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Review Article

Effect of Probiotics/Synbiotics on Postoperative Outcomes in Patients Undergoing Abdominal Surgery

In Ja Park, M.D., Ph.D.

Department of Colon and Rectal Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

ABSTRACT

Environmental factors, drugs, diet, and surgery alter the composition of the gut microbiota leading to the production of different metabolites or toxins that can cause disease or delay postoperative recovery. Surgical damage leads to gut barrier disruption, increased intestinal permeability, gut microbial imbalance, and immunologic compromise of the host with subsequent bacterial translocation from the gastrointestinal tract to systemic circulation. Therefore, perioperative stabilization of the intestinal microbiota is a potential method of reducing postoperative complication rates. Probiotics have been proposed as a viable option for prophylaxis of postoperative infections through increased intestinal motility to prevent bacterial overgrowth, improve gut barrier function, and modulate immune response. This review investigates microbial changes after surgery and the influence of probiotics on postoperative microbial composition. Infectious postoperative complications and immunologic changes related to probiotics/synbiotics were also reviewed in patients who underwent abdominal surgery.

Keywords: Gastrointestinal microbiota; General surgery; Postoperative complications; Probiotics; Synbiotic

INTRODUCTION

Symbiosis between host and microbiome is essential for human health, and dysbiosis has been related to various diseases. The human gastrointestinal tract is the principal residence of microorganisms termed the "gut microbiota".

The gut microbiota has been reported to play an essential role in the development of various diseases such as cardiovascular diseases, obesity, cognitive dysfunction, cancer, and inflammatory bowel disease [1-5]. In addition, gut microbiota also affects surgical outcomes.

The gut microbiota can be affected by various external and environmental factors such as diet, drugs, and physical activity [6-8]. Surgical procedures induce massive stress and can cause alterations in the gut microbiota and dysbiosis.

There is increasing evidence that gut microbiota dysbiosis plays a major role in postoperative complications, including surgical site infection, sepsis, and delayed recovery. Preoperative bowel preparation and antibiotic use in abdominal surgery have been used to control microorganisms that could cause postoperative surgical infection; however, this might lead to bacterial translocation by altering gut microbiota and influence the quality/production of the protective mucosal layer. Therefore, manipulating gut microbiota composition and modifying environmental factors to a healthier status would alter gut microbiota and be helpful for surgical patients. Probiotics, prebiotics, and synbiotics can be used to decrease postoperative complications and enhance recovery from surgical stress. Probiotics are beneficial microbes, prebiotics are the fiber used by beneficial microorganisms, and synbiotics are pre/probiotics.

In this study, I reviewed the alteration of gut microbiota

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Corresponding author: In Ja Park
E-mail ipark@amc.seoul.kr **ORCID** https://orcid.org/0000-0001-5355-3969

caused by abdominal surgery and probiotics/prebiotics/synbiotics influenced postoperative complications.

ALTERATIONS IN GUT MICROBIOTA AFTER ABDOMINAL SURGERY

Although previous reports suggested a role for gut microbiota in postoperative recovery and complications, studies reporting gut microbiota changes in surgical patients are not sufficient. Patients who are plan to undergo abdominal surgery receive prophylactic or therapeutic antibiotic treatment and these preparation make gut microbiota alterations. Therefore, it is challenging to observe the effects of the surgery itself on gut microbiota composition changes [9,10].

Many studies observed a reduced number of bacteria after surgery [11-15]. In the study by Ohigashi et al. [11], patients receiving colorectal resection for cancer underwent preoperative oral antibiotic bowel preparation with kanamycin and metronidazole, as well as intraoperative intravenous antibiotic prophylaxis with first-line cephalosporin. The bacterial counts in postoperative stool samples were significantly decreased compared with those in a preoperative sample [11]. Usami et al. [12] reported a change in fecal flora and organic acid concentrations in hepatectomy patients with or without liver cirrhosis. They aimed to evaluate the effect of symbiotic treatment on mucosal integrity, infectious complications, blood inflammatory marker changes, and fecal bacterial flora. Fecal bacterial counts revealed a transient decrease in beneficial bacteria such as *Bifidobacterium* and an increase in pathogenic organisms such as *Candida* species after hepatectomy in both control and synbiotic-treated groups. Decreased bacteria after surgery was also reported in patients who received esophagectomy for esophageal cancer [13], elderly patients older than 70 years old treated with gastroenterological surgery [14], and colorectal cancer patients [15].

However, some studies did not show a change in total bacterial amount in the postoperative period [16-18]. Kanazawa et al. [16] examined 54 patients with biliary cancer treated with hepatectomy. Patients were randomly allocated to enteral feeding plus synbiotics or enteral feeding only groups. All patients underwent intestinal preparation with an iso-osmotic solution given the day before the operation, and received antibiotic prophylaxis as a single intravenous drip infusion 30 minutes before surgery. The total number of anaerobic bacteria and the number of *Bacteroidaceae*, the dominant anaerobic species, were unchanged before and after surgery in both the control and synbiotic groups. However, the synbiotic composition was beneficial, as harmful bacteria differed between groups in the postoperative period. The control group showed an increased number of harmful microorganisms, including *Enterobacteriaceae*, *Pseudomonas*, and *Candida*. The number of *Enterococci* was also increased after surgery and the number of beneficial bacteria, including *Bifidobacteria* and *Lactobacilli*, was decreased.

Sugawara et al. [17] investigated the effects of perioperative oral administration of synbiotics on microflora in patients undergoing high-risk hepatobiliary resection. He compared groups received synbiotics perioperatively (pre and postoperative period) and postoperative period only in his trial. The total number of anaerobic bacteria and *Bacteroidaceae*, the dominant anaerobic species, was unchanged before and after surgery in the two groups.

Surgery alone results in a significant shift in gut microbiota composition. Local environmental changes during intestinal surgery can cause changes in gut microbiota composition. Intestinal resection exposes the bowel lumen to oxygen, which is usually anaerobic, and results in tissue ischemia by interrupting the local blood supply. Therefore, the composition of obligatory and facultative anaerobes is altered. During the postoperative period, harmful bacterial, including *Pseudomonas*, *Staphylococcus*, and *Enterococci*, which could be causes of postoperative infection, were found to be increased in many studies [11-17]. Beneficial intestinal flora protects the intestinal tract from proliferation of harmful bacteria, while harmful bacteria manifest pathogenicity when host resistance is decreased [19]. Although many trials categorize gut microbiota into "beneficial" or "harmful" categories, the function of gut flora is poorly understood. Therefore, we need to further investigate the fundamental role of gut microbiota compositional changes in postoperative recovery.

INFLUENCE OF PROBIOTICS/SYNBIOTICS ON GUT MICROBIOTA COMPOSITION IN PATIENTS WHO RECEIVED ABDOMINAL SURGERY

Probiotics, which are live microorganisms, have been proposed as a viable option for the prophylaxis of postoperative infections through increased intestinal motility to prevent bacterial overgrowth, improved gut barrier function, and modulated immune response. Prebiotics are nondigestible fiber compounds that stimulate the growth or activity of probiotics by acting as nutritional substrates. Synbiotics combine probiotics and prebiotics. The validated probiotics currently listed by the Health Functional Foods Act are *Lactobacillus*, *Lactococcus* (*Lactococcus lactis*), *Bifidobacterium*, *Streptococcus* (*Streptococcus thermophilus*), and *Enterococcus* (*Enterococcus faecium*, *Enterococcus faecalis*) [20]. However, the effects of these probiotics have also been shown to be strain-specific. Recognizing this, the Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) [21] Joint Probiotics Expert Committee has recommended using *Bifidobacterium* and *Lactobacillus* for functional and safety reasons. In addition, the WHO/FAO guidelines recommend restrictions on the use of *Enterococcus* (*Streptococcus faecalis*) and *E. faecium*, which have been commonly used since 2002 in different probiotic formulations [22]. In 2003, Canada banned the use of *Enterococcus*

species, *Bacillus cereus*, *Bifidobacterium dentium*, *Parascardovia denticles*, *Scardovia inopinta*, *Bacillus clausii* CNCM MA23/3V & CNCM MA66/4M, and *Pediococcus acidilactici* CNCM MA28/6B as probiotics [23].

The species and concentration of microbes in probiotics/synbiotics and the timing and treatment length varied among studies (Table 1) [12-18,24-40]. Therefore, detailed compositional changes were different among studies. However, both probiotics and synbiotics showed similar changes in gut microbiota composition in surgical patients. Many studies comparing probiotic-treated groups to a control group showed increased *Bifidobacterium* and *Lactobacillus* species in the treated group (Table 2) [12-18,28,33,36,39]. However, *Enterobacteriaceae*, *Pseudomonas*, and *Candida* numbers were decreased compared to a placebo group. Synbiotic-treated groups showed similar changes to probiotics groups. In contrast, decreased numbers of beneficial microbes and increased abundance of harmful species (*Enterobacteriaceae*, *Pseudomonas*, *Staphylococcus*, and *Candida*) were reported in control groups.

A few studies showed no significant differences in bacterial species abundance between groups [24,25]. Usami et al. [12] showed that microbiota composition was similar to patients' preoperative status regardless of synbiotic treatment two weeks after surgery.

The microbiota plays an essential role in regulating systemic inflammatory response [41]. The postoperative healing process shows that in the inflammatory phase, the second stage of anastomotic repair, neutrophils prevent infection, and lymphocytes enter the wound and initiate a proliferative phase in the late inflammatory phase [42]. During this process, the microbiota plays an essential role in intestinal mucosa vascularization and the wound healing process, as well as regulating immunity and renewal of epithelial cells through the production of many metabolites [43]. Laboratory inflammatory tests related to postoperative infectious complications or mucosal barrier integrity showed variable outcomes. C-reactive protein (CRP), white blood cells, lactulose/mannitol (L/M) permeability, and interleukin-6 (IL-6) were tested in many studies. In patients supplemented with pro-/synbiotics, CRP and IL-6 significantly decreased compared to non-treated patients. D-amino acid oxidase (DAO) and L/M ratio tests were used to evaluate mucosal permeability. DAO, an intracellular enzyme catalyzing the oxidation of diamines, exists in high concentrations in the intestinal mucosa, is produced at the tip of villi, and represents the mucosal integrity of the small bowel. Serum DAO activity is proportional to the amount of intestinal DAO, making it a reliable marker of intestinal mucosal integrity [12,17], and it correlates with inflammatory markers such as CRP and IL-6. Therefore, it might be indicative of whether synbiotics/probiotics reduce the extent of postsurgical gastrointestinal mucosal damage.

Bacterial metabolites play an important role in supporting epithelial cell viability and barrier integrity and downregulating proinflammatory cytokines [44]. Another parameter for controlling the effect of synbiotics/probiotics is the concentration of organic acids in the stool. Short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate may have beneficial effects on intestinal epithelial cell integrity. These have an essential role, such as epithelial proliferation or stimulation of intestinal motility, and are an energy source for epithelial cells. Fecal SCFA concentrations were reported to decrease postoperatively [11]. Many studies reported that patients showed an increase in the concentration of SCFA in stool after treatment with synbiotics [13,14,16,17]. An increase in SCFAs accompanied by beneficial bacteria suggests that probiotics/synbiotics contribute to the maintenance of SCFA levels after surgery.

ASSOCIATION BETWEEN POSTOPERATIVE COMPLICATIONS AND MICROBIOTA IN PATIENTS WHO RECEIVED ABDOMINAL SURGERY

Infectious complications are associated with high mortality and morbidity rates after abdominal surgery [45-47]. Gut microbiota has been suggested to be involved in postoperative complications after abdominal surgery [48-50]. Many studies have suggested that the gut microbiota is related to wound infection and surgery-related complications such as anastomotic leakage after gastrointestinal surgery [51-53]. Although most of the pathogens related to postoperative complications are normal inhabitants of the human body, dysbiosis destroys mucosal integrity and leads to bacterial translocation [15,54]. The expected spectrum of microbes in postoperative anastomotic complications varies according to anastomosis location. Gram-negative and anaerobic bacteria were found more frequently in patients receiving surgery below the upper gastrointestinal tract [26]. *Enterococci*, which are facultative anaerobic bacteria, have caused infectious complications in patients who received abdominal surgery [55-57]. In patients who underwent pancreatic surgery, *Akkermansia*, *Enterobacteriaceae*, and *Bacteroidales* were reported frequently in patients with postoperative complications, and *Enterococci* were found in drain fluid in patients with anastomotic leakage after pancreaticoduodenectomy [58-60]. An abundance of *Enterococci* and Lachnospiracease was also related to anastomotic leakage after colorectal surgery [61,62]. However, the role of each microbe in postoperative complications has not been confirmed. *Lachnospiraceae*, which were suspected to be associated with anastomotic leakage, have also been postulated to be beneficial through production of SCFAs [63,64].

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Table 1. Probiotics/synbiotics used in clinical trials of patients undergoing abdominal surgery

Author	Year	Patient number	Indication for surgery	Duration of treatment (day)	Included strains (substrates in synbiotics)
Synbiotics					
Rayes et al. [31]	2002	90	Major surgery	5[a]	*Lactobacillus plantarum* 299v (oat fiber)
Kanazawa et al. [16]	2005	55	Biliary cancer	14[a]	*Bifidobacterium breve*, *Lactobacillus casei* (galacto-oligosaccharides)
Sugawara et al. [17]	2006	101	Liver/ biliary surgery	28[b] (14/14)	*Lactobacillus casei* Shirota, *Bifidobacterium breve* strain Yakult (galacto-oligosaccharides)
Rayes et al. [27]	2007	89	Pancreatic surgery	9[b] (1/8)	*Pediococcus pentosaceus, Leuconostoc mesenteroides, Lactobacillus plantarum, Lactobacillus paracasei* (beta glucan, inulin, pectin, resistant starch)
Horvat et al. [24]	2010	76	Colorectal surgery	3[a]	Mixture of 4 *Lactobacilli* (beta-glucan, inulin, starch, pectin)
Eguchi et al. [36]	2011	50	Liver transplantation		*Bifidobacterium breve*, *Lactobacillus casei* (galacto-oligosaccharides)
Usami et al. [12]	2011	67	Liver resection	26[b] (14/12)	*Yakult BL seichoyaku* (galacto-oligosaccharides)
Tanaka et al. [13]	2012	64	Esophagectomy	22[b] (1/21)	*Lactobacillus casei* Shirota, *Bifidobacterium breve* strain Yakult (galacto-oligosaccharides)
Okazaki et al. [14]	2013	53	Upper GI, hepatobiliary, pancreatic cancer	17[b] (7/10)	*Lactobacillus casei* Shirota, *Bifidobacterium breve* Yakult (galacto-oligosaccharides)
Sommacal et al. [32]	2015	54	Periampullary tumor	14[b] (4/10)	*Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus casei*, *Bifidobacterium bifidum* (fructo-oligosaccharides)
Komatsu et al. [33]	2016	379	Colorectal surgery (laparoscopic)	9~18[b] (7~11/2~7)	*Lactobacillus casei* Strain Shirota, *Bifidobacterium breve* strain Yakult (galacto-oligosaccharides)
Yokoyama et al. [28]	2017	50	Pancreatico-duodenectomy	21[b] (7/14)	*Lactobacillus casei* Strain Shirota, *Bifidobacterium breve* strain Yakult (galacto-oligosaccharides)
Flesch et al. [35]	2017		Colorectal cancer	19[b] (5/14)	*Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus paracasei*, *Bifidobacterium lactis* (fructo-oligosaccharides)
Polakowski et al. [34]	2019	77	Colorectal cancer	7[a]	*Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus casei*, *Bifidobacterium lactis* (fructo-oligosaccharide)
Park et al. [40]	2020	68	Colorectal cancer	28[b] (7/21)	*Bifidobacterium animalis* subsp. *lactis* HY8002, *Lactobacillus casei* HY2782, *Lactobacillus plantarum* HY7712 (lactose, xylitol, maltitol)
Probiotics					
McNaught et al. [25]	2002	129	Major surgery	14[b] (9/5)	*Lactobacillus plantarum* 299v
Nomura et al. [37]	2007	70	Pancreatic surgery	Variable[b]	*Enterococcus faecalis*, *Clostridium butyricum*, *Bacillus mesentericus*
Liu et al. [18]	2011	120	Colorectal surgery	16[b] (6/10)	*Lactobacillus plantarum*, *Lactobacillus acidophilus*, *Bifidobacterium longum*
Zhang et al. [15]	2012	60	Colorectal cancer	3[a]	*Bifidobacterium longum*, *Lactobacillus acidophilus*, *Enterococcus faecalis*
Liu et al. [26]	2013	161	Colorectal cancer	16[b] (6/10)	*Lactobacillus plantarum*, *Lactobacillus acidophilus*, *Bifidobacterium longum*
Sadahiro et al. [29]	2014	310	Colorectal cancer	7~23[b] (2~8/5~15)	*Bifidobacteria*
Kotzampassi et al. [38]	2015	164	Colorectal cancer	14[a]	*Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Bifidobacterium lactis*, *Saccharomyces boulardii*
Yang et al. [30]	2016	92	Colorectal cancer	12[b] (5/7)	*Bifidobacterium longum*, *Lactobacillus acidophilus*, *Enterococcus faecalis*
Grąt et al. [39]	2017	55	Liver transplantation	Variable[a]	*Lactobacillus lactis*, *Lactobacillus casei*, *Lactobacillus acidophilus*, *Bifidobacterium bifidum*

GI = gastrointestinal.
[a]Postop only; [b](/)Pre & postop (duration of preoperative treatment/postoperative treatment).

Table 2. Changes in microbiota composition after probiotic/synbiotic treatment

Author	Probiotics/synbiotics		Control	
	Increase	Decrease	Increase	Decrease
Synbiotics				
Kanazawa et al. [16]	*Lactobacillus, Bifidobacteriuma, Enterococci*		*Enterobacteriaceae, Pseudomonas, Candida*[a], *Enterococci*	
Sugawara et al. [17]	*Lactobacillus, Bifidobacterium*[a]	*Candida*		
Eguchi et al. [36]	No significant difference between groups			
Usami et al. [12]	*Candida*	*Bacteroidaceae, Bifidobacterium*		
Tanaka et al. [13]	*Bifidobacterium, Lactobacillus*[b]	*Enterobacteriaceae*[a]		
Okazaki et al. [14]	*Bifidobacterium*[a]	*Enterobacteriaceae, Staphylococcus*[a]		*Bifidobacterium*
Komatsu et al. [33]	*Clostridium leptum subgroup, Bifidobacterium, Lactobacillus*[a]	*Enterobacteriaceae, Staphylococcus, Pseudomonas*[a]	*Enterobacteriaceae, Staphylococcus, Pseudomonas, Clostridium difficile*[a]	*Clostridium coccoides* group, *Clostridium leptum* subgroup, *Bacteroides fragilis* group, *Bifidobacterium, Prevotella, Lactobacillus*[a]
Yokoyama et al. [28]	*Bifidobacterium*, *Lactobacillus*[a]	*Enterobacteriaceae, Pseudomonas*[a]	*Pseudomonas, Staphylococcus, Enterobacteriaceae*[a]	
Probiotics				
Liu et al. [18]	*Bifidobacterium*[a], *Enterococci*	*Enterobacteriaceae, Pseudomonas, Candida*[a]	*Enterobacteriaceae*, *Pseudomonas*, *Candida*[a], *Enterococci*	
Zhang et al. [15]	*Bifidobactrium longum*[b]	*Escherichia coli*[b]	*Bifidobacterium–Escherichia coli* ratio *inversion*[b]	
Grąt et al. [39]	*Enterococcus*[a], *Lactobacillus*			

[a,b]Statistically significant comparing with control group ([a]P<0.05, [b]P<0.01).

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EFFECT OF PROBIOTICS/SYNBIOTICS ON POSTOPERATIVE COMPLICATIONS IN SURGICAL PATIENTS

Clinical trials suggested that the application of probiotics/synbiotics might be able to reduce infectious complications after surgery (Table 3) [12,14-16,18,24-30,32-36,38-40,65]. However, the results of existing clinical studies concerning the use of probiotics and synbiotics to prevent postoperative infections are inconsistent [27,66-70]. In LT and primary pancreatic resection, the perioperative use of probiotics dramatically reduced perioperative infection rates. However, one study including 129 major abdominal surgeries reported that probiotics did not change bacterial translocation or septic morbidities. These discrepancies can be attributed to the small sample size, heterogeneous definition of postoperative complications, and various extents of surgical resection. Postoperative mortality rates were usually low, and there were no significant differences in mortality demonstrated between probiotic/synbiotic-treated groups compared with a control group in many studies [17,28,66,71].

Perioperative probiotic/synbiotic use reduced postoperative infectious complication rates in many studies, including patients undergoing pancreaticoduodenectomy, hepatectomy, liver transplant, or colectomy. A recent pooled analysis of 34 randomized controlled trials (RCTs) demonstrated that the perioperative administration of probiotics and synbiotics significantly reduced the risk of infectious complications following abdominal surgery [70]. The risk of developing a postoperative infectious complication was almost halved (relative risk [RR]=0.56; 95% confidence interval [CI]=0.46~0.69; P<0.001). The reduction in risk of infections was more significant with synbiotics than with probiotics, and infection risk was lower regardless of treatment duration.

Meta-analysis of 20 studies [72] that investigated the role of probiotics/synbiotics in postoperative infection prevention showed that probiotics/synbiotics reduced surgical site infections (RR=0.63; 95% CI=0.41~0.98) and mortality (RR=1.20; 95% CI=0.58~2.48). Pooled results of 28 RCTs [73] reported that wound infection was less frequent (odds ratio [OR]=0.58; 95% CI=0.42~0.80) among patients who received probiotics/synbiotics than in control groups. However, the intra-abdominal abscess rate (OR=0.65; 95% CI=0.28~1.55) and postoperative mortality (OR=1.19; 95% CI=0.52~2.74) did not vary between groups.

However, which strains included probiotic or synbiotic

Table 3. Comparison of mortality and postoperative infectious complications after abdominal surgery in clinical studies of probiotic/synbiotic treatment

Author	Infectious complications (%)		Mortality (%)	
	Probiotics/synbiotics	Control	Probiotics/synbiotics	Control
Kanazawa et al. [16]	19.0	52.2	0	0
Rayes et al. [27]	12.5	40.0	2.5	2.5
Horvat et al. [24]	0	5.0	0	0
Eguchi et al. [36]	4.0	24.0	12.0	12.0
Usami et al. [12]	0	17.2	0	0
Okazaki et al. [14]	24 .0	47.8	0	0
Sommacal et al. [32]	26.1	69.6	0	10.0
Komatsu et al. [33]	17.2	22.7	0	0
Yokoyama et al.[28]	40.9	36.4	0	4.5
Flesch et al. [35]	2.0	21.4	-	-
Polakowski et al. [34]	2.8	18.9	0	8.1
Park et al. [40]	6.0	28.5	-	-
McNaught et al. [25]	10.9	15.4	10.9	3.1
Nomura et al. [37]	23.3	52.9	0	2.9
Liu et al. [18]	14.0	46.0	0	0
Zhang et al. [15]	10.0	33.3	-	-
Liu et al. [26]	54.7	73.3	0	0
Sadahiro et al. [29]	24.0	25.3	-	-
Kotzampassi et al. [38]	19.0	28.8	-	14.0
Yang et al. [30]	10.0	30.0	-	-
Grąt et al. [39]	25.0	19.2	-	-

- = not available.

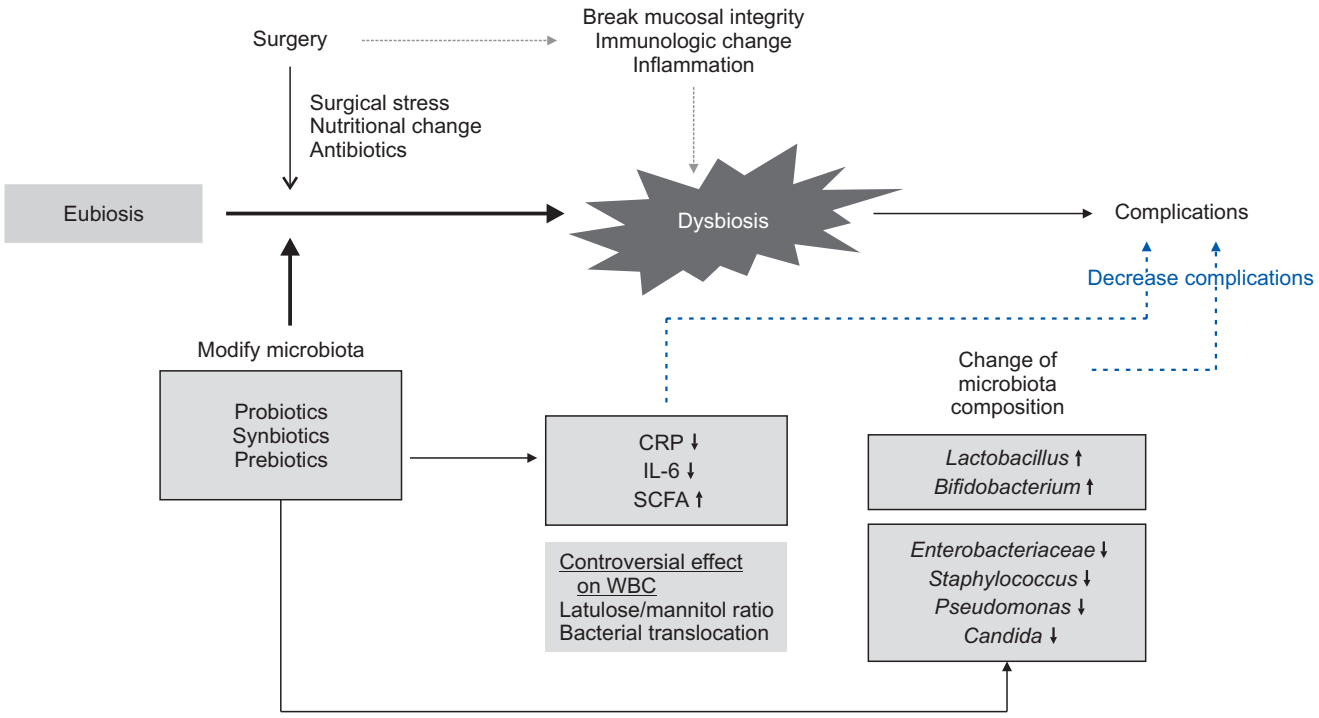

Fig. 1. Summary of effect of probiotics/synbiotics on postoperative complications.
CRP = C-reactive protein; IL-6 = interleukin-6; SCFA = Short chain fatty acid; WBC = white blood cell.

effectively reduced infectious complications was not clear because previous studies used various strains. For example, *Lactobacilli* and *Bifidobacteria* were widely used with prebiotics [14-16,29,30,74,75]. In addition, the same probiotics showed different results in different circumstances [76,77]. Therefore, the effectiveness of different strains in surgical patients requires further investigation.

CONCLUSION

Abdominal surgery alters gut microbiota composition, and is thought to play a role in preventing or accelerating postoperative complications in patients who received abdominal surgery (Fig. 1). Therefore, maintaining homeostasis by modulating microbiota could decrease postoperative complications and improve recovery. In addition, previous studies showed beneficial effects of probiotics/synbiotics in patients who underwent various types of abdominal surgery, including shortened hospital stay and improved functional recovery.

However, the results have been inconsistent, as type of microbes, dose, duration of treatment, and surgery type varied widely among studies. The mechanism of action has also not been sufficiently evaluated. Further studies need to be conducted to identify the effect of specific strains of microbiota and their potential clinical use.

CONFLICTS OF INTEREST

The author of this manuscript has no conflicts of interest to disclose.

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