levels were related to BMI and high-sensitivity C-reactive protein and that LBP levels decreased significantly one year after bariatric surgery compared with preoperative levels. The exact mechanisms leading to changes in LPS and LBP concentrations in the blood of patients after bariatric surgery are not known. They appear to be related to changes in gut microbiota composition, diet, and severity of inflammation [77,78].

Due to significant limitations, this study should be considered a pilot study. Small study groups, high heterogeneity and difficulties in compliance were the biggest limitations. However, the topic addressed is very interesting and requires further well-designed clinical and mechanistic studies.

5. Conclusions

In our study, we noted a reduction in the severity of depressive symptoms, although it was not related to the probiotic therapy used. Of note, in patients who have undergone bariatric surgery, special attention should be paid to the proper balance of meals (as one of the elements contributing to the maintenance of mental health). In addition, the noted differences in the composition of the gut microbiota (RYGB vs SG) may be one of the determinants of the functioning of the gut-brain microbiota axis, although there is currently a need for further research on this topic with a larger group of patients and different probiotic doses.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Figure S1: Gut microbiota - the different abundance of taxa at higher levels of taxonomy

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, N.K. and E.S.; methodology, E.S., I.L.; software, M.K., A.M-VK., A.N.; validation, E.S., I.L. and M.W.; formal analysis, M.K.; investigation, N.K., K.K., B.K.; resources, K.K., B.K.; data curation, N.K., E.S.; writing—original draft preparation, N.K.I.L., M.F., E.S.; writing—review and editing, E.S.; visualization, M.K.; supervision, I.L., M.K.; project administration, E.S.; funding acquisition, E.S.. All authors have read and agreed to the published version of the manuscript."

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