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ORIGINAL ARTICLE

The Adjuvant Therapeutic Effect of Probiotics on the Anthropometric Measurements and Metabolic Parameters in Laparoscopic Sleeve Gastrectomy: A Randomized Controlled Clinical Trial

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Abstract

Background and aim: **Metabolic diseases, such as chronic low-grade inflammation, insulin resistance and adipocyte hypertrophy have been linked to obesity. The influence of perioperative probiotic administration on bariatric surgery yielded conflicting results. We directed this randomized controlled study to outline the effects of probiotic administration on the effects of laparoscopic sleeve gastrectomy (LSG).**

Patients and methods: **This randomized, double-blinded, placebo-controlled study included 83 cases, undergoing LSG, to take either probiotics or placebo. The primary result was the anthropometric measurement at 3 months after the surgery. The secondary outcomes included lipid profile, glycemic control, and serum vitamins D and B12.**

Results: **The anthropometric measurements showed nonsignificant comparison between probiotics and placebo, 3 months after LSG. Probiotics were associated with better glycemic control, reduced triglyceride and cholesterol levels, and higher values of serum vitamin D and B12. No significant difference was reported among the two groups, regarding the rate of complications.**

Conclusion: **Our findings suggested that probiotic supplementation had little effect on the anthropometric measures in the early postoperative period after bariatric surgery. Probiotic administration improves the lipid profile by lowering triglyceride and cholesterol levels. This randomized controlled trial demonstrated a substantial increase in vitamins B12 and D levels in the probiotics group. Finally, further increased quality trials are required in demonstrating the dose- and strain-dependent effects of probiotics administration after bariatric surgery.**

Keywords: Anthropometric indices, Laparoscopic sleeve gastrectomy, Metabolic outcomes, Probiotics

1. Introduction

It has been reported that obesity is associated with dysbiosis, a condition characterized by compositional alterations of the gut microbiota and low microbial genes.[1] Metabolic problems like low-grade inflammation, insulin resistance and adipocyte hypertrophy have been linked to this shift in microbial gene richness, which may be present in up to 40% of obese individuals.[2] Indeed, bariatric operation has long been recognized as a treatment for severe obesity that has the highest success rate and longest duration. Importantly, bariatric surgery has multiple beneficial effects, including not only weight loss but also type two diabetes mellitus (DM-2) remission and restoration of intestinal aerobiosis.[3] Nevertheless, the influence of bariatric surgery on the work and function of gut microbiota remains debatable.[4] Roux-en-Y gastric bypass (RYGB) has been reported to have a stronger positive impact on

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the microbiome of the gut than sleeve gastrectomy.[5] Moreover, conflicting results has been reported on the consequence of perioperative administration of probiotics on the results of bariatric surgery. Probiotics were also proposed as an additional technique for the submission of inflammatory markers and glycemic control.[6]

This randomized controlled trial aimed to examine the effect of probiotics administration on the metabolic outcomes, diabetes remission, and weight reduction after laparoscopic sleeve gastrectomy (LSG).

2. Patients and methods

2.1. Ethical approval

In total 84 patients were enrolled after receiving individual written informed consent and official ethical approval from Al-Azhar University ethics board.

2.2. Study design

This is a placebo-controlled, randomized clinical research. It was conducted at the bariatric surgery center, Al-Azhar University Hospitals from (July 2021 to September 2022).

2.3. Sample size calculation

MedCalc Software version 11.3.0.0 was used in calculating sample size to establish the representative sample and assure the validity of the results. The expected effect size is estimated based on the data revealed by Ramos and colleagues who reported that percentage excess weight loss (% EWL) was 50.87 in the probiotics group and 47.94 in the placebo.[7] Adjusting the confidence interval (CI) to 95%; power 80% and ratio among groups to 1 : 1; at least a sample of 80 cases was found reliable. Estimating a dropout ratio of 10%, we finally included 90 case (45 cases in each group).

2.4. Eligibility criteria

We enrolled patients, undergoing LSG, with age (18–65 years), ASA (I-III), and BMI (more than 40) kg/m^2 or greater than 35 associated with comorbidities. The criteria of exclusion included refusal to complete the study, antibiotics administration during or 10 days before the study period, probiotics or food-fortified probiotics administration throughout the study period or 1 month before, and chronic gastropathy, renal or hepatic disorders.

2.5. Randomization and allocation concealment

To allocate individuals, a computer-generated randomization procedure was utilized. Forty five patients were allocated in each probiotic and placebo groups. The researchers tested a telephone-mediated central allocation strategy for allocation concealment. Participants and result assessors were blinded to the group allocation and description.

Probiotics group received Linex Forte capsules BID 1 month before and 3 months after LSG. Each capsule contains 1×10^9 (one billion) colony forming units (CFUs) of lyophilized Lactobacillus acidophilus and Bifidobacterium animalis subsp. lactis and prebiotics (inulin with oligofructose).

Placebo group received inactive starch capsules with the same regimen used in the probiotics group.

2.6. Preoperative evaluation

Each patient was reviewed clinically; medical and surgical history, physical examination including vital signs, height and weight obtained on a calibrated scale and investigated by routine blood tests, ECG, chest radiography, thyroid and growth hormone levels assessment, upper gastrointestinal tract endoscopy, pulmonary function studies, and other potential imaging or cardiac other referral and psychological consultation.

2.7. Procedure

LSG was performed with anti-embolic measures and suitable preoperative antibiotics. The patient was supine while under general anesthesia with endotracheal intubation. All patients were given 40 IU of enoxaparin (Clexane), the night before the surgery. A pneumoperitoneum was created with a closed method and a Veress needle. Three 12 mm ports were implanted in an arc, 15–18 cm under the xiphoid. They were located 3 cm to the left of the midline (optical port), also right and left midclavicular lines (working ports). A 5 mm trocar port (assistant port) was put along the left subcostal margin and another 5 mm port was implanted in the epigastric area for liver retraction.

The operating table was reverse Trendelenburged and the left lobe of the liver was cephalic withdrawn to reveal the esophageal hiatus. A laparoscope with a 30° angle was employed. Gastric secretion and gas were evacuated through nasogastric tube. The stomach's pylorus was detected and the greater curvature of the stomach was lifted. The laparoscopic ultrasonic scalpel (Ethicon) was used to devascularize the greater curvature of the stomach. A 35 Fr orogastric bougie

was inserted near the pylorus. The incision was made starting between 5 and 6 cm from the pylorus and going all the way to the His angle.

At first, a 60 mm green cartridge was utilized for stapling (proximal to pylorus). The second cartridge, gold, was placed proximal to the angular is, taking attention to avoid stenosis. Using a blue cartridge, stapling was continued until the gastroesophageal junction was 1–2 cm away. A laparoscopic grasper was used to grasp the resected stomach through one of the working port locations. Following the completion of the stomach transection, methylene blue injection through the bougie with the pylorus compressed by a surgical grasper to assess staple line leakage. The staple line was then thoroughly examined for leakage. With the bougie, the dye is removed. Along the suture line, an 18 Fr Nelaton drain was placed. The trocar sites were closed by Vicryl 0. Broad-spectrum antibiotics were given to all patients.

2.8. Postoperative follow-up

The initial evaluation took place on the first appointment, 10 days after surgery. Patients returned for assessments at 4, 8, and 12 weeks. Both groups got the identical diet direction, protein and multivitamin supplements prescription, as per the hospital's routine procedure. Patients who did not follow the protocol or who developed acute postoperative complications were screened out during the intervention period via weekly phone calls to determine compliance. Visits included clinical and anthropometric evaluations.

2.9. Treatment of the patients with leak

The treatment plan is determined by the hemodynamic condition, the existence of peritonitis, the volume of collection, and whether the collection is confined or widespread. Based on these factors, the choice amongst noninvasive and invasive investigation is decided upon.

Abdominal and pelvic computed tomography (CT) scans with oral and intravenous contrast, as well as upper gastrointestinal endoscopy, are performed when a leak is suspected. CT-guided percutaneous drainage is performed when a CT scan reveals a localized collection or abscess in the subphrenic space. If the individual is hemodynamically stable and there is no systemic peritonitis, Endoscopic stenting may be performed if there is a leak but no stricture. Temperature, white blood cell count, and drain output are being tracked. If the participants' overall health enhanced, white blood cells reverted to normal and the drain stopped emptying after 1 week, a CT scan was conducted to check there was no leak and oral intake was restarted. Following drain removal, patients were discharged. At 2, 4, and 12 weeks, a clinical examination and abdominal ultrasound are conducted. If the unstable leak cases can be stabilized, laparoscopic investigation, washing out and drainage will follow. A jejunostomy tube for feeding might be placed at the same time. Monitoring the quantity and composition of drain outflow after operation.

2.10. Primary and secondary outcomes

The primary result was the anthropometric measurements at 3 months after surgery. The secondary outcomes included prevalence of complications and their management, lipid profile, glycemic control and serum vitamins D and B12.

2.11. Statistical analysis

SPSS version 23.0 was considered for analysis. The presentation was based on the type, normality, and distribution of the variables. Kolmogorov test was first applied. Normally distributed variables, explicated mean and standard deviation, whilst non-normal data explicated median and IQR. The student-t test and the Mann–Whitney U test were mentioned in this study for inter-group analysis regarding the nonparametric and parametric numerical variables, respectively. In addition, categorical variables were analyzed using the χ^2 test. A point of 0.05 was set as the significant level.

3. Results

3.1. Patients and demographic characteristics

After obtaining ethical approval from Al-Azhar ethical review board, and an individual informed consent, this randomized controlled trial finally enrolled 83 postsleeve gastrectomy cases to assess the evidence of probiotics supplementation on the metabolic profile and anthropometric indices. Fig. 1 showed the flow diagram of the study process and reasons for exclusion throughout the study period. Regarding the demographic and patients characteristics, no significant change was reported amongst the two study groups (P more than 0.05). The baseline anthropometric indices, including BMI, weight, and waist circumference (WC) were comparable in both groups in the studies. Also, no significant comparison was reported regarding the associated comorbidities, including hypertension and DM-2 (Table 1).

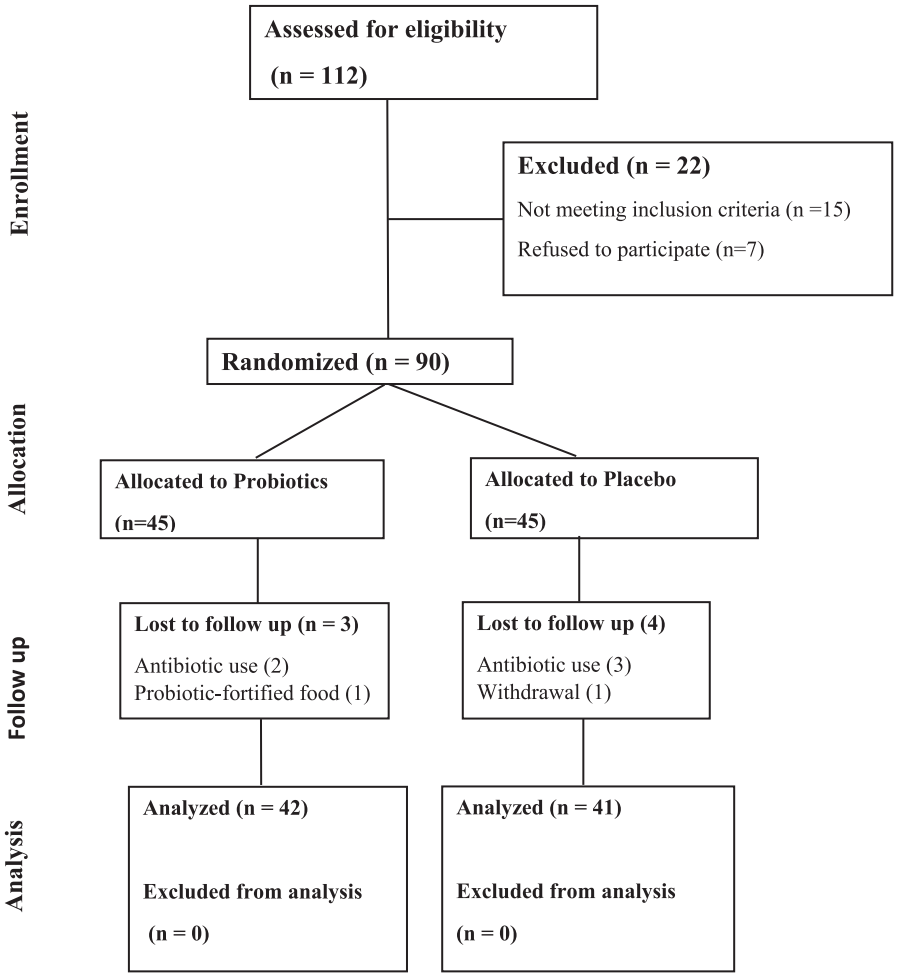

Fig. 1. CONSORT flow diagram.

Table 1. Comparison between the two study groups regarding patient and demographic characteristics.

Demographic data	Probiotics (n = 42)	Placebo (n = 41)	P value
Age (y)	42.72 ± 11.35	40.10 ± 9.17	0.361
Sex n (%)			
Male	7 (16.77)	5 (12.19)	0.740
Female	35 (83.33)	36 (87.81)	
BMI (kg/m^2)	43.85 ± 5.42	44.61 ± 4.35	0.379
Weight (kg)	123.14 ± 13.10	119.61 ± 12.83	0.441
WC (cm)	125.91 ± 10.52	123.09 ± 13.18	0.306
25-OH vitamin D (ng/mL)	46.29 ± 10.16	42.28 ± 14.32	0.126
Vitamin B12 (pmol/L)	193.52 ± 24.61	203.83 ± 22.73	0.635
HbA1c	6.15 ± 1.03	6.34 ± 1.15	0.815
Baseline Comorbidities			
Type-2 DM	7 (16.76)	9 (21.95)	0.601
Hypertension	11 (26.19)	13 (31.71)	0.710
Dyslipidemia	24 (57.14)	29 (70.73)	0.251
Hypothyroidism	3 (7.14)	4 (9.76)	0.139

BMI, body mass index; WC, waist circumference.

Table 2. Comparison among the two study groups regarding metabolic and anthropometric parameters.

	Probiotics ($n = 42$)	Placebo ($n = 41$)	P value
%EWL	42.72 ± 11.35	40.10 ± 9.17	0.410
BMI (kg/m^2)	32.18 ± 3.17	34.07 ± 4.11	0.130
Weight (kg)	99.01 ± 7.11	97.26 ± 6.03	0.302
WC (cm)	101.16 ± 3.16	105.27 ± 2.57	0.863
25-OH vitamin D (ng/mL)	83.11 ± 8.07	55.31 ± 7.15	0.001*
Vitamin B12 (pmol/L)	438.16 ± 22.17	351.76 ± 18.29	0.022*
Cholesterol	124.72 ± 16.86	132.59 ± 23.17	0.025*
Triglycerides	107.16 ± 52.26	125.22 ± 43.08	0.001*
LDL	79.15 ± 23.18	83.53 ± 22.47	0.477
HbA1c	5.13 ± 0.57	5.43 ± 0.93	0.082

%EWL, percentage excess weight loss, * Significant P value, LDL, low-density lipoprotein.

3.2. Anthropometric measurements

This study reported higher percentage of excess weight loss in the probiotics group, equated to placebo with nonsignificant comparison amongst the two groups (42.72 vs. 40.10, $P = 0.410$). In addition, the anthropometric indices, including BMI, weight and WC showed significant reduction from the baseline values after 3 months of LSG, with the nonsignificant inter-group difference between probiotics and placebo ($P = 0.130$, 0.302, and 0.863), respectively (Table 2).

3.3. Lipid profile

No inter-group difference was detected at 3 months postoperatively, regarding low-density lipoprotein ($P = 0.477$). Interestingly, this study showed significant reduction in cholesterol and triglycerides within groups compared with the baseline values and between probiotics and placebo after 3 months of the operation (124.72 vs. 132.59, $P = 0.025$ and 107.16 vs. 125.22, $P = 0.001$), respectively.

3.4. Vitamins

Comparison of 25-OH vitamin D revealed a significant improvement in the probiotics and placebo 3 months after LSG, compared with baseline (46.29 vs. 83.11, $P = 0.01$ and 42.28 vs. 55.31, $P = 0.03$), respectively (Fig. 2). Similarly, vitamin B12 showed significant improvement in the baseline values in the probiotics and placebo with significant intra-group differences. Moreover, inter-group comparison

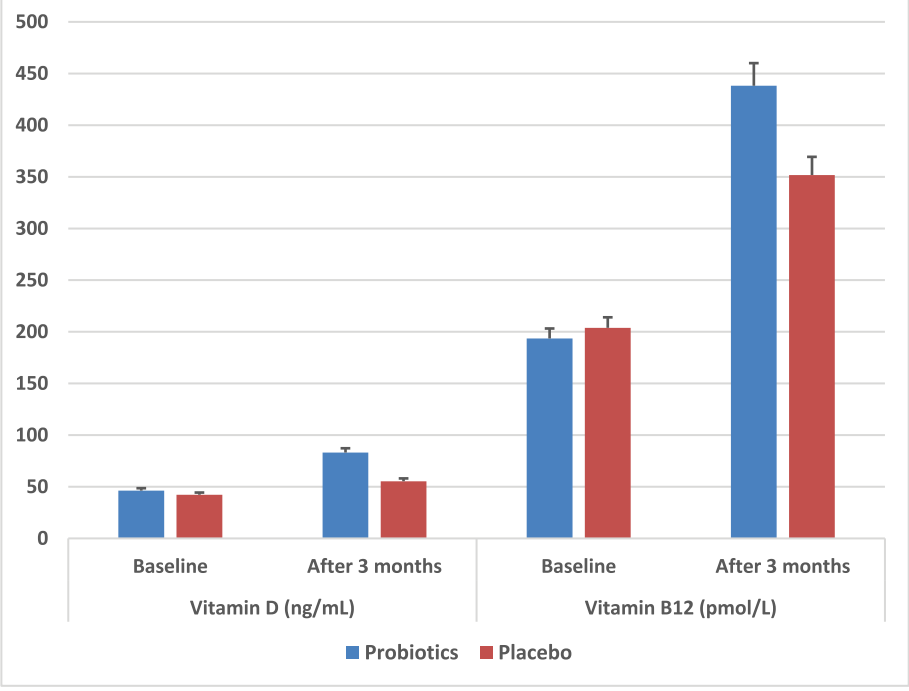

Fig. 2. Comparison among the two study groups regarding serum vitamins D and B12.

showed that probiotics had higher values of vitamin B12 and vitamin D_3 months after LSG ($P = 0.022$ and 0.001), respectively (Table 2 and Fig. 2).

3.5. Glycemic control

HbA1c was utilized as an indicator of glycemic control in this study. This study reported a lower HbA1c value in the probiotics set, related to placebo, indicating a better glycemic control in the probiotics group. Nevertheless, the contrast was not statistically significant ($P = 0.082$) (Table 2). Consequently, future large-scale well-intended randomized controlled trials are recommended to show that difference.

3.6. Comparison between the groups regarding complications

No significant alteration was reported among the two study groups regarding the prevalence of postoperative leakage and bleeding. Overall seven cases of leakage were reported in the two groups, of them 3 cases were managed conservatively, 2 cases by laparoscopy and stenting of the leakage line, 1 case by drainage of the localized collection under CT, and 1 case required laparotomy. In addition, three cases reported mild to moderate bleeding which was managed conservatively (Table 3).

4. Discussion

This randomized controlled study examined the adjuvant therapeutic effects of two probiotic strains, Lactobacillus acidophilus and Bifidobacterium animalis in patients undergoing LSG. We found diverse effects in terms of anthropometric measurements and metabolic outcomes, 3 months after surgery. This study highlighted that probiotics was associated with better glycemic control, reduced triglyceride and cholesterol levels and higher values of serum vitamin D and B12.

Multiple studies showed hopeful outcomes regarding the value of probiotics in terms of weight loss. One systematic review of randomized controlled clinical trials (RCTs) on probiotic doses in overweight or obese people found that probiotics resulted in a significant greater decrease in weight (MD, 2.60; 95% CI, 21.19 to 2.01), BMI (MD, 2.27; 95% CI, 2.45 to 2.08) and fat percentage (MD, 2.60; 95% CI, 21.20 to 2.01).

Compared with placebo.[8] Another meta-analysis examined the impact of probiotics on weight variation in people with normal weight or obesity. They highlighted that probiotic therapy resulted in considerable weight reduction (MD, 2.54; 95% CI, 2.83 to 2.25) related with placebo at the conclusion of the period of treatment (12 weeks).[9] Furthermore, other studies revealed that probiotics or synbiotics had a favorable influence on waist boundary but had no influence on other variables.[10] One of the processes by which probiotics reduce visceral adipose tissue is by modulating the expression of adipogenesis genes in the liver.[11] As a result, the decline in WC is most likely attributed to a decrease in abdominal fat formation. However, the substantial impact of bariatric operation on obesity may obscure this tiny contribution of probiotics. They found no significant difference in the other anthropometric measures, rather than WC.[12]

On the contrary, several studies found contradictory results. The systematic review conducted by Mohammadi et al.[13] combined data from 9 RCTs, encompassing 410 overweight children and adolescents with obesity. They found no significant improvements in BMI, %EWL, or WC. Suzumura et al.[14] similarly discovered the same results in the adult members. Furthermore, Swierz et al.[15] conducted an organized review and meta-analysis in 2020 to analyze the data supporting the efficiency and safety of probiotics used in individuals with severe obesity receiving bariatric surgery. Weight change was measured at 6 weeks, 3, 6, and 12 months. The authors reached the conclusion that probiotics had little or no influence on long-term weight change. Indeed, existing evidence demonstrates that the impact on the anthropometric measurements may be affected by the variety of

Table 3. Comparative analysis of postoperative complications in the two study groups.

	Probiotics ($N = 42$)		Placebo ($N = 41$)		*P* value
	n (%)	Management	n (%)	Management	
Leakage	4 (9.5)	Conservative (2) Drainage under CT (1) Stent (1)	3 (7.3)	Conservative (1) Stent (1) Surgical Laparotomy (1)	0.831
Bleeding	1 (2.4)	Conservative (1)	2 (4.9)	Conservative (1) Blood transfusion (1)	0.295

probiotic supplement (single or multiple species), the type of species and strains, the duration of administration, and the type of bariatric surgery. Dietary modifications have a large impact on gut microbiota composition and function and consequently weight reduction, with various bacteria species related with the use of specific diets.[16] Most trials on bariatric surgery do not account for or analyze the influence of pre- or post-surgery food intake and the times and dates of sample collection for microbiome, also the differences in the analytic methodologies between studies.

Regarding the lipid profile, several studies shared supporting evidence to our findings. They showed that probiotic supplementation can lower triglyceride and cholesterol levels via various techniques (intracellular cholesterol transfer to the cellular surface, ferulic acid synthesis, cholesterol precipitation by deconjugated bile salt hydrolysate and increased salt hydrolase expression by lactic acid bacteria).[17] Moreover, out study reported better glycemic control with probiotic administration, evidenced by the lower HbA1c value. Supporting, Yao et al.[18] found that probiotic supplementation was related with substantial improvements in HbA1c and fasting insulin in DM-2 individuals in a meta-analysis of 12 RCTs. The main function of gut bacteria in insulin resistance explained this impact.[18] Nevertheless, we showed that probiotics impact on glycemic control was not significant. Several factors, including the heterogeneity of intestinal microbiota, surgical method, and probiotics utilized, might explain these contradictory findings. Since it appears that the effect of probiotics on gut microbiota varies with strain and with dose. Consequently, probiotics administration is recommended to be strain and dose dependent.[19]

Importantly, the probiotics group had significant greater levels of vitamins B12 and D than the control group. Indeed, probiotic supplementation may be an acceptable method for improving vitamin B12 and D level via gut microbiota modification.[20] A randomized controlled study with patients following gastric bypass surgery, who were supplied with Lactobacillus species for six months found substantially greater postoperative vitamin B12 levels in the probiotic supplemented group.[21] Furthermore, a rise in vitamin D levels is predicted following substantial weight reduction due to vitamin D release from adipose tissue.[22] Furthermore, recent research has shown that vitamin D level is relevant to the nature of the gut microbiota and that probiotic therapy can enhance 7-dehydrocholesterol production as well as vitamin D receptor expression and function.[23]

4.1. Strengths and limitations

One of the most prominent features in this randomized controlled trial is the inclusion of only two probiotic strains, as probiotics effect is strain-dependent, which gives a greater degree of evidence. We included metabolic parameters as well as the anthropometric measurements to the outcome assessment. On the contrary, there are certain limitations to this study. One of the most significant weaknesses was the insufficient results from none extended follow-up period on the anthropometric parameters. Only three months of follow-up resulted in the conclusion that probiotics had no effect on anthropometric parameters. Furthermore, the limited sample size is another limitation. In addition, multiple confounding factors may be present, limiting the validity of our results.

4.2. Conclusion

Our findings suggested that probiotic supplementation had little effects on the anthropometric measures in the early postoperative period after bariatric surgery. Probiotic administration improved the lipid profile by lowering triglyceride and cholesterol levels. This randomized controlled trial demonstrated a substantial increase in vitamins B12 and D levels in the probiotics group. Finally, additional high-quality studies are required to demonstrate the dose- and strain-dependent effects of probiotics administration after bariatric

Conflicts of interest

The authors declared no conflict of interest.

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