THE EFFECT OF INULIN SUPPLEMENTATION

ON THE QUALITY OF LIFE OF PATIENTS WITH ILEAL POUCH

ANAL ANASTOMOSIS

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ABSTRACT

Objectives: Ileal pouch anal anastomosis (IPAA), the removal of the colon and formation of a reservoir from ileum, is the surgery of choice for ulcerative colitis and familial adenomatous polyposis. Yet, 10 to 35% of patients develop pouchitis, an inflammation of the pouch mucosa. Microbial imbalances are observed in pouchitis and inulin has been suggested as a prebiotic treatment. Our objectives were to determine the effect of inulin supplementation on quality of life (QOL), and its practicality and safety as a treatment in IPAA patients.

Methods: Adults with IPAA (n= 8) consented to a blinded, placebo-controlled trial of inulin supplementation. Baseline symptoms were measured for 1 month prior to supplementation, followed by a blinded low-dose (5 g of inulin) or placebo (maltodextrin) for 2 weeks and a higher-dose (10 g) for 5.5 months. Participants recorded any symptoms that they experienced in a diary and QOL was assessed using the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) at the beginning and end of the study.

Results: Two participants in the same group developed significant side effects on the 10 g supplementation; abdominal discomfort, severe gas, and small amounts of blood with defecation were reported. Unblinding determined that these participants were taking the active treatment (inulin); therefore, the study was stopped early. No differences were observed in SIBDQ scores.

Implications & Conclusions: In this pilot study, inulin appeared to be ineffective in improving QOL and may have contributed to unpleasant side effects.

Future research should explore synbiotic therapy in IPAA, by combining prebiotics and probiotics for optimal results.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

AI	Adequate Intake
DE	Dextrose Equivalents
DP	Degree of polymerization
FAP	Familial Adenomatous Polyposis
FODMAPs	Fermentable oligo-, di-, and mono-saccharides and polyols
FOS	Fructooligosaccharides
GIT	Gastrointestinal tract
IBD	Inflammatory Bowel Disease
IPAA	Ileal Pouch Anal Anastomosis
mPDAI	Modified Pouchitis Disease Activity Index
PDAI	Pouchitis Disease Activity Index
QOL	Quality of life
SCFA	Short chain fatty acid
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SRB	Sulfate-reducing bacteria
TOS	Trans-galactooligosaccharides
UC	Ulcerative Colitis

CHAPTER 1

INTRODUCTION

1.1 Background

Ileal pouch anal anastomosis (IPAA) is the surgical procedure of choice for the management of ulcerative colitis (UC) and familial adenomatous polyposis (FAP) (Welters et al., 2002). The IPAA procedure involves removal of the colon and formation of a reservoir from 30 to 40 cm of ileum and preserves the anal sphincter to maintain anal continence (Blumberg & Beck, 2002). As reviewed by Winkler (2003), the villi of the IPAA adapt to become more histologically similar to colonic mucosa.

While IPAA is a positive experience for many patients, between 10 to 35% will develop pouchitis in the first 10 years, with a peak incidence at 18 months after surgery (Blumberg & Beck, 2002). Pouchitis involves inflammation of mucosa, characterized by abdominal pain, urgency, bloody or mucous diarrhea, fever and/or general malaise (Turina et al., 2006). Pouchitis can be either acute or chronic in nature and the quality of life of patients is negatively impacted (Winkler, 2003). Quality of life, satisfaction with IPAA surgery, subjective health, and energy levels have been found to be significantly lower in patients with chronic pouchitis ($p<0.01$) (Turina, et al., 2006). Conventional treatment of pouchitis with antibiotics is not satisfactory for all patients, as relapse is common (5-15% with IPAA for UC), a condition known as "refractory or frequent recurrent pouchitis" (Mimura et al, 2004).

The predominant theory of the pathogenesis of pouchitis is a microbial imbalance of the pouch (Ohge et al., 2005). Studies of fecal flora from pouches are associated with decreased counts of *Lactobacillus* and *Bifidobacterium* (Winkler, 2003).

Thus, increasing the counts of these bacteria may restore the microbial balance of the pouches. Prebiotics are being considered as an alterative treatment for pouchitis, as prebiotics are food ingredients that stimulate the growth of *Lactobacillus* and *Bifidobacterium* in the gut (Cummings & Macfarlane, 2002). Winkler (2003) suggested that prebiotics may facilitate recolonizing the pouch with these beneficial bacterial with no known harmful effects. A potential prebiotic intervention for pouchitis is inulin supplementation to create positive shifts in intestinal flora. Inulin is a prebiotic dietary fibre supplement that is fermented into short chain fatty acids and leads to lower intestinal pH (Kruse, Kleesen, & Blaut, 1999).

One known study has investigated the use of inulin in patients with pouchitis. In a three-week cross-over design study, twenty patients with pouchitis received either large doses of inulin or placebo (24 g). Fecal samples were analyzed for pH, short chain fatty acids, microflora, and bile acids. The researchers concluded that inulin fibre supplementation led to decreased inflammation of the pouch mucosa (Welters et al., 2002). This short-term study by Welters et al. provides evidence for the effect of inulin supplementation at the microbial level; however, no studies have addressed the effectiveness of long-term inulin supplementation on the reduction of pouchitis and pouch problems. In addition, we were unable to find studies of the effect of inulin supplementation on the quality of life of individuals who are afflicted by chronic pouchitis.

1.2 Purpose

This study builds on the short-term inulin supplementation study by Welters et al. (2002). The Welters et al. trial was short in duration and therefore did not examine

the long term practicality of inulin supplementation. The purpose of this study was to determine if consuming inulin will decrease pouchitis and pouch problems and improve the quality of life of patients with IPAA. Positive results from this study could provide evidence for inulin supplementation and may affect the treatment and prevention of pouchitis, and ultimately may improve quality of life for patients with IPAA.

1.3 Objectives

There are three main objectives of this study:

1. To determine if inulin supplementation is a practical and safe nutritional recommendation for patients with chronic pouchitis.

2. To determine if inulin supplementation affects the incidence of pouchitis and problems of fecal frequency in patients with IPAA.

3. To determine if inulin supplementation affects the quality of life in people with IPAA.

1.4 Hypothesis

It is hypothesized that the administration of inulin fibre will decrease the incidence of pouchitis and problems of fecal frequency and abdominal symptoms in patients with IPAA. It is also hypothesized that inulin fibre supplementation will be associated with positive quality of life scores in people with IPAA.

CHAPTER 2

LITERATURE REVIEW

2.1 Fermentation and the Role of Microbial Competition in Colonic Health

Competition for substrates within the microbial community of the intestines has been implicated in the maintenance of gastrointestinal health and in the etiology of diseases of the colon (Louis, Scott, Duncan, & Flint, 2007).

2.1.1 Carbohydrate Fermentation

The major products of carbohydrate fermentation are short chain fatty acids (SCFAs), carbon dioxide (CO_2), methane (CH_4), hydrogen gas (H_2), and heat (Topping et al., 2001).

SCFAs are monocarboxylic hydrocarbons that contain 1 to 6 carbon atoms (Kles & Chang, 2006). As presented in Table 2, the SCFAs produced in the colon are acetate, propionate, and butyrate. Acetate is the principal SCFA in the colon; however, butyrate is the preferred nutrient for colonic epithelial cells, favored over acetate or propionate, and over glucose or glutamine supplied from the blood (McGarr et al., 2005).

Table 2.1 Relative Percent of the SCFAs Produced in the Colon
(adapted from McGarr et al., 2005)

SCFA	Acetate	Propionate	Butyrate
Formula	CH3COO⁻	CH3CH2COO⁻	CH3CH2CH2CHOO⁻
Approximate percent of total SCFA produced	70	20	10

The SCFA butyrate has been studied for its cancer preventing role. Butyrate prevents cell differentiation, enhances apoptosis of transformed colonocytes, and

decreases the transformation of primary to secondary bile acids (McGarr et al., 2005). Several reviews have demonstrated that low concentrations of butyrate increase the risks of both colorectal cancer and inflammatory bowel diseases (McGarr et al; Pryde et al., 2002; Topping et al., 2001).

Carbohydrate fermentation also yields gases: CO_2, CH_4 and H_2 (Topping et al., 2001). Efficient mechanisms for H_2 disposal has evolved into three groups of bacteria found in the colon: methanogenic archaea (methanogens), sulfate-reducing bacteria (SRB), and to a much less extent by acetogenic bacteria (McGarr et al., 2005). Hence, the main competition for hydrogen is between the methanogens and SRB. However, when an adequate sulfate source is available, SRB quickly outcompete methanogens for H_2 (McGarr et al., 2005). Competition for H_2 may have implications for development of colon cancer (McGarr et al., 2005). Methane, produced from the oxidation of H_2 by methanogens, is absorbed into portal blood and excreted in the breath (Segal, Walker, Lord, & Cummings, 1988), whereas SRB produce cytotoxic hydrosulfide anions (H_2S), which is not excreted in the breath, and has local, detrimental effects on the colon (McGarr et al.; Picton, Eggo, & Singh, 2007).

Hydrosulfide anions permeate the colonocyte membranes easily and affect cell functions (Fiorucci, Distrutti, Cirino, & Wallace, 2006) and prevent the oxidation of butyrate, the main nutrient for colonic epithelial cells (Picton et al., 2007). In addition, higher than normal levels of H_2S have been found in individuals with colon cancer and inflammatory bowel disease, and research efforts have attempted to link excess H_2S exposure and impaired H_2S clearance to the pathogenesis of these diseases (Picton et al., 2007).

Individuals exhibit variation in levels and activity of SRB, ranging from undetectable to high (Florin, Neale, Gibson, Christl, & Cummings, 1991; McGarr et al., 2005). The individual variability of SRB is significantly related to dietary practices (McGarr, et al., 2005). Food sources of sulfate include meat, seafood, commercially-prepared bread, beer, dried nuts, dried fruit, brassica vegetables (such as broccoli and cauliflower), and drinking water (Florin et al., 1991). Due to the abundance of sources of sulfate in the average diet, an individual could reduce their intake of sulfate-containing food, but complete avoidance of sulfate ingestion would be extremely difficult. Moreover, avoidance of all dietary sources of sulfate would also be inadvisable, because H_2S is also interestingly implicated in the prevention of tissue damage and inflammation. As reviewed by Fiorucci et al. (2007), studies show that H_2S helps to prevent cardiovascular disease and some gastrointestinal conditions, such as Aspirin-induced gastritis.

2.1.2 Protein Fermentation

At least 50% of protein fermented in the colon is from dietary protein. Other sources of protein fermented in the colon are enzymes, sloughed-off epithelial cells, bacterial lysis products, and mucins (Leu et al., 2007). Colonic fermentation of proteins results in formation of ammonia, nitrosamides, thiol, phenolic compounds, and branched chain fatty acids (Ichikawa & Sakata, 1998; Leu et al., 2007). The products of protein fermentation in the colon are believed to be toxic to colonocytes. For instance, ammonia has been associated with shortened colon cell life span, altered DNA synthesis in the colon, and is thought to promote colon carcinogenesis (Ichikawa & Sakata, 1998).

Carbohydrate fermentation decreases bacterial metabolism of proteins and increases bacterial uptake of intermediary metabolites of protein breakdown (Leu et al., 2007). Thus, carbohydrate fermentation protects the colonic mucosa from the detrimental effects of protein metabolism. Supplementation with probiotics and prebiotics could also protect from protein fermentation in the colon; as lactic acid bacteria primarily ferment carbohydrate, and could outcompete microbiota that ferment protein (MacFarlane, MacFarlane, & Cummings, 2006).

2.1.3 Balanced Intestinal Microbiota

Healthy (or balanced) intestinal microbiota has been associated with reduced risk of colon disease (MacFarlane et al., 2006; Wong et al., 2006). Healthy microbiota contains high levels of bacteria from the genera Bifidobacterium and Lactobacillus (MacFarlane et al., 2006; Wong et al., 2006). Interestingly, species of the genera Lactobacillus and Bifidobacterium are not the most numerous bacteria ordinarily present in the colon. Rather, it is the Bacteriodetes and the Firmicutes, which includes Bacilli, Clostridia, and Mollictues, that are the most abundant (Louis, et al., 2007; Todar, 2005, Duncan et al., 2003). The Bacteriodetes and Clostrida primarily metabolize protein and ferment amino acids, resulting in products that are harmful to the colon (MacFarlane et al., 2006). In contrast, Lactobacillus and Bifidobacterium are primarily carbohydrate fermenting, and yield products that are beneficial to colon health, such as SCFAs (MacFarlane et al., 2006). Lactobacillus and Bifidobacterium do not contain any pathogens and are associated with colonization resistance to pathogens (Gibson, McCartney, & Rastall, 2005). Prebiotic and probiotic supplementation has emerged to

increase the representation of Lactobacillus and Bifidobacterium, and selectively

promote the growth of these healthy colon microbiota (Wong et al., 2006).

2.1.4 Probiotics

Probiotics are live microorganisms which, when administered in adequate

amounts, benefit the host (Food and Agriculture Organization of the United Nations and

World Health Organization [FAO/WHO] Report, 2002). The most commonly used

bacteria in probiotic supplements are the lactic acid- producing bacteria, including the

species Lactobacillus and Bifidobacterium (Parvez, Malik, Ah Kang, & Kim, 2006).

Probiotics compete with other bacteria for nutrients and thus create a colonic

environment that is less conducive for the growth of potentially pathogenic or protein-

fermenting bacteria (Bongaerts & Severijinen, 2001).

Marteau, de Vrese, Cellier, and Schrezenmeir (2001) and Santosa, Farnworth,

and Jones (2006) conducted systemic reviews of the potential health claims for

probiotics, as related to gastrointestinal health. They observed an overall protective

effect of probiotics for the prevention and treatment of antibiotic-associated diarrhea,

with particularly strong evidence for Lactobacillus in treating rotavirus infection-

induced diarrhea. In addition, clinical trials have demonstrated a reduction of irritable

bowel syndrome symptoms due to probiotic administration. Santosa et al. also note there

is some evidence from animal studies for the efficacy of probiotics in the treatment of

inflammatory bowel disease and for cancer prevention; however, they caution that there

are a limited number of randomized-control trials to draw conclusions about these

specific health claims.

2.1.5 Prebiotics

2.1.5.1 Prebiotics Defined

Prebiotics are non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and activity of specific bacteria in the colon (Gibson, Probert, Van Loo, Rastall, & Roberfroid, 2004). In particular, prebiotics stimulate the growth of lactobacilli and bifidobacteria (Cummings & MacFarlane, 2002). Gibson et al. and Roberfroid (2007) describe strict criteria for the classification of prebiotics. Prebiotics must demonstrate (1) resistance to hydrolysis by mammalian enzymes, to gastric acidity, and to gastrointestinal absorption; (2) fermentation by intestinal microflora; and (3) selective stimulation of the growth and/or activity of those intestinal bacteria that contribute to health and well-being. According to Gibson et al., only three food ingredients can be classified as prebiotics based on these criteria: inulin (including fructooligosaccharides (FOS) or oligofructose), trans-galactooligosaccharides, and lactulose.

Roberfroid contradicts the decision regarding the third food ingredient (lactulose) by stating, "Presently there only two food ingredients that fulfill this criteria, i.e. inulin and trans-galactooligosaccharides (TOS)" (Roberfroid, 2007, p. 831S). This statement is not in agreement with a table in this same article which states that lactulose does have prebiotic status (Table 4: Summary and conclusion on the prebiotic effect of various oligosaccharides, Roberfroid, 2007, p. 853S).Galactoooligosacchardies and lactulose appear identical in terms of meeting the criteria; however, in the text of the article Roberfroid only remarks on inulin and galactooligosaccharides as prebiotics.

Table 2.2: Prebiotic Status of Oligosaccharides
(Adapted from Prebiotics: The Concept Revisited, Roberfroid, 2007)

Oligosaccharides Classified as Prebiotics
Inulin and oligofructose
Galactooligosaccharides
Oligosaccharides: Candidates* for Prebiotic Status
Lactulose
Isomaltooligosaccharides
Lactosucrose
Xylooligosaccharides
Soybean oligosaccharides
Glucooligosaccharides
(*More research is required to determine if the properties of non-digestibility, selectivity or fermentation are satisfied)

MacFarlane, Steed, and MacFarlane (2008) recently been amended the Gibson et al. (2004) and Roberfroid (2007) prebiotic definition to: "a prebiotic is a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microbiota that confers benefits upon host well-being and health."

Kuisma et al. (2003) postulated that lactose may also be a prebiotic, based on the negative correlation they observed in aerobes and lactose consumption in IPAA patients and a review of early observational studies. However, lactose was not mentioned in the Gibson et al. review (2004) or the Roberfroid et al. review (2007). A possible reason for the exclusion of lactose in this discussion would be that, in lactose-tolerant adults, lactose is absorbed in the small intestine, thus it would not fulfill the first and second criteria of prebiotics (resistance to hydrolysis by mammalian enzymes, to gastric acidity, and to gastrointestinal absorption and fermentation by intestinal microflora) according to Roberfroid et al. and Gibson et al.

The results of prebiotic trials for the treatment and prevention of diseases of the colon are promising; yet MacFarlane et al. (2006) criticize the lack of randomized-control trials to test the clinical effects of prebiotics on irritable bowel syndrome and inflammatory bowel disease, and judge the evidence for prebiotics in the prevention of diarrhea and colon cancer as weak.

Non-starch polysaccharides (dietary fiber), resistant starches, sugar alcohols, and lactose become substrates for microbial fermentation when they reach the colon. Compared to prebiotics, microbial growth stimulation by these undigested carbohydrates is non-specific, and promotes the growth of both pathogenic and beneficial bacteria, whereas prebiotics, by definition, specifically stimulate the growth of mainly beneficial bacteria (MacFarlane et al., 2006). Ingestion of prebiotics increases the production of butyrate (Louis et al., 2007).

One might assume that it is the Lactobacilli and the Bifidobacterium that predominantly produce butyrate, due to their association with a healthy gut environment, and because prebiotics stimulate the production of both these beneficial bacteria and butyrate. Yet, it is actually bacteria from Clostridia that are primary butyrate producers (Louis et al., 2007). The concept of metabolic cross-feeding is used to explain the increase in butyrate that is accompanied by the increase in lactic acid bacteria (Louis et al., 2007). Metabolic cross-feeding occurs when the products yielded from the metabolism of prebiotics by one bacterial species may then provide substrates to support the growth of other populations (Belenguer et al., 2006).

In light of cross-feeding in anaerobic communities, it is important that prebiotics can influence non-target populations in the gut microflora (Flint, Duncan, Scott, & Louis, 2007). MacFarlane et al. (2006) remark that inulin has also been associated with

increases in other bacterial genera: Roseburia, Ruminoccocus, and Eubacterium. Duncan et al. (2003) found that inulin was associated with increases in two groups of Clostridium-related bacteria and in *Roseburia inulinvorans.* Flint et al. state that *Roseburia inulinvorans* is regarded as potentially beneficial due to its butyrate-producing capabilities; however, the health effects of modulating the other bacterial groups are generally not known.

2.1.5.2 Inulin

Inulin is a heterogeneous blend of fructose polymers naturally present in a variety of fruits and vegetables, including wheat, onions, leeks, garlic, asparagus, Jerusalem artichokes, and bananas (Carabin & Flamm, 1999). Inulin has therefore has been part of the human diet for centuries. Inulin from chicory root is commercialized as a purified food ingredient, and always contains a small amount (up to 10 %) of naturally occurring sugars (Coussement, 1999). Inulin is also extracted commercially from stems of the blue agave plant (Waleckx, Gschaedler, Colonna- Ceccaldi, and Monsan, 2008).

Inulin is a generic term which represents all β (1$\leftarrow$ 2) linear molecules of fructans (a polymer of fructose monomers) of varying lengths, from 2 to 60 units (Niness, 1999; Roberfroid, 2007). Oligofructose and fructooligosaccharide (FOS) are synonymous names for the mixture of small inulin oligomers with degree of polymerization of less than 10 (a short length) (Roberfroid, 2007). As a partial hydrolysate of inulin, FOS is used as a food ingredient. Inulin and FOS are used in the food industry to replace fats and sugar (Coussement, 1999). Inulin is easier to tolerate than oligofructose in terms of gastrointestinal symptoms, since inulin is more slowly fermented (Coussement, 1999).

The β (1← 2) linkage gives inulin the ability to resist digestion by human intestinal enzymes. The structure of inulin is below in Figure 1; the n represents the number of fructose monomers.

Figure 2.1: Chemical Structure of Inulin (Fisch, 2008).
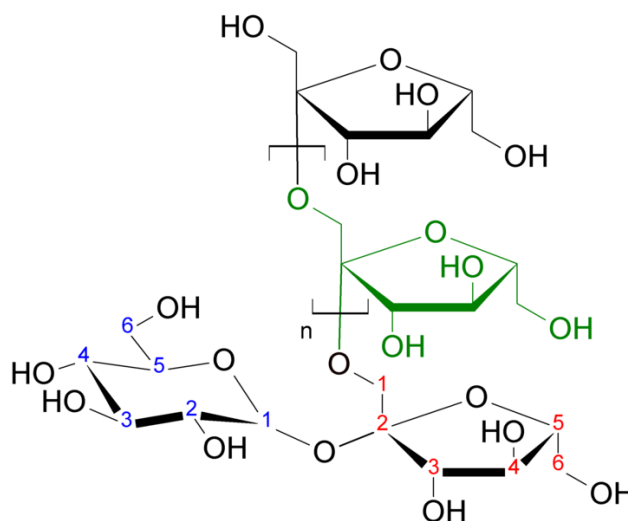
2.1.5.2.1 Safety and Dosing of Inulin

According to Coussement (1999), most people can consume 10 g of inulin without any gastrointestinal side effects, whereas some individuals may experience some discomfort and rarely diarrhea. The fermentation of dietary fibre by anaerobic bacteria produces gas, including H_2, CH_4 and CO_2, which may be related to complaints of distension or flatulence (American Dietetic Association, 2008). Carabin and Flamm (1999) conducted a review on the safety of inulin by evaluating numerous toxicological and clinical studies. They state that these studies have demonstrated no evidence of toxicity from inulin, and purport that real issue is not that of safety, but rather of gastrointestinal tolerance. The toxicological and clinical studies reported signs of gastrointestinal intolerance observed in healthy adults with intakes above 20–30 g.

The actual tolerable intake of inulin appears to still be a topic of debate. The effect of adding 14 g/d of inulin to a low-fat spread was studied in seventy-two healthy women aged 20-36 years. The study was performed as a double-blind randomized crossover experiment with two periods of 4 weeks without any washout period. The degrees of discomfort from the gastrointestinal symptoms, including of rumbling in stomach, rumbling in gut, stomach cramps, gut cramps, bloating, and flatulence, were all ranked significantly higher in the inulin test period compared with the control test period ($p<0.001$). Throughout the experiment, discomfort from flatulence was the most profound symptom. Discomfort from flatulence was ranked as severe by 12 % of the volunteers when consuming the inulin spread and the participants did not adapt to consumption of the inulin over time ($p<0.05$) (Pedersen, Sandstrom, & van Amelsvoort, 1997).

Davidson and Maki (1999) examined the effects of providing 3 servings of inulin containing foods per day to 25 male and female adults with hypercholesterolemia in a randomized, double-blind crossover study (three six-week periods of inulin or placebo, wash-out, and placebo or inulin. A total of 18 g/d of inulin was provided. Gastrointestinal discomfort was more common during the inulin phase than the placebo phase (5/21 participants reported no gastrointestinal side effects in the inulin phase, vs. 13/21 participants in the control phase; $p<0.003$). The symptoms included flatulence, abdominal cramping, bloating, and changes in the frequency and consistency of bowel movements. The symptoms generally did not reduce in frequency or severity during the six weeks of treatment on inulin, indicating that the patients' gastrointestinal systems did not adapt to the inulin.

Kruse, Kleesen, and Blaut (1999) evaluated the effects of inulin on eight healthy adults under free-living conditions over a period of 10 weeks. They examined gastrointestinal compatibility, effects on fecal microflora, SCFA, and blood lipid variables. The subjects consumed a fat-reduced diet for a period of 64 days using inulin as a fat replacer. The amounts of inulin consumed by the subjects varied, as they were based on individual energy requirements. Participants consumed up to 34 g/d. Inulin significantly increased bifidobacteria and caused a moderate increase in the gastrointestinal symptoms of flatulence and bloating for the participants. These symptoms occurred 8–9 hours after intake of inulin. The formation of hydrogen as a by-product of bacterial fermentation was deemed the likely cause of these symptoms. However, the authors emphasized that bifidobacteria are not capable of H_2 gas formation.

In contrast to the findings of Pedersen et al. (1997), Kruse et al. (1999) observed adaptation of participants' gastrointestinal systems to inulin supplementation. Even though the Pedersen group provided nearly half of the dose of inulin as Kruse et al., Pedersen et al. noted no adaptation of subjects to inulin. Thus, it appears that there is variability in the amount of inulin that is tolerable in healthy adults, and reports of adaptability of gastrointestinal systems to inulin supplementation are also inconsistent.

Coussement (1999) states that individual variation in the sensitivity to inulin exists. Orafti, a European food company, developed three categories regarding sensitivity to fermentable carbohydrates (Table 2.3).

Table 2.3: Categories of Sensitivity to Fermentable Carbohydrates
(Adapted from Coussement,1999)

Category	Reaction to fermentable carbohydrates
I. Nonsensitive persons	Can consume ≥ 30 g/d without undesirable reactions
II. Sensitive persons	Can consume 10 g/d without undesirable reactions, but may experience reactions at ≥ 20 g/d
III. Very sensitive persons	Experience undesirable reactions at ≤ 10 g/d

2.1.5.2.2 Prebiotic Effects of Inulin: Bifidus Stimulation

Bouhnik et al. (1999) examined the dose-dependent bifidus stimulation in FOS supplementation for healthy adults. In interpreting the results of their study, it is important to recall that a longer chain inulin is more slowly fermented than FOS, therefore the bifidogenic effects would differ and the tolerance to inulin would be greater (Coussement, 1999). Bohnik et al. concluded that the optimal and well-tolerated dose of FOS that significantly increases fecal bifidobacteria in healthy adults is 10 g/d ($p<0.05$). At the dose of 20 g/d, flatus was more frequent and intense than at the 10g/d dose ($p<0.05$).

These results for healthy adults cannot be applied to patients with IPAA. The amount of inulin that is tolerable in patients with IPAA has only been evaluated by the Welters et al. (2002) trial, who did not report any side effects at 24 g of inulin per day.

2.1.6 Synbiotics

Synbiotics are a mixture of probiotics and prebiotics (Bengmark, 2001). The approach of mixing the two supplements improves the implantation and survival of the probiotics in the gastrointestinal tract. Synbiotics activate the metabolism and/or selectively stimulate the growth of one or a few health-promoting bacteria (Gibson & Roberfroid, 1995).

2.2 Relevant Diseases of the Colon

2.2.1 Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is a relapsing and remitting condition of chronic inflammation at various sites along the gastrointestinal tract (GIT) lining, which can result in severe bouts of watery or bloody diarrhea and abdominal pain. IBD includes Crohn's disease and ulcerative colitis (UC) (Yantiss & Odze, 2006). IBD affects approximately 1 in 200 individuals in Canada (Crohn's and Colitis Foundation of Canada, 2008). The inflammation of IBD results from a cell-mediated immune response in the GIT mucosa and the precise etiology is unknown, but it has been suggested that in patients with multifactor genetic predispositions, the normal intestinal (commensal) flora trigger an immune reaction (Wexner & Stollman, 2007).

The symptoms of UC and Crohn's disease are similar, but they are quite different diseases. UC is limited to the mucosa of the intestinal tract, while Crohn's disease involves much deeper mucosal tissue. UC only affects the colon and rectum, whereas Crohn's disease can occur anywhere along the digestive tract. Unlike UC, in which inflammation occurs uniformly throughout an affected area; Crohn's disease can develop in several places simultaneously, with healthy tissue in between (Wexner & Stollman, 2007).

Medical treatment for IBD involves steroids and other immunomodulating systemic and topical drugs, such as 5-Aminosalicyclic acid and 6-mercaptopurine. All of these treatments may have serious adverse effects. One promising therapeutic agent for the treatment of UC is probiotics; researchers have shown positive results in several controlled trials (Wexner & Stollman, 2007). A minority of patients opt for elective

surgery of removing the entire colon and rectum, which has the potential to cure UC (Wexner & Stollman, 2007).

2.2.2 Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is a rare inherited disease which is characterized by hundreds to thousands of polyps formed on the lining of the lower intestine (Galiatsatos & Foulkes, 2006) and accounts for less than 1% of all colorectal cancer cases (Vasen et al., 2008). The two main options of prophylactic removal of the large intestine are proctocolectomy with ileal pouch anal anastomosis (IPAA) and colectomy with ileorectal anastomosis (IRA) (Vasen et al., 2008).

2.3 Ileal Pouch Anal Anastomosis

2.3.1 The procedure of Ileal Pouch Anal Anastomosis

The ileal pouch anal anastomosis (IPAA) is a surgical procedure following total proctocolectomy for UC, Crohn's disease, and FAP, in which the surgeon forms a functional reservoir of intestine for the accumulation of feces. The purpose of the reservoir is to avoid the need for a permanent discharging stoma for patients (Taylor, 1986). The IPAA procedure involves removal of the colon and formation of a reservoir from 30 to 40 cm of ileum. The anal sphincter is preserved to maintain anal continence (Blumberg & Beck, 2002). The villi of the ileum after an IPAA adapt to their function and become more histologically similar to colonic mucosa (Winkler, 2003); the cells of the mucosa undergo a transformation from ileal to become colon-like. This cellular transformation is accompanied by the development of microflora that is qualitatively intermediate between the ileum and the colon (Stocchi & Pemberton, 2001). The first successful IPAA was performed in 1980 (Utsonomiya et al., 1980) and it has now

become the surgical procedure of choice for the management of UC and FAP (Welters et al., 2002). Oresland, Fasth, Nordgren, Akervall and Hulten (1990) measured pouch volumes of 67 patients over a 2-year period and found the mean pouch volume increased during the first year post-surgery, from 132 ml to 282 ml.

2.3.2 Microbial Differences Before and After IPAA Surgery

One study compared patients with ileostomies as controls to patients with IPAA and determined that patients with IPAA had higher ratios of anaerobes: aerobes and higher concentrations of anaerobic gram-negative rods (Bacteriodes species) (Sandborn et al., 1995). Almeida et al. (2008) sought to indentify the microflora in patients (n=10) with severe UC pre-IPAA surgery and 2 and 8 months post-IPAA surgery. The authors found that no bacterium could be indentified that could be exclusively responsible for the maintenance of the inflammatory process in IPAA. The microflora underwent significant alterations post-IPAA surgery but returned to normal ileal values for some bacteria.

2.3.3 Nutritional Guidelines for Patients with IPAA

Literature on food-related problems with IPAA surgery is scarce. Steenhagen, Roos, Bouwman, Van Laarhoven, and Van Staveren (2006), administered a survey to identify the foods causing intolerance and to determine the nature and severity of symptoms of 105 patients with IPAA. All of the patients reported intolerance to one or more foods. Spicy foods, cabbage, and citrus fruits and juice were the foods most often attributed to increased stool frequency (patient-reported), decrease stool consistency, or perianal irritation. Onions, cabbage, or leeks were reported by 28% of the patients to cause flatulence. The urgency of bowel movements was reported to be more intense after a cooked meal (45% of patients within ½ hour) than after sandwiches (15% within

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½ hour). Foods reported to increase stool consistency were potato products, bread, and bananas. Based on these subjective reports, the researchers concluded that food intolerance is a common, but a mild problem after IPAA. They suggested that nutrition professionals should encourage patients to choose foods based on individual tolerance, rather than providing patients with a list of foods that may cause discomfort, as this may cause unnecessary avoidance of foods.

2.3.4 Pouchitis and Other Outcomes of the IPAA Procedure

2.3.4.1 Pouchitis

Patients with IPAA may develop pouchitis. Pouchitis is inflammation of the pouch mucosa. It involves abdominal abdominal pain, urgency, bloody or mucous diarrhea, fever and/or general malaise (Turina et al., 2006). Patients with pouchitis have a varying range of clinical presentation, clinical course, and prognosis (Yamamoto-Furosho, 2007).

Pouchitis can be acute or chronic in nature (Winkler, 2003) and there are varied reports of the occurrence of pouchitis, reflecting varying degrees of accuracy and types of diagnostic evaluation (Stocchi & Pemberton, 2001). The incidence of pouchitis has been reported to range from 10% to 35% in the first 10 years after surgery, with a peak incidence at 18 months post-procedure (Blumberg & Beck, 2002). Other authors have reported even higher incidents of pouchitis, up to 59% (Simchuk & Thirlby, 2000).

Inflammation in pouchitis is thought to be caused by the mucosal invasion of bacteria, pathogenic toxins, or secondary changes, such as SCFA profile disruptions in the pouch (Lim, Sagar, Finan, Burke, & Schuster, 2006). The etiology and pathogenesis

of pouchitis is still debated, but the predominant theory of the pathogenesis of pouchitis is a microbial imbalance or dysbiosis of the pouch mucosa (Ohge et al., 2005).

2.3.4.2 Pathogenesis of Pouchitis

The predominant theory of the pathogenesis of pouchitis is a microbial imbalance or unstable microflora of the pouch (Ohge et al., 2005). The instability of the microflora in the pouch causes a disruption of the homeostasis, known as dysbiosis. The protection by mucus of the pouch epithelium layer is negatively affected by the increased activity of bacteria and host derived enzymes (Ruseler-van Ebden, Schouten, & van Lieshout, 1994).

The role of microflora in the inflammation of pouchitis is suspected due to the differing response of patients with pouchitis to antibiotics such as metronidazole and ciproflaxin. In addition, use of probiotics such as VSL#3 can prevent the first onset of inflammation within the pouch (Lim et al., 2006). VLS is a mixture of viable bacteria (Vsl Pharmaceuticals Inc.) and specifically contains four strains of Lactobacillus (*L. casei, L. plantarum, L. acidophilus,* and *L. delbrueckii subsp. bulgaricus*), three strains of Bifidobacterium *B. longum, L. breve,* and *B. infantis*), and *Streptococcus thermophilus* of the *Streptocuccus salivarius subsp*. (Elahi, Nikfar, Derakhshani, Vafaie & Abdollahi, 2007).

However, researchers have still failed to demonstrate any one organism or toxin responsible for pouchitis (Lim et al., 2006). As reviewed by Lim et al., several differences in the microflora composition of healthy pouches exist when compared to pouches afflicted with pouchitis. The combined results of several studies indicate that pouchitis is associated with increased counts of aerobic bacteria and decreased counts of anaerobic bacteria, Lactobacillus and Bifidobacterium (Brandi et al., 1992; Ruseler-van

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Emben, et al., 1994). These authors noted the following microbial imbalances in pouchitis: increased clostridia, decreased bifidobacteria, and decreased lactobacilli. A reduction in bifidobacteria and lactobacilli is associated with decreased SCFA production and consequently a less acidic environment. A relatively high pH in patients with pouchitis is a symptom of the instability of the microflora (Ruseler-van Embden et al., 1994).

Kuisma et al. (2003) compared 11 patients with optimal pouch function to 21 patients with pouchitis history following IPAA construction for UC. No significant differences existed in mean nutrient intake, composition of fecal bile acids, or microbial tissue biopsy cultures between the groups. Dietary intake was not significantly correlated to the presence or absence of pouchitis. Those patients with optimal outcome tended to have more benign disease course of UC than patients with a history of pouchitis. In those patients with histories of pouchitis, fecal concentrations of both anaerobes and aerobes were significantly higher (p=0.007) than patients with optimal outcome. Low intake of lactose was associated with sulfomucin predominance. A negative correlation existed between fecal aerobes and dietary lactose consumption. Kuisma et al. concluded that a higher total load of fecal anaerobic bacterial flora is strongly associated with the degree of villous atrophy, colonic metaplasia, and inflammation activity after IPAA surgery. Interestingly, Kuisma et al. also found an association between dietary lactose, fecal bacteria, and pouch morphology and suggested that lactose may have prebiotic properties. Lactose was inversely correlated with total aerobes (p=0.019).

Hydrogen sulfide (H_2S) has also been proposed as a fecal bacteria product that may cause pouchitis. Ohge et al. (2005) investigated H_2S release and SRB counts in

pouch contents to determine if H_2S correlates with pouchitis. During an eight-month period, patients with IPAA after proctocolectomy for FAP (n=5) and UC (n=45) provided fecal samples for analysis. Release of H_2S when pouchitis was active or had occurred in the past year was significantly higher ($p < 0.05$) than when pouchitis had never occurred or had been inactive. H_2S release from pouch contents of UC patients not receiving antibiotics was five to ten times more rapid than observed for FAP patients, possibly suggesting a difference in sulfide metabolism between these groups.

In one study, SRB appeared to be exclusive to IPAA patients with an UC background only. SRB were not found in the pouches of patients with a background of FAP (Duffy et al., 2005). Levels of Lactobacilli, Bifidobacterium, Bacteriodes, *Clostridium perfringens,* enterococci, and coliforms were similar in both UC and FAP patients. Because pouchitis mainly affects patients with a UC background, and SRB appear to be exclusive to UC pouches, it is postulated that SRB may play a role in the pathogenesis of pouchitis (Duffy et al., 2005).

Despite the numerous studies implicating the role of dysbiosis in the pathogenesis of pouchitis, some researchers dispute the role of dysbiosis. Sandborn et al. (1995) found no differences in the fecal concentrations of bacteria, bile acids, or SCFAs in patients with pouchitis versus patients without pouchitis, and Sandborn et al. concluded that these factors cannot be the sole cause of pouchitis. Although Lim et al. (2006) do not address this specific article in their review; they do address other studies that do not show differences in bacterial concentrations in patients with pouchitis compared to those without. Lim et al. criticize these studies for providing poor categorizing and classification of pouchitis. However, Lim et al. also criticize the studies that support the theory of dysbiosis causing pouchitis. They note slight differences in the

candidate species or shifts in flora. Lim et al. conclude their review in stating that the evidence that dysbiosis is a cause of pouchitis is still poor and propose the need for more studies to determine if there is an unidentified pathogen, a broad imbalance of bacterial populations, or an exaggerated host response to commensal bacteria (the bacteria that is normally present in the intestines). They suggest future studies include proper selection of pouchitis patients according to established criteria and better culture and molecular techniques to study bacterial flora to expand the evidence of the dysbiotic theory of pouchitis.

Komanduri, Gillevet, Sikaroodi, Mutlu, and Keshavarzian (2007) used cloning and sequencing of the length heterogeneity polymerase chain reaction amplicons to evaluate the microflora of 20 post-IPAA surgery patients (range 1-5 years post-IPAA surgery). Komanduri et al. conclude that their data provide direct evidence of the role of microflora in the pathogenesis of pouchitis. They found an increased presence of Fusobacter and Enteric species associated with the presentation of pouchitis. In addition, the authors found decreased presence of Streptococcus species in inflamed pouches.

Another, less favored theory of pathogenesis is the belief that fecal stasis causes chronic recurring overgrowth of bacteria. However, critics of the fecal stasis theory argue that stasis as a cause of pouchitis is not likely in the absence of sphincter spasm, stenosis, or impaired evacuation of feces (Winkler, 2003). Kroesen et al. (2006) examined a theory of bacterial permeation of the pouch. They observed increased bacterial permeability in pouches of those patients with pouchitis ($p < 0.001$) but they were unable to link the permeability to decreased function of the pouch and did not state if the bacterial permeability was a cause of pouchitis or if it was as a results of pouchitis.

Disagreement exists on the factors that influence the risk of developing pouchitis. Simchuk and Thirlby (2000) performed a retrospective review of 114 patients who underwent IPAA by a single surgeon. Stool frequency was 6.1 ± 0.2 per day and the incidence of pouchitis occurred in 67 patients (59%). Patient gender was significantly associated with the incidence of pouchitis 74% of women and only 47 % of men developed pouchitis ($p = 0.008$). Duration of follow-up was another factor; at 6 months post-surgery 27% of patients developed pouchitis, at one year 37%, and at 3 years 50% ($p=0.02$). However, Stocchi & Pemberton (2001) state that age, gender and postoperative sepsis do not appear to have an influence on the risk of developing pouchitis. Although pouchitis occurred in more than half of the patients reviewed, the mean patient satisfaction with the procedure was high, 8.4 (on a scale of 0 being dissatisfied and 10 being extremely satisfied).

Lovegrove et al (2006) performed a meta-analysis of studies comparing the outcomes of IPAA surgeries for patients with FAP versus patients with UC. The occurrence of pouch fistulation was significantly increased in those patients with UC (10.5% vs. 4.8%; $p< 0.001$), and the incidence of pouchitis, which was significantly greater in the UC patients (30.1 % vs. 5 %; $p< 0.001$). Stool frequency was also higher in the UC patients; on average UC patients had one more bowel movement per 24 hours than FAP patients.

Similarly to the findings on UC, smoking appears to reduce the risk of pouchitis. Pouchitis afflicts patients with a history of UC and is uncommon in patients with FAP, supporting a view that pouchitis is a form of UC that has recurred in the ileal pouch (Stocchi & Pemberton, 2001). In addition, immunologic alterations in pouchitis resemble the alterations in UC: cytokine production of IL-1β, IL-6, IL-8 and tumor

necrosis factor-α (Stocchi & Pemberton). Yet, the immunologic component of the pathogenesis of pouchitis has not been clearly established, as Schmidt et al. (2006) contradicts Stocchi & Pemberton in stating that cytokine and chemokine patterns in pouchitis are not typical of UC.

Although the etiology and the dysbiotic theory of the pathogenesis of pouchitis has not yet reached consensus by leading IPAA researchers, there is still sufficient evidence that increasing the counts of Lactobacillus and Bifidobacterium bacteria may restore the microbial balance of the pouches. Both prebiotics and probiotics are agents that could increase the levels of beneficial bacteria. Prebiotics and probiotics are not known have any harmful effects and are being considered as an alterative treatment for pouchitis to recolonize the pouch with beneficial bacterial (Winkler, 2003).

2.3.4.3 Quality of Life

The poor quality of life (QOL) of UC patients improves in most clinical studies after the IPAA procedure. Nevertheless, QOL and bowel function is still not considered normal, since many patients have problems with urgency, leakage, nocturnal soiling, sexual dysfunction, and pouchitis (Lichtenstein, Cohen, Yamashita & Diamond, 2006). The occurrence of pouchitis has a particularly negative impact on patients following IPAA. Over a ten-year period, 68 patients were administered Global QOL Questionnaires and telephone interviews. Overall QOL, satisfaction with IPAA surgery, subjective health, and energy levels were significantly lower in patients with chronic pouchitis ($p<0.01$) than patients without pouchitis (Turina et al., 2006).

2.3.4.4 Pouchitis Disease Activity Index

The Pouchitis Disease Activity Index (PDAI, Table 2.4) is a diagnostic instrument that was developed by Sandborn et al. (1994) to assess pouchitis in an

objective and quantitative manner. PDAI is the most commonly used diagnostic

instrument in pouchitis research and consists of three principle component scores:

symptom, endoscopy, and histology (Shen et al., 2003). Patients who are graded a score

of seven or more are classified as having pouchitis. In comparison to the previously

established diagnostic scoring systems for pouchitis, the PDAI is more sensitive in

detecting pouchitis (Sandborn et al., 1994).

Table 2.4: The Pouchitis Disease Activity Index

(Developed by Sandborn et al., 1994)

The Pouchitis Disease Activity Index[4]

Criteria	Score
Clinical	
Stool frequency	
Usual postoperative stool frequency	0
1–2 stools/day > postoperative usual	1
3 or more stools/day > postoperative usual	2
Rectal bleeding	
None or rare	0
Present daily	1
Fecal urgency or abdominal cramps	
None	0
Occasional	1
Usual	2
Fever (temperature > 37.8° C)	
Absent	0
Present	1
Endoscopic inflammation	
Edema	1
Granularity	1
Friability	1
Loss of vascular pattern	1
Mucous exudates	1
Ulceration	1
Acute histologic inflammation	
Polymorphic nuclear leukocyte infiltration	
Mild	1
Moderate + crypt abscess	2
Severe + crypt abscess	3
Ulceration per low-power field (mean)	
>25%	1
25–50%	2
>50%	3

Shen et al. (2003) criticize the PDAI because its practical use is limited due to the cost of endoscopy and histology. Also, the PDAI is limited due to complex calculation and a time delay in diagnosis in determining scores. Accordingly, Shen et al. developed a Modified PDAI (mPDAI) which omits histological evaluation. They tested their instrument to determine if removing the measure of histology would affect the test sensitivity or specificity. They concluded that the mPDAI provides similar specificity (100%) and sensitivity 97% compared to the PDAI. The mPDAI provided 0% false-positives and 4% false-negative tests (1 of 27). Although Shen et al. (2003) were able to address some of the impracticality, expense, and time delay of using the PDAI by eliminating the histological measures; they were not able to omit the endoscopic component. Symptoms, endoscopy and histology do not correlate with each other, and consequently one can not rely on a single component, such as symptom scores, to accurately diagnose pouchitis (Shen et al., 2003).

2.4 Treatment of Pouchitis

2.4.1 Conventional Treatment

Antibiotics such as metronidazole, ciproflaxin, tetracycline, clarithromysin, amoxicillin/clavulanic acid, and rifaximin are used to treat pouchitis (Winkler, 2003). Other treatment regimes may include topical steroids, suppositories, enemas, and anti-diarrheal agents (Winkler, 2003). Conventional treatment of pouchitis with antibiotics is not satisfactory, as relapse is common and antibiotics inflict negative alterations of the normal microflora of the intestines (Winkler, 2003). Therefore, effective treatments that also improve the microfloral balance of the IPAA are more attractive than the

conventional options. The following sections will review probiotics and prebiotics, two treatments which could potentially achieve this goal.

2.4.2 Probiotics for the Management of Pouchitis

According to Hedlin et al. (2007), the most convincing evidence for the use of probiotics in pouchitis comes from randomized, double-blind, placebo-controlled trials of VSL# 3. VSL #3 has two innovative characteristics: a very high bacterial concentration of 300 billion live bacteria/g and a mixture of bacterial strains which creates the potential for synergistic relationships to enhance the suppression of pathogenic agents (Gionchetti et al., 2000).

Elahi et al. (2007) performed a meta-analysis of controlled clinical trials that examined the effect of probiotics in preventing pouchitis as defined by the Pouchitis Disease Activity Index (PDAI). Only five randomized, placebo-controlled clinical trials were included in the meta-analysis; four studies investigated VSL #3 and one study examined *Lactobacillus rhamnosus GG*. The majority of the randomized controlled trials reviewed were limited by small sample sizes and therefore a low power in determining a true positive effective of probiotics (Elahi et al., 2007). They also only chose similar studies for their meta-analysis to estimate a combined effect. The pooling of the results from the trials reviewed by Elahi et al. yielded an odds ratio of 0.04 with a 95% CI of 0.01–0.14 ($P<0.0001$) in the treatment group in comparison with the placebo group.

Table 2.5: Summary of the Trials Included in Elahi et al. Meta-analysis
(Adapted from Elahi et al., 2007)

Study	Number of Participants	Type and Dose of Probiotic	Median Months of Follow-up	Reported Pouchitis: Control	Reported Pouchitis: Treatment
Gosselink et al. (2004)	200	*Lactobacillus rhamnosus GG* 1.4×10^{10} CFU/d	60 (control); 32 cases	46/85	4/42
Gionchetti et al. (2000)	40	VSL #3 6 g/d	4	20/20	3/20
Gionchetti et al. (2003)	40	VSL #3 6 g/d	12	8/20	2/20
Mimura et al. (2004)	36	VSL #3 6 g/d	12	15/16	3/20
Kuhbacher et al. (2006)	15	VSL #3 6 g/d	2	5/5	0/10

Elahi et al. (2007) concluded that their meta-analysis confirmed that probiotics are beneficial in the management of pouchitis and suggested that further research should contain sufficient sample sizes and should be focused on determining the proper dose and timing of probiotic administration. They warn that the results should be interpreted carefully, since the meta-analysis did not allow for adjustment of clinically relevant variables such as characteristics of the patients (i.e. age and gender), duration of the therapy, and choice of probiotic supplement. Other substances present in fermented products may also have an effect on the results.

No adverse effects were reported by Gionchetti et al. (2000), Kuhbacher et al. (2006), or Gionchetti et al. (2003). Mimura et al. (2004) reported that one of the twenty patients receiving the VSL #3 dropped out due to abdominal cramps, vomiting, and diarrhea.

The Gosselink et al. (2004) trial should not have been included in their meta-analysis, based on their criteria of requiring the trials to be randomized. Gosselink et al. performed a non-randomized study of IPAA patients (n=85 controls versus n=42 patients on the probiotic *Lactobacillus rhamnosus GG* contained in a fermented product). Patients who had surgeries performed between March 1996 and March 2001 were given the probiotic. Patients who had surgeries performed between October 1986 and March 1996 never used any probiotics and therefore served as the control. Therefore, this study is not randomized and should not be included in the Elahi et al. meta-analysis. Nevertheless, the results of are promising: first episodes of pouchitis were observed less frequently in the group taking the probiotic. The cumulative risk at 3 years was 7% (probiotic group) vs. 29% (control) (p=0.011). They concluded that a daily intake of 1-2 x 10^{10} *Lactobacillus rhamnosus GG* should be recommended to IPAA patients to delay the onset of pouchitis.

As previously mentioned, several studies are not included in the meta-analysis by Elahi et al. (2007). Most studies were excluded from the meta-analysis because they were not randomized or double-blinded, or because their sample sizes were too small. Other studies were excluded because they did not examine the desired outcome measure of pouchitis defined as a PDAI $\geq$ 7. However, several of these studies still warrant discussion.

Laake et al. (2005) examined the effects of a fermented milk product containing live lactobacilli (La-5) and bifidobacteria (Bb-12) for 4 weeks on 69 patients with IPAA in an open-label intervention. They observed a significant reduction in endoscopic score (p= 0.0001) and a significant increase in lactobacilli (p= 0.017) and bifidobacteria (p= 0.006). Patients with a history of UC experienced significantly decreased symptoms (involuntary defecation, leakage, abdominal cramps, need for napkins, fecal number and consistency, mucus and urge to evacuate stools) during the intervention.

Kuisma et al. (2003) conducted a three-month, randomized, double-blind, placebo-controlled prospective trial of *Lactobacillus GC* supplementation (n=20) which demonstrated that the probiotic was effective in changing participants' pouch intestinal flora; the probiotic was associated with an increased ratio of total fecal lactobacilli to total fecal anaerobes (p=0.03). But, the probiotic therapy was ineffective as the primary therapy. There were no clinical improvements for the treatment group based on the PDAI or the total anaerobes or aerobes of fecal or tissue biopsy samples. The authors suggest the need for more clinical trials to determine the proper dosage and placement of probiotics within a pouchitis treatment regimen.

Shen et al. (2005) studied VSL #3 in maintaining antibiotic-induced remission in pouchitis patients (n=31). All patients received 2 weeks of the antibiotic Ciprofloxacin and subsequent treatment with the probiotics. At the 8 month follow-up, 25/31 patients had discontinued taking the probiotics due to either recurrent symptoms (23/31; 74.2%) or to intolerable adverse effects (2/31; 6.5%). One patient developed bloody bowel movements immediately after starting the treatment, and one patient developed severe constipation, bloating, and gas. The remaining 6/31 (19.4%) patients underwent clinical and endoscopic evaluation, and their PDAI scores were not significantly different from

baseline (p= 0.27). Shen et al. concluded that only a minority of the patients were compliant on long-term maintenance probiotic therapy and suggest the need for more clinical trials on the safety and efficacy of probiotics before incorporating them into daily clinical practice for managing pouchitis. One limitation of this study was the fact that patients had to purchase, store, and self-administer the VSL #3, which may have led to decreased compliance, since probiotics are costly. However, this reflects a realistic setting of the use of probiotics in pouchitis.

In summary, amongst the mixed results of probiotic trials for pouchitis, some positive convincing evidence exists. Although most trials did not report any adverse effects, Mimura et al. (2004) and Shen et al. (2005) did report some side effects that suggest more investigation on the safety and dosing of probiotics for the prevention and management of pouchitis is needed.

2.4.3 Prebiotics for the Management of Pouchitis

To date, there have only been two studies of prebiotics for the management of pouchitis published. Both studies implement the prebiotic inulin and they will be discussed in detail.

Welters et al. (2002) conducted a three-week cross-over design study of twenty patients with pouchitis receiving either large doses of inulin or placebo (24 g). Fecal samples were analyzed for pH, SCFAs, microflora and bile acid. Compared to the placebo, significant improvements on inulin included increased butyrate concentrations (p= 0.01), lowered pH (p= 0.02), decreased numbers of Bacteriodes fragilis (p= 0.02), and decreased concentrations of secondary bile acids (p= 0.01 for deoxycholic acid and p= 0.04 for ursodeoxycholic acid). The researchers concluded that inulin

supplementation leads to decreased inflammation of the pouch mucosa (Welters et al.). No adverse effects were studied, with the exception one participant who dropped-out of the study due to lactose intolerance from the lactose-containing drink in which the inulin was administered. However, the authors did not describe how the lactose intolerance was diagnosed, so it may be possible that the symptoms of lactose intolerance could actually be due to side effects of the inulin supplementation.

This short-term study by Welters et al. (2002) provides evidence for the effect of inulin supplementation at the microbial level. However, no studies have addressed the effectiveness of long-term inulin supplementation on the reduction of pouchitis and pouch problems. In addition, to our knowledge, no one has investigated the effect of inulin supplementation on the quality of life of individuals who are afflicted by chronic pouchitis.

The Welters et al. (2002) study is frequently cited as evidence for the use of prebiotics in inflammatory bowel disease and pouchitis. The other study of inulin for pouchitis (Meijer et al., 2000) is actually the exact same study that was published by Welters et al., but with a very different spin on the results. It is also important to note that Welters was the second author for the Meijer et al. article, and both articles are published in Diseases of the Colon and Rectum. Meijer et al. does refer to the positive results by Welters et al. as "unpublished data", but Welters et al. does not refer to the Meijer et al. article.

In contrast to the conclusions of the Welters et al. article (2002), in the Meijer et al. (2000) article, the authors concluded that inulin did *not* influence inflammation or have an effect on pouch mucosal functioning because neither epithelial gene expression nor epithelial homeostasis was significantly changed by inulin supplementation.

Mucosal morphology, epithelial cell proliferation and cell death were not altered by inulin supplementation. It is not clear why the results of the same three-week trial would be published with two separate and contrasting conclusions.

Croagh et al. (2007) take a very different approach to the use of inulin in pouchitis. They hypothesized that fermentable oligo-, di, and monosaccharides and polyols (FODMAPs), which are poorly absorbed short-chain carbohydrates, should increase fecal output following IPAA or ileorectal anastomosis (IRA) due to their osmotic effects. FODMAPs include fructans (inulin), free fructose and lactose (in cases where maldigestion is present), and polyols such as sorbital. Croagh et al. studied 15 patients (13 with IPAA and 15 IRA) to determine the effect of reducing FODMAPs. Therefore, in contrast to Meijer et al. (2000) and Welters et al. (2002), inulin was treated as an agent that causes pouch problems as opposed to protecting against pouch problems, and they aimed to determine the effect of removing inulin and other short-chain carbohydrates.

The 15 patients underwent symptomatic and dietary evaluation before and after the low-FODMAP diet and carbohydrate malabsorption was measured by breath H_2 tests. Pouchitis was assessed clinically/endoscopically or by fecal lactoferrin. These methods were limited, since the authors did not use the PDAI for the pouchitis diagnosis and did not have histological measures. Additionally, by reducing a combination of factors in the diet makes it difficult to isolate the effects of the nutrient of interest, inulin. However, the results of the trial are interesting: overall, none of the patients who had pouchitis showed improvement with the low FODMAP diet. However, median daily stool frequency decreased significantly; from 8 bowel movements/day to 4 bowel movements/day (p= 0.001) in patients without pouchitis. Again, since a combination of

dietary factors was reduced, we cannot conclude from this study that decreasing inulin specifically would reduce the pouch problem of frequency, but it is possible that it could be a contributing factor.

2.4.4 Synbiotic Therapy for the Treatment of Pouchitis

The literature on synbiotic therapy for the management of pouchitis is limited to an abstract by Friedman and George (2000). Ten patients with either refractory pouchitis or requiring long-term antibiotic uses were treated with *Lactobacillus GG* and the prebiotic FOS (fructooligosaccharide; amount not listed), one capsule twice daily for one month. All ten patients had reversal of macroscopic and endoscopic alterations and complete suppression of their symptoms. They concluded that prebiotic and probiotic therapy provides effective adjunctive therapy for patients with refractory pouchitis.

2.5 Summary

In summary, IPAA is the surgical procedure of choice for the management of UC and FAP; however, the quality of life of some patients is negatively affected by a mucosal inflammation known as pouchitis. The etiology and pathogenesis of pouchitis is still debated in the literature, but the predominant theory is a microbial imbalance or dysbiosis of the pouch mucosa. Balanced microbiota contain high levels of bacteria from the genera Bifidobacterium and Lactobacillus, which are primarily carbohydrate fermenting, do not contain any known pathogens, and are associated with colonization resistance to pathogens. Both prebiotics and probiotics are agents that could increase the levels of these beneficial bacteria to restore microbial balance.

Although the results of probiotic trials for pouchitis are mixed, the majority of trials provide convincing evidence for probiotic supplementation. In contrast, the

research available on prebiotics and synbiotics for pouchitis treatment and prevention is very limited. The only prebiotic studied for pouchitis is inulin, and there is insufficient data to determine the acceptable dose of inulin for patients with IPAA. However, inulin, at 10 g/d, appears to cause the least discomfort in most healthy adults and has a significant bifidogenic effect at this dose.

CHAPTER 3

RESEARCH METHODS

3.1 Study Design

The study was initially approved as a 12-month, randomized, placebo-controlled, double-blind trial. Participants with IPAA were to be recruited from Royal University Hospital patient health records and from one local surgeon's referrals. Several amendments were made to the original design. The researchers felt that a 12-month period might create subject burden, so the study was shortened to seven months, and included a one-month period for baseline measurements. The sample size goal was 25 participants. To create balanced groups with a small sample size, the participants were matched to either the placebo or control, as opposed to randomization.

3.2 Ethical Approval

Approval for this study was granted by the Biomedical Research Ethics Board of the University of Saskatchewan in Saskatoon, Saskatchewan (Bio-REB #06-65) and the Saskatoon Health Region (Appendix 1). The study coordinator signed a Non-Disclosure Agreement to ensure that the information contained in the health records reviewed was kept confidential. Written informed consent was provided by the participants (Appendix 2).

3.3 Participant Inclusion and Exclusion Criteria

Patients of both genders aged 18-75 years with recurrent pouch problems or pouchitis were eligible for enrollment. Patients who did not have documented pouch

problems or pouchitis were excluded. Patients with Crohn's disease were excluded because their condition affects the ileum. In addition, patients with diabetes mellitus were also excluded as non-resistant maltodextrins can affect blood glucose concentrations, as maltodextrin contains 9.4 g of carbohydrate per 10 g dose.

3.4 Recruitment

To assess for eligibility, Health Records of the Saskatoon Health Region retrieved health charts patients with a history of the IPAA procedure. A review was conducted of 94 health charts of patients in the Saskatoon Health Region who had received the IPAA procedure in the past ten years. In addition, a surgeon who specializes in gastroenterology referred several of his patients to the study. A letter requesting referrals was also sent to all surgeons who may have conducted IPAA procedures; however, no additional referrals were received.

If a patient was eligible for the study, an information package containing a letter of invitation to the study and a consent form were sent to their home address (Appendices 2 and 3). Patients were followed up by a telephone call after the information package was mailed-out. During the follow-up call, details of the study and consent form were reviewed, and questions that potential participants had about eligibility and allowance for taking other medications and supplements during the study were answered. Contact information was provided and interested patients were encouraged to contact researchers if they had any further questions. If patients were interested in participating in the study, they were requested to complete and return the consent form to the study coordinator.

3.5 Randomization of Participants

Participants were matched in order of priority by 1) time passed since pouch surgery, 2) gender, 3) diagnosis (UC or FAP), and 4) comorbid medical conditions. The participants were matched to either Group A or Group B. The treatment allocation was blinded to the participants and the researchers.

3.6 Study Protocol

3.6.1 Supplement Dosing

The first month of the study was the baseline period. Participants did not consume any supplements for this month. Following the baseline period, the participants received a low-dose supplement of 5 g/d for of either the active treatment of inulin or a placebo of non-resistant maltodextrin for two weeks. If the low-dose supplement was tolerated, the participants then received a high-dose of 10 g/d of the same supplement for an additional five and a half months.

The inulin used in this study was Frutafit® CLR provided by Sensus America LLC (Monmouth Junction, JJ, USA). The Frutafit® CLR inulin is a mixture of oligosaccharides of 8 to13 monomers in length. The maltodextrin, Globe Plus® 18 dextrose equivalents (DE), was provided by Corn Products International, Inc. (Casco Incorp. Etobiocoke, Ontario, Canada). Maltodextrin is a highly digestible dextrin that was selected as the placebo because it is a white, dissolvable powder that resembles inulin in appearance and taste. The inulin and maltodextrin were weighed on an electronic scale and placed in individual plastic sachets by the research assistant and the study coordinator. Participants were instructed to dissolve the supplement in a hot beverage.

3.6.2 Compliance

Participants were asked to mark in their study diaries whether or not they consumed the treatment each day, and also provided reasons for any missed doses. Compliance was calculated as a percent of days per period that the full dose was consumed.

3.7 Data Collected

3.7.1 Demographic Data

Demographic data collected through Health Records on the participants included gender, age at baseline, date since IPAA surgery, comorbid medical conditions, and diagnosis.

3.7.2 Assessment of Safety and Symptoms

For each day of the study, including the baseline period, the low-dose supplementation stage, and the high-dose supplementation stage, the participants were asked to record any symptoms they experienced in a Symptom Diary (Appendix 4). The participants were asked to return the Symptom Diary as soon as it was completed. During the supplementation stages, participants were asked to report any adverse effects immediately to the research coordinator.

The participants recorded the following data in the Symptom Diary:

1. Ingestion of the supplement

2. Subjective Overall Health Rating

3. BM frequency (number of bowel movements per 24 hour period)

4. Any symptoms associated with pouchitis

Participants were asked to record if they experienced the symptoms of bleeding (defined as blood in feces and upon wiping), fecal urgency (defined as the urgent feeling of need to defecate), abdominal cramping and pain, diarrhea and fever. In addition, participants were instructed to record any other symptoms they experienced. For the Subjective Overall Health Rating, the participants recorded their subjective overall health in their study diary daily as either: 5= Excellent, 4= Very Good, 3= Good, 2= Fair and 1= Poor.

Participants were to record any medications or other supplements they took during the study on the Medications page of their diary (Appendix 8). Any supplements and medications that a participant was taking at baseline were permitted during the treatment period.

3.7.3 Assessment of Quality of Life

Participants' quality of life was assessed using the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) (Appendix 5). The SIBDQ measures physical, social, and emotional status (Jowett, Seal, Barton, & Welfare, 2002) and was developed and validated to assess health related quality of life for patients with inflammatory bowel disease. Each participant's total score (all 10 items) on the SIBDQ was also compared at baseline and post-supplementation. For each SIBDQ question, a score of 1 is a low quality of life score, and a 7 is a high quality of life score. Thus, an increase in SIBDQ scores represents an increase in quality of life.

3.8 Data Analysis

3.8.1 Sample Size Calculation

The sample size goal of n= 40 was based on two studies by Gionchetti et al. using probiotics in patients (n=40) with pouches (Gionchetti et al., 2000 and Gionchetti, et al., 2003).

3.8.2 Statistical Analysis

All Statistical Analysis was performed using Office 2003 Excel and SPSS 16.0. A p-value of < 0.05 (two sided) was used to denote statistical significance. For each test, the inulin group was compared to the placebo group. A paired-t test was used to determine statistical difference between group means for SIBDQ scores. Each participant's total score (all 10 items) on the SIBDQ was also compared at baseline and post-supplementation. Repeated measure ANOVA was used to determine statistical difference between group means for the symptoms, at three measures: baseline, 5 g dose supplementation and 10 g dose supplementation.

CHAPTER 4

RESULTS

4.1 Participant Flow

Figures 4.1 and 4.2 depict the flow of participants through all stages of the trial. Only 24 (25%) of the 93 patients met the inclusion criteria. Of the 24 eligible patients, 9 consented to participation in the study, which represents a 37.5% participation rate (Figure 4.1).

Figure 4.1 Schematic of Recruitment

```
          ┌─────────────────────────────┐
          │  Health charts reviewed for │
          │     eligibility (n=93)      │
          └─────────────────────────────┘
            ╱                       ╲
           ╱                         ╲
┌──────────────────┐   ┌────────────────────────────────────────────┐
│  Enrolled (n=9)  │   │ Excluded (n= 84)                           │
└──────────────────┘   │ Did not meet inclusion criteria (n= 69)    │
                       │ Refused to participate (n= 10)             │
                       │ Not contacted due to early cessation of    │
                       │ study (n= 5)                               │
                       └────────────────────────────────────────────┘
```
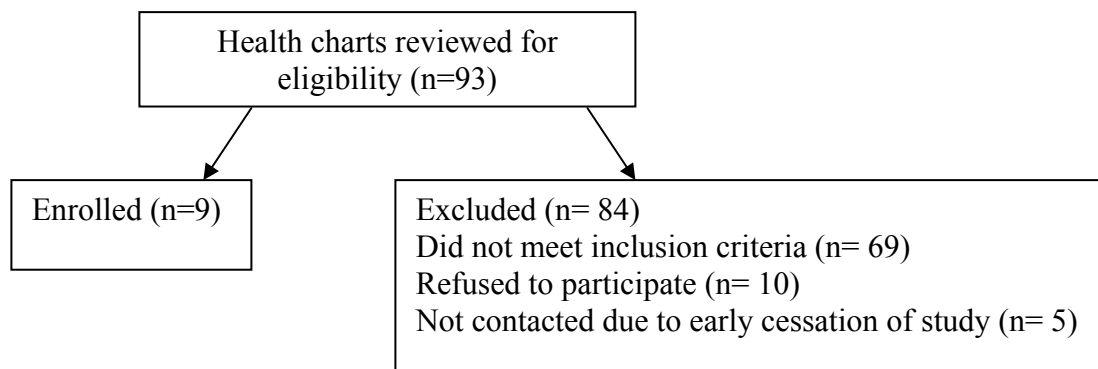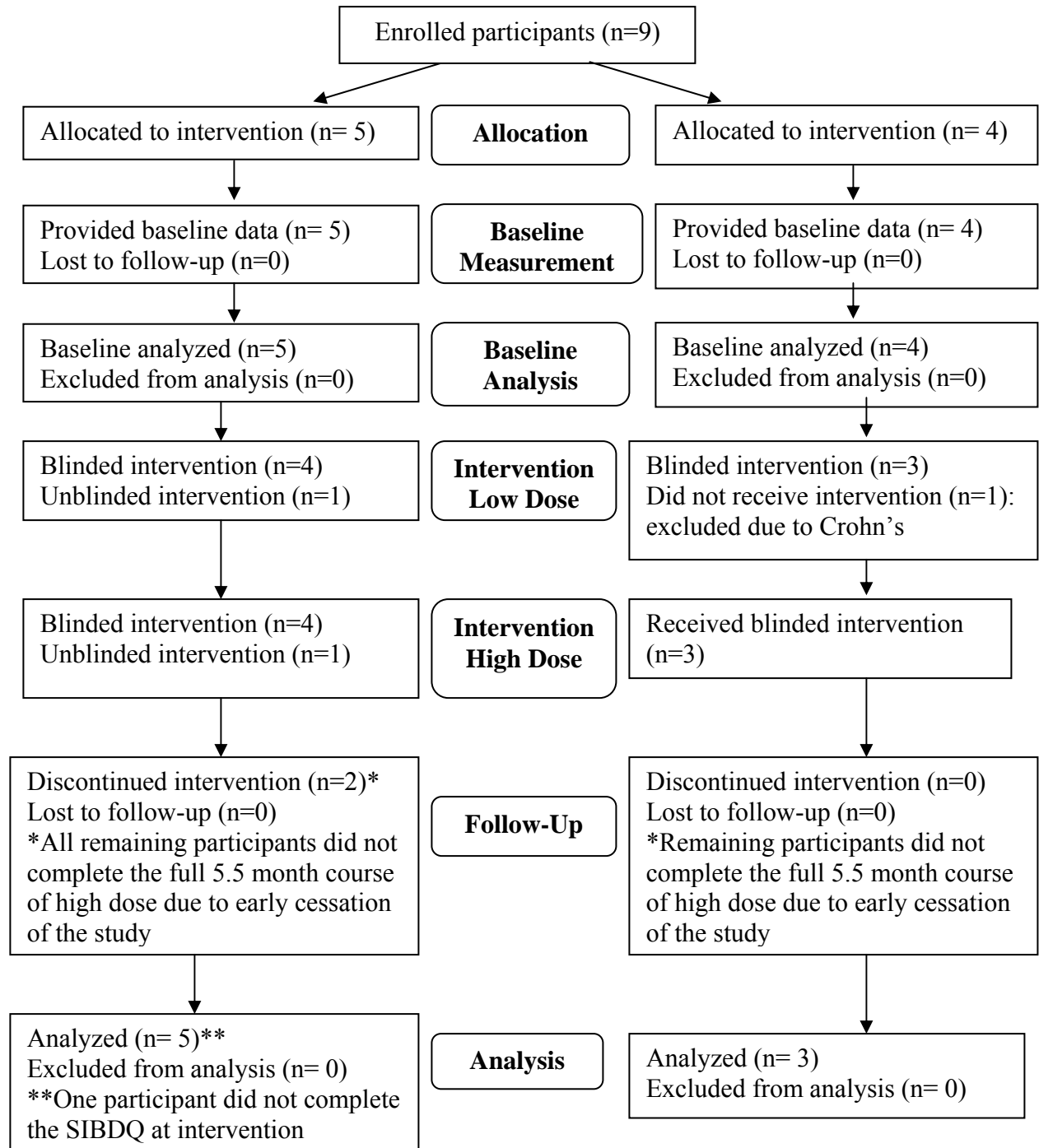
Figure 4.2 shows the flow of participants through allocation, baseline measurement, treatment, follow-up and analysis. The nine participants were matched to the two different arms of the study and baseline data was collected on all participants. One of these participants, P-09, was diagnosed with Crohn's Disease at the start of treatment period and was consequently excluded from further participation. Another participant, P-07, was deemed a special case. This special case participant was placed on the active treatment of inulin rather than matched to either group for ethical reasons. The participant was experiencing extreme abdominal discomfort to the point of wishing to

reverse the IPAA procedure. The research team felt it was unethical to place the participant in the placebo arm of the study, when a possible treatment was available, which could potentially avoid surgery. In addition, this participant was only asked to provide two (rather than four) weeks of baseline data. The rationale for a shorter baseline period was to provide the potential treatment as soon as possible, since this participant was in so much discomfort.

The participants (not including the participant with Crohn's disease and the special case) started either the blinded low-dose treatment (5 g of inulin) or placebo, then subsequently received the high-dose treatment (10 g of inulin or placebo) two weeks later.

Two participants in the same high-dose arm discontinued taking the treatment due to significant side effects including cramping, abdominal discomfort, severe gas, small amounts of blood in feces, and upon wiping. At this point, the Biomedical Research Ethics Board was alerted and the Principle Investigator unblinded the study. It was determined that the participants who were experiencing significant side effects were in the inulin group; therefore, the researchers decided to stop both arms of the treatment intervention and terminate the study. All participants were informed of the early cessation of the study and were asked to submit their data. All participants (n= 9) submitted their study diaries, and seven participants submitted their intervention SIBDQ. One participant did not submit their SIBDQ data. Figure 4.2 shows the participant flow in the study.

Figure 4.2: Flow of Participants

	Enrolled participants (n=9)	
Allocated to intervention (n= 5)	**Allocation**	Allocated to intervention (n= 4)
Provided baseline data (n= 5) Lost to follow-up (n=0)	**Baseline Measurement**	Provided baseline data (n= 4) Lost to follow-up (n=0)
Baseline analyzed (n=5) Excluded from analysis (n=0)	**Baseline Analysis**	Baseline analyzed (n=4) Excluded from analysis (n=0)
Blinded intervention (n=4) Unblinded intervention (n=1)	**Intervention Low Dose**	Blinded intervention (n=3) Did not receive intervention (n=1): excluded due to Crohn's
Blinded intervention (n=4) Unblinded intervention (n=1)	**Intervention High Dose**	Received blinded intervention (n=3)
Discontinued intervention (n=2)* Lost to follow-up (n=0) *All remaining participants did not complete the full 5.5 month course of high dose due to early cessation of the study	**Follow-Up**	Discontinued intervention (n=0) Lost to follow-up (n=0) *Remaining participants did not complete the full 5.5 month course of high dose due to early cessation of the study
Analyzed (n= 5)** Excluded from analysis (n= 0) **One participant did not complete the SIBDQ at intervention	**Analysis**	Analyzed (n= 3) Excluded from analysis (n= 0)

4.2 Participant Characteristics

The participant characteristics are compared for the inulin group vs. the placebo group in Table 4.1.

Table 4.1: Comparison of Participant Characteristics by Allocated Treatment

	Total participants (n= 9)	Inulin group (n= 5)	Placebo group (n= 4)
Mean Age (Years) (Range)	43.8 (20-60)	44.6 (20-60)	42.8 (25-57)
Average years since surgery (SD)	3.9 (+/-13.9)	4 (+/-15.4)	3.8 (+/-14.0)
	(n/%)	(n/%)	(n/%)
Diagnosis of FAP	1 (11.1)	0 (0)	1 (25)
Diagnosis of UC	8 (88.9)	5 (100)	3 (75)
Gender			
Male	6 (66.7)	3 (60)	3 (75)
Female	3 (33.3)	2 (40)	1 (25)

4.3 Compliance

The mean percentage of days of compliance on the 5 g dose is 95.6% for the inulin group vs. 100% for the placebo group (Table 4.2). The mean percentage of days compliant on the 10 g dose is 70.4% for the inulin group vs. 100% for the placebo group.

The mean percent of days in which participants required a half dose of the treatment, due to intolerance of the full dose, was 15.6 % for the inulin group vs. 0% for the placebo group. Two participants, P-01 and P-04, had very low compliance due to side effects at the 10 g dose and their dose was reduced to 5 g. Both participants subsequently asked to stop participation in the study when their symptoms continued at the 5 g dose.

Table 4.2: Comparison of Percent Compliance by Participants and Comparison by Allocated Supplement

Allocated Supplement	Participant Number	Days compliant on 5 g dose (%)	Days compliant on 10 g dose (%)	Percent of days requiring half dose
Inulin	P-01	100	33	67
Inulin	P-03	86	88	0
Inulin	P-04	100	46	11
Inulin	P-07	92	85	0
Inulin	P-08	100	100	0
Mean for Inulin Group		95.6	70.4	15.6
Placebo	P-02	100	100	0
Placebo	P-05	100	100	0
Placebo	P-06	100	100	0
Placebo	P-09	N/A	N/A	N/A
Mean for Placebo Group		100	100	0

4.4 Symptoms

Repeated measures ANOVA were performed to compare group means (inulin group versus placebo group) for the symptoms. However, due to a small sample size, a lower power of 0.2 was established and no statistical significance was determined for any of the symptoms. The comparisons of group means have been presented graphically. More detailed individual participant data, graphs, and analysis are presented in the Appendix 7: Detailed Symptom Data and Analysis.

4.4.1 Bleeding

Figure 4.3 shows the percent of days participants experienced the symptom of bleeding for the placebo group compared to the inulin group. This symptom increased in the inulin group upon consuming the 10 g dose, from 1.4% of days at baseline, to 0 % of days on the 5 g dose and 32.1% of days on the 10 g dose.

Figure 4.3: Bleeding- Comparison of Treatment Group Means

Error bars: +/- 1 SE
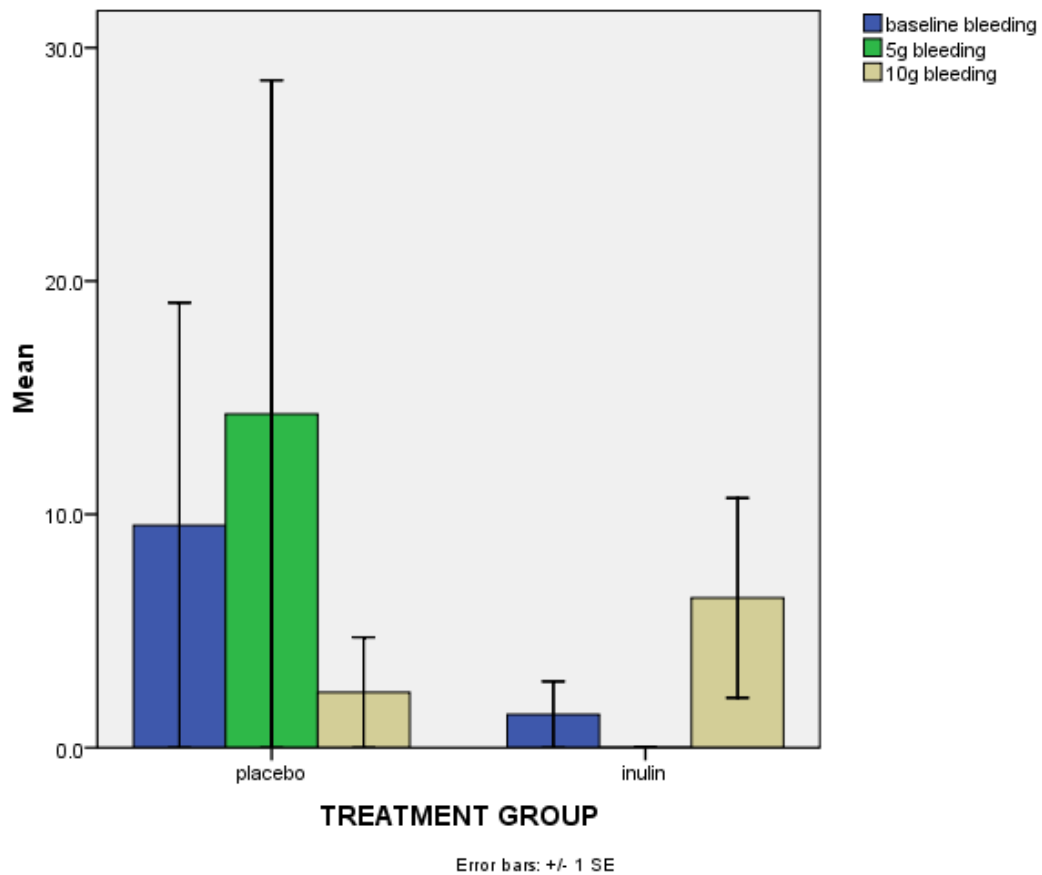
4.4.2 Fecal Urgency

The symptom of fecal urgency is presented in Figure 4.4. Mean fecal urgency decreased in the inulin group, from 10% at baseline to 5.7% on the 10 g dose of inulin. Mean fecal urgency in the placebo group was 47.8% of days at baseline to 7.2% on the placebo.

Figure 4.4: Fecal Urgency- Comparison of Treatment Group Means

Error bars: +/- 1 SE
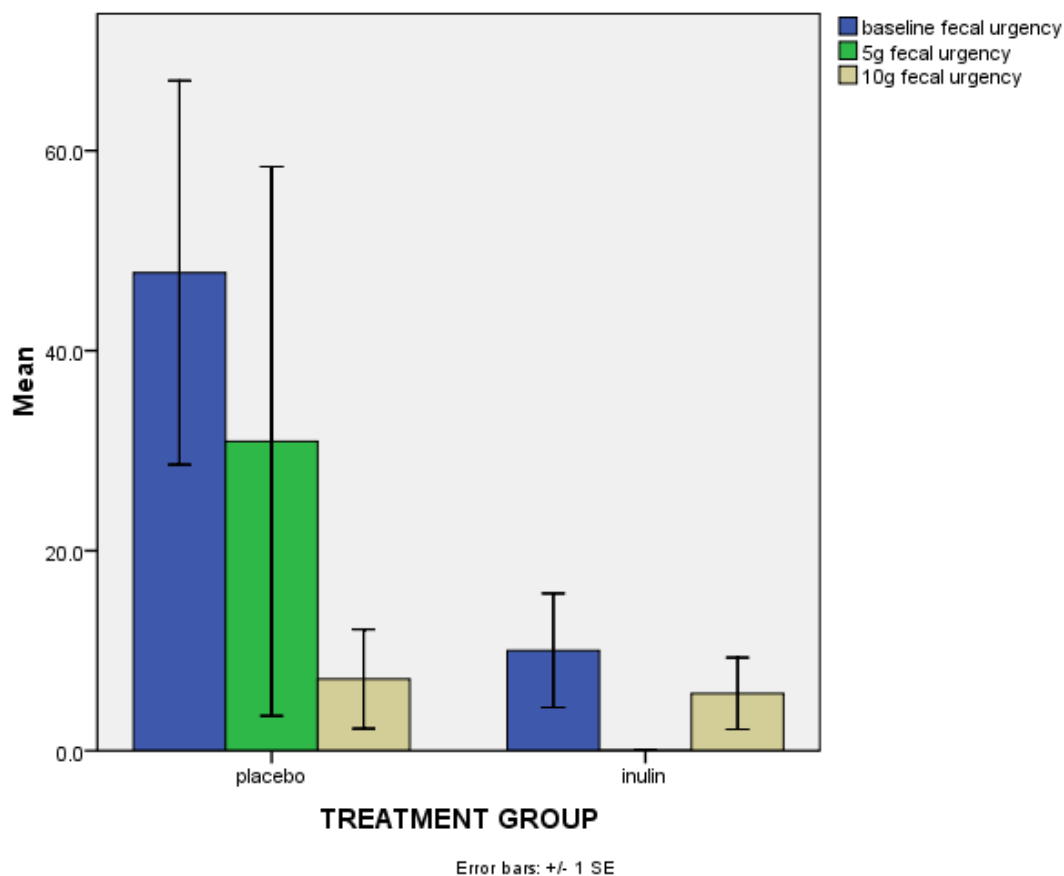
4.4.3 Abdominal Cramping and Pain

Figure 4.5 shows a comparison of group means for percent of days with the symptoms of abdominal cramping and pain. For the inulin group, there was a decrease from 19.3 % at baseline to 14.3% at 5 g, then an increase to 18.0% on the 10 g dose of inulin. For the placebo group, there was a decrease in symptoms, from 23.8% at baseline to 0% on 5 g to 1.2 % on 10 g.

Figure 4.5: Abdominal Pain & Cramping- Comparison of Treatment Group Means

Error bars: +/- 1 SE
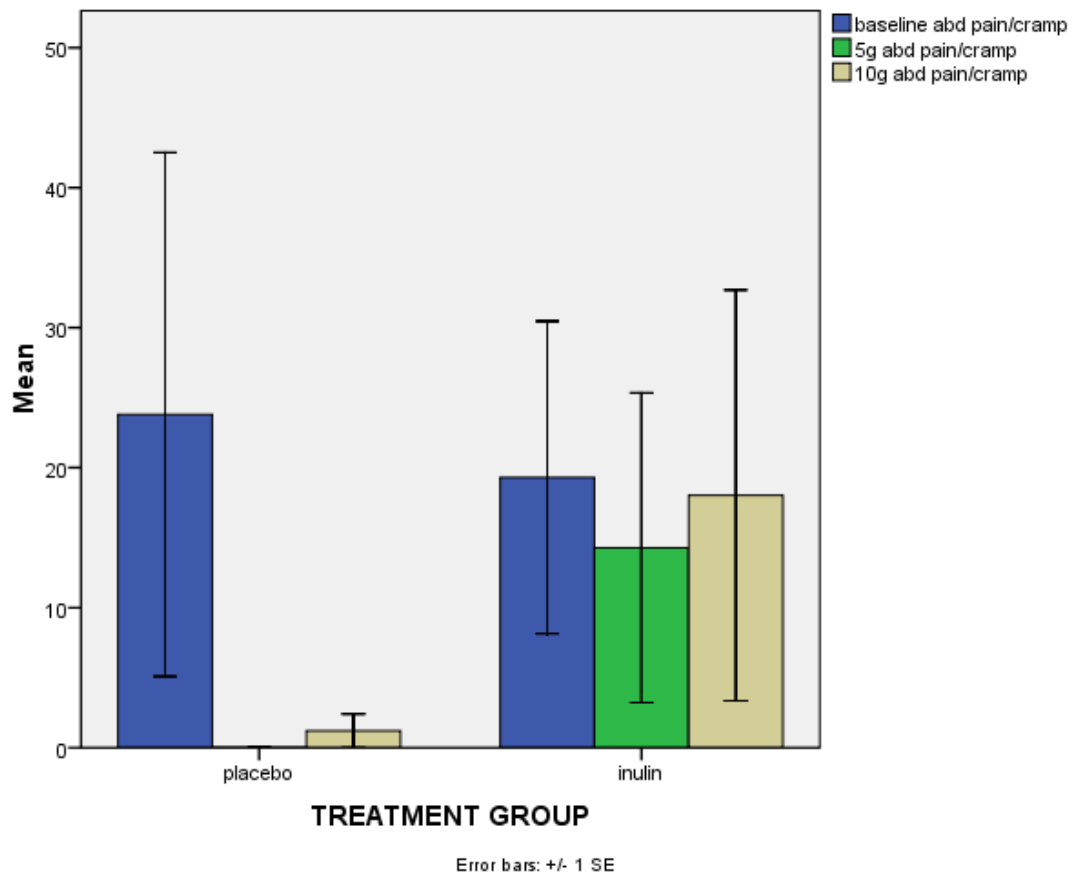
However, when the individual data is examined (Appendix 7.3), one participant (P-07) in the inulin group experienced an increase in abdominal cramping and pain upon treatment, increasing from 50% at baseline to 76.2% at the 10 g dose. Another participant in the inulin group (P-04) did not experience any abdominal pain or cramping at baseline, but reported an increase in abdominal cramping upon treatment (14.3 % at 5 g and 10.7 % at 10 g). This participant cited this abdominal cramping as a reason for dropping out of the study.

4.4.4 Diarrhea

The symptom of diarrhea is presented in Figure 4.6. There is a slight increase in percent of days with diarrhea for both the placebo and inulin groups when increasing from baseline to the 5 g dose.

Figure 4.6: Diarrhea- Comparison of Treatment Group Means
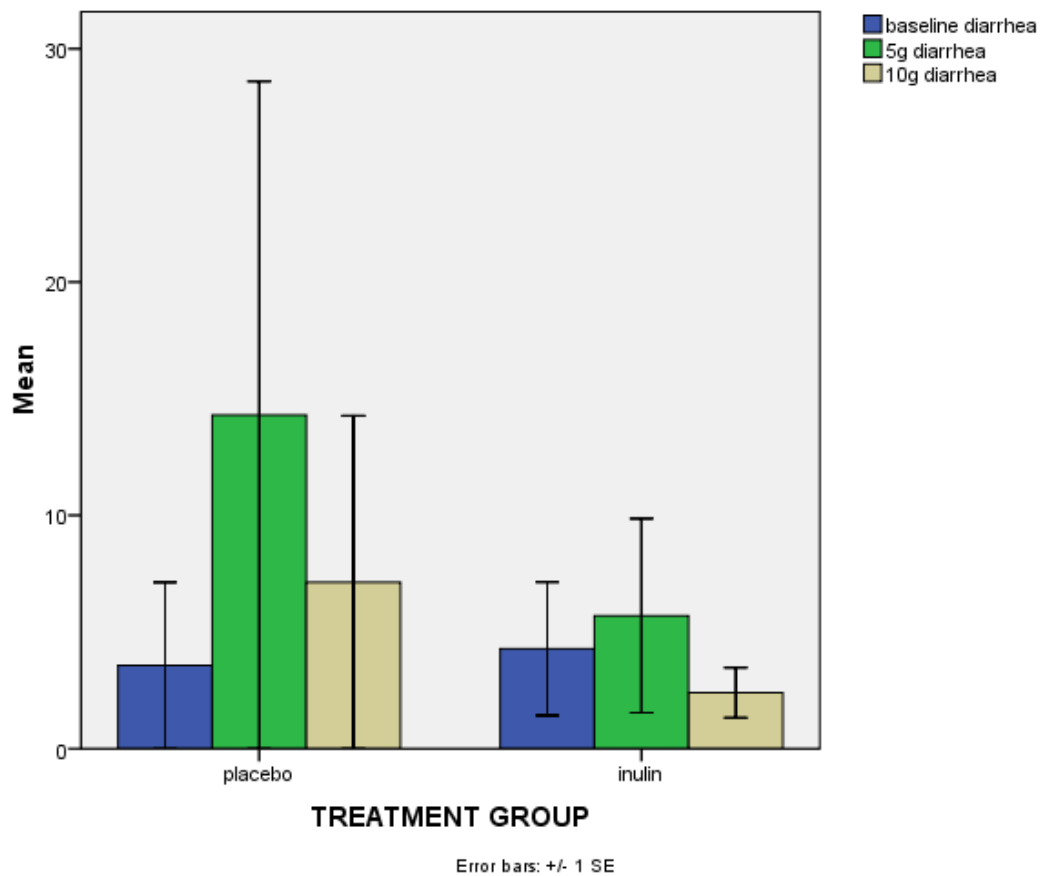
4.4.5 Gas

Figure 4.7 shows a comparison of treatment group means for the percent of days that participants experienced the symptom of gas. The increase in this symptom in the inulin group is from 0% at baseline to 15.2% on the 10 g dose.

Figure 4.7: Gas- Comparison of Treatment Group Means

Error bars: +/- 1 SE
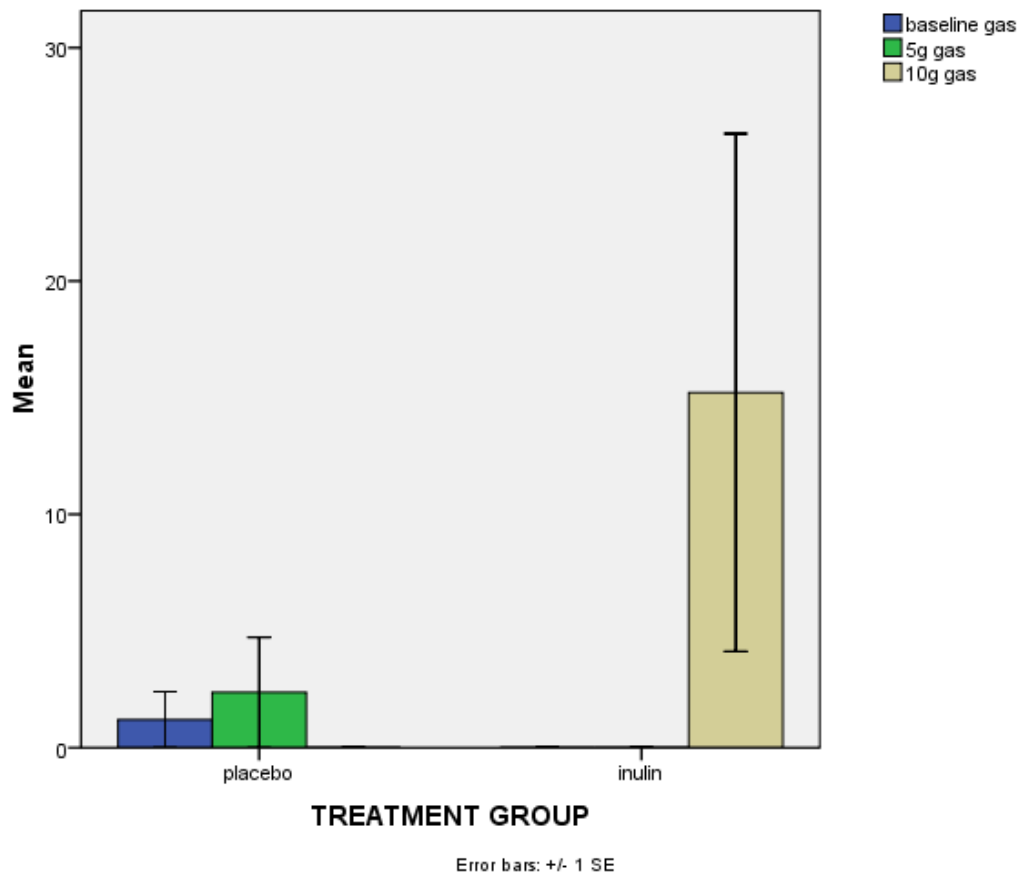
Two participants (P-01 and P-03) in the inulin group experienced gas at the 10 g dose (Appendix 7.5). P-01 felt that gas was so severe that this participant had to discontinue taking the treatment, despite halving the dose to 5 g. This participant dropped out of the study due to severe gas.

4.4.6 Other Symptoms Reported

One participant, (P-07) of the inulin group reported pain in the rectal area. This pain increased from 35.7% at baseline to 78.6% at the 5 g dose and 88.1 % at the 10 g dose. No participants in the placebo group reported pain in the rectal area. One participant in the placebo group reported one day with a fever on the 10 g dose. No other

participants in either group reported any fevers at any period. Another participant (P-06)

of the placebo group reported feeling tired and weak at the 5 g dose of inulin (64.3% of

the days). No other participants reported this symptom at any time in the study.

4.5 Bowel Movement Frequency

4.5.1 Bowel Movement Frequency Baseline Data

Bowel movement (BM) Frequency was examined for all nine participants. The

maximum, minimum, and mean were compared for each participant (Table 4.3) and a

range of 4 to 18 BMs per 24 hour period was established.

Table 4.3: Mean BM Frequency and Range for Each Participant at Baseline		
Group	Participant	Mean number of BM/day (Range)
Inulin	P-01	10.7 (9 – 12)
Inulin	P-07	11.3 (8-16)
Inulin	P-08	5.5 (4-8)
Inulin	P-03	7.3 (6-9)
Inulin	P-04	10.4 (9-12)
Placebo	P-05	7.3 (6-9)
Placebo	P-06	8.7 (7-13)
Placebo	P-02	10.5 (6-14)
Placebo	P-09	8.1 (4-18)

4.5.2 Bowel Movement Frequency Baseline Data vs. Treatment Periods

Figure 4.8 shows the treatment group mean comparisons of BM Frequency for

baseline, 5 g dose and 10 g dose. A mean of 9 BM per day was observed at baseline

compared to 8.6 BM per day at the 5 g dose of inulin and 8.9 BM per day at the 10 g

dose.

Figure 4.8: BM Frequency- Comparison of Treatment Group Means

Error bars: +/- 1 SE
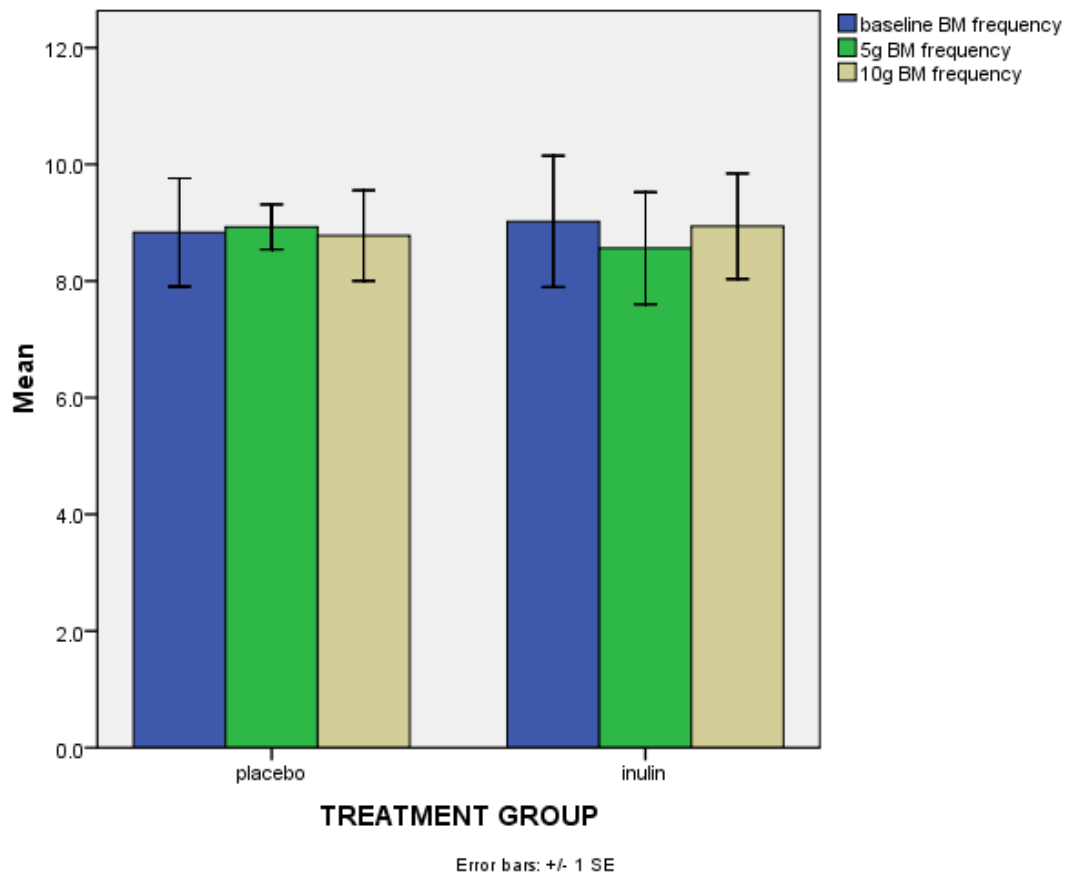
4.6 Subjective Overall Health Rating

Figure 4.9 shows a comparison of the mean scores for between the participants at baseline and treatment. No trends between the inulin group and the placebo group were noted. Figure 4.10 shows a comparison of the group mean scores.

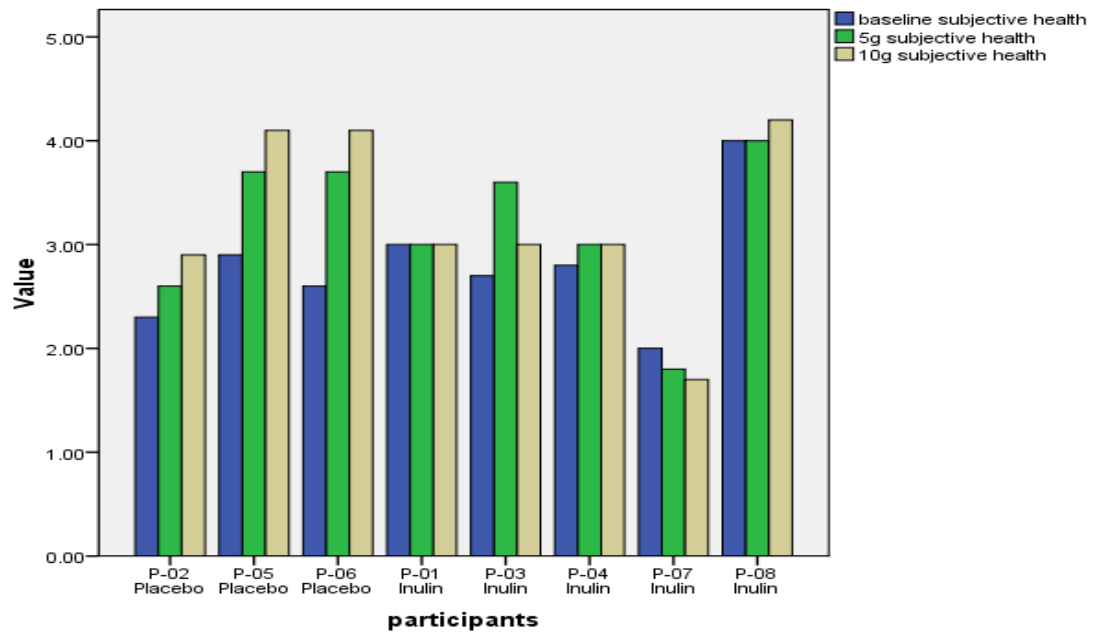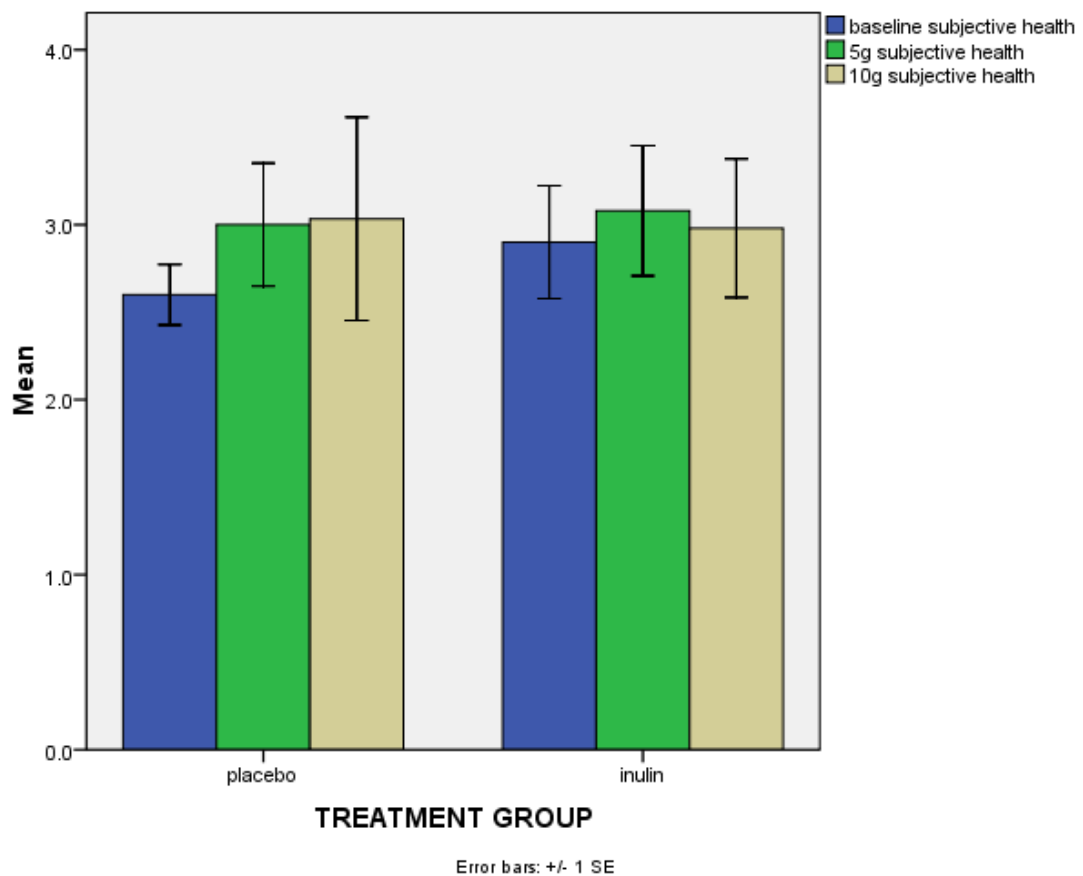**Figure 4.9: Subjective Overall Health- Comparison of Individual Participant Data**

Figure 4.10: Subjective Overall Health- Comparison of Treatment Group Means

4.7 SIBDQ Scores

4.7.1 Comparison of SIBDQ Scores at Baseline vs. Supplementation

A paired-t test was performed for each of the 10 questions in the SIBDQ, comparing baseline versus supplementation for the inulin group and the placebo group (Table 4.5). No statistical difference was found between the groups for any of the questions.

Table 4.4: Comparison of SIBDQ Scores for Inulin and Placebo Groups: Baseline vs. 5g dose Treatment

Question #	Measure	Category	Test Statistic (p)
1	Fatigue/Tiredness	Systemic	0.172
2	Delay/Cancel Social Engagement	Social	0.103
3	Difficulty Sport/Leisure	Social	0.673
4	Pain in Abdomen	Bowel	0.253
5	Depressed/Discouraged	Emotional	0.172
6	Large Amounts of Gas	Bowel	0.604
7	Problems Maintaining Weight	Systemic	0.436
8	Feeling Relaxed	Emotional	0.534
9	Feeling of Need to Use Toilet	Bowel	0.604
10	Feeling of Anger	Emotional	0.321

P-04 and P-09 did not provide SIBDQs during the 5 g supplementation period, and were therefore excluded from this analysis. The SIBDQ total score was significantly improved at supplementation compared to baseline for P-01 (p= 0.002) and P-03 (p= 0.034).

Table 4.5 SIBDQ Scores Compared at Baseline and 5 g Dose Treatment for Each Participant

Allocated Supplement	Participant	Difference in Total Score	p*
Inulin	P-01	17	0.002*
Inulin	P-03	14	0.034*
Inulin	P-07	3	0.434
Inulin	P-08	0	1
Inulin	P-04	N/A	N/A
Placebo	P-02	-5	0.138
Placebo	P-05	0	1
Placebo	P-06	2	0.343
Placebo	P-09	N/A	N/A

4.8 Incidents of Pouchitis

Two participants self-described incidents of pouchitis in their study diaries and reported that they were prescribed Metronidazole by their physicians for the treatment of this condition. Participant P-02 (placebo) was diagnosed with pouchitis once in the baseline period and three times on the 10 g dose treatment period. Participant P-03 (inulin) was diagnosed once with pouchitis during the 10 g dose treatment period, but not during the baseline or 5 g dose period.

4.9 Medications and Supplements

Appendix 4 describes the medications and supplements that participants took at baseline and throughout the treatment periods.

Participant P-01 (inulin) took a low dose of Metamucil (containing 3.4 g of psyllium/day) during baseline and treatment periods. Participant P-02 (placebo) and participants P-03, P-07, and P-08 of the inulin group all required Metronidazole at baseline and/or during treatment for incidents of pouchitis. Metronidazole is an

antibacterial agent against anaerobic bacteria (Canadian Pharmacists Association, 2005).

Participant P-03 (inulin) took many herbal supplements and probiotic supplements:

"Jade Windscreen" herbal formula for respiratory health, Acidophilus and Bifidus,

UNDA # 3, 37, 50 (Herbal Supplements), and Replete Probiotic Formula (130 billion

CFU of *L. acidophilus*, *B. bifidum*, *B. lactis*, and *L. salivarius*) and also took Lomotil

and Imodium. Participant P-04 of the inulin group consumed once weekly medications

for Rheumatoid Arthritis, including Methotextrate.

CHAPTER 5

DISCUSSION

5.1 A Discussion of the Results

This discussion provides a detailed response to the findings of the study in relation to the literature. The efficacy and safety of inulin supplementation in IPAA patients with chronic pouchitis and the impact on the quality of life is examined. Also, future directions for research are proposed.

5.1.1 Practicality and Safety of Inulin Supplementation

The first objective was to determine if inulin supplementation is a practical and safe nutritional recommendation for patients with chronic pouchitis. Based on the adverse effects reported, the subsequent drop-outs, and the low compliance observed in this study in participants taking the inulin versus those on placebo, at this point the author would not advise that inulin is a practical nutritional recommendation. These results are in sharp contrast to Welters et al., (2002); in which 20 participants received 24g/d of inulin, but no side effects were reported. They did report that one patient dropped out of the study due to lactose intolerance and that there were no other adverse effects. The authors did not describe how the lactose intolerance was diagnosed and differentiated from other causes of similar symptom patterns, so it may be possible that the symptoms of lactose intolerance as they report could actually be due to side effects of the inulin supplementation.

The participants of our study received a maximum dose of only 10 g/day, yet 2 of 5 participants on inulin experienced side effects severe enough that they were

required to discontinue supplementation and stop participation in the study. Thus it is surprising to see that Welters et al. (2002) did not report any side effects when they used more than twice the dose of inulin supplementation provided in our study. The recommended average nutrient intake level for fibre, the Adequate Intake (AI) for adults aged 19-50 is 25 g/day for females; 38 g/day for males (Health Canada, 2006). Thus the 24 g/d of supplemented fibre nearly fulfills the AI for fibre for women before any usual dietary fibre is even considered.

Gastrointestinal distress such as cramping, bloating, flatulence, and diarrhea has been observed in healthy individuals at intakes of inulin ranging from 14 to 18 g/d (Davidson & Maki, 1999; Pedersen, Sandstrom, & Amelsvoort, 1997). An ileal pouch is smaller than a colon and therefore, it would be expected that participants would have less capacity for flatulence and would experience pain sooner from smaller amounts of inulin. Since the participants in our study were already experiencing gastrointestinal discomfort due to problems with their IPAA, we tried to protect our participants from potential side effects of the additional fibre of the inulin supplementation by starting them on 5 g and then increasing the dose to 10 g after 2 weeks. Welters et al. (2002) did not slowly introduce the inulin and therefore we would expect to see gastrointestinal symptoms with the sudden ingestion of 24 g/d of supplemented fibre.

The adverse effect of cramping and gas experienced by one of the participants can be reasonably linked to the fermentation of inulin which could be expected to occur within the pouch. However, with regards to the adverse effect of bleeding experienced by one of the participants in this study, it is difficult to determine if inulin was specifically responsible for the symptoms since the researchers did not conduct physical, histological, or endoscopic examinations. It is possible that the rectal bleeding occurred

from peri-anal irritation due to wiping after frequent bowel movements, which may or may not have been exacerbated by inulin supplementation. The participant who experienced rectal bleeding also took once weekly medications for Rheumatoid Arthritis, including Methotextrate, a medication that could cause diarrhea and gastrointestinal ulceration/bleeding (Canadian Pharmacists Association, 2005). There is a possibility that the bleeding experienced by this patient could potentially be linked to the use of Methotextrate; however, the participant had been on these medications for a long period of time before the start of this study and had not previously experienced bleeding.

The allowance for participants to take other medications and supplements in this trial may also partially explain the adverse symptoms experienced by the other participant who dropped-out. Participant P-01 of the inulin group took a low dose of Metamucil (containing 3.4 g of psyllium/day) for years before the trial and continued during baseline and the treatment periods. The gastrointestinal effects of Metamucil include bloating, abdominal pain, flatulence, and diarrhea (Canadian Pharmacists Association, 2005). Nevertheless, the symptoms that this participant experienced could not be blamed solely on the Metamucil, as the participant had tolerated it for many years before taking the inulin. Psyllium, the main component of Metamucil, is resistant to fermentation by typical microflora and therefore it may have only contributed minimally to gas production (Marlett & Fisher, 2003).

In comparing the adverse effects that we report in our findings to those effects observed in the probiotic literature, there are some interesting similarities. Although most probiotic trials did not observe any adverse effects (Elahi et al., 2007), Mimura et al. (2004) reported that 1/20 of participants receiving VSL #3 dropped out of their study

due to abdominal cramps, vomiting, and diarrhea. Shen et al. (2005) reported that at the 8 month follow-up, (2/31; 6.5%) of patients had discontinued taking VSL #3 due to intolerable adverse effects; one patient developed bloody bowel movements immediately after starting the treatment, and one patient developed severe constipation, bloating, and gas. Neither Shen et al. nor Mimura et al. discuss these adverse effects, but it is interesting that bloody bowel movements occurred in both our prebiotic trial and two probiotic trials. Future research may wish to examine the heme content of stools during prebiotic and probiotic trials of IPAA patients.

5.1.2 The Effect of Inulin on Pouchitis and Problems of Fecal Frequency

The second objective was to determine if inulin supplementation affects the incidence of pouchitis and problems of fecal frequency in patients with IPAA. Based on the findings reported, we conclude that inulin appears to be ineffective in reducing the incidence of pouchitis and fecal frequency; although the trial did not have a large enough sample size to determine statistical significance.

In determining average fecal frequency in IPAA patients, Simchuk and Thirlby (2000) report an mean 24 hour frequency of 6.1 ± 0.2 for 114 patients and Shibata et al (2006) reported a mean 24 hour frequency of 7 (range 4-18) for 67 patients. Therefore the mean 24 h frequency range we found (4-18 per BM per day at baseline) is consistent with the averages found in the literature. Inulin supplementation did not appear to have an effect on fecal frequency in this study.

5.1.3 The Effect of Inulin on Quality of Life of Patients

The third objective was to determine if inulin supplementation affects the quality of life in people with IPAA. Unfortunately, no changes in group mean SIBDQ scores observed. However, the SIBDQ total score was significantly improved at supplementation compared to baseline for P-01 (p= 0.002) and P-03 (p= 0.034). This is an interesting observation, since P-01 dropped out of the study due to reported side effects.

Turina et al. (2006) reported significantly lower QOL in patients with chronic pouchitis (p< 0.01) than patients without pouchitis. However, despite suffering from chronic pouchitis, our participants in the inulin group started with high SIBDQ scores, thus a regression toward the mean might explain why we did not observe a change in group mean scores. In contrast to Turina et al. (2006), Stocchi and Pemberton (2001) followed-up on patients post-IPAA and reported that although pouchitis occurred in more than half of the patients reviewed, the mean patient satisfaction with the procedure was high, 8.4 (on a scale of 0 being dissatisfied and 10 being extremely satisfied). Lichtenstein et al. (2006) purport that the QOL of UC patients is so poor that most clinical studies have shown an increase in quality of life in patients after the IPAA procedure. Thus the high baseline SIBDQ scores observed in the inulin group could potentially be explained by previously poor QOL prior to the IPAA procedures.

5.2 A Comparison to the Current Literature

There are several differences between our study and the Welters et al. (2002) study. As previously mentioned, Welters et al. provided 24 g/d of inulin, versus the doses of 5 and 10 g/d of inulin our participants ingested in this study. No other

medications or supplements were reported as being taken by participants in the Welters et al. study. Welters et al. used the PDAI to diagnose pouchitis, whereas our study relied on a symptom diary to evaluate the presence of pouchitis.

Another difference between our study and the Welters et al. (2002) is the method of inulin delivery. The participants of our study were instructed to add inulin to a hot beverage in the morning and evening. Welters et al. study participants consumed inulin via a component of a commercially-available milk-based (and therefore lactose-containing) beverage that they drank twice daily. Interestingly, Kuisma et al. (2003) found an association between dietary lactose, fecal bacteria, and pouch morphology, and suggested that lactose may have prebiotic properties. They reported that lactose was inversely correlated with total aerobes ($r = -0.45$; $p = 0.019$). Thus, it is the possible that our results varied so greatly from the Welters et al. study because the inulin in our study was not paired with lactose. More research is required to determine if lactose, alone and in conjunction with inulin, has prebiotic properties in IPAA patients.

However, in contrast to the conclusions of the Welters et al. article (2002), in the Meijer et al. (2000) article (a different set of data published from the Welters et al. article), the authors concluded that inulin did *not* influence inflammation or have an effect on pouch mucosal functioning because neither epithelial gene expression nor epithelial homeostasis was significantly changed by inulin supplementation. Mucosal morphology, epithelial cell proliferation and cell death were not altered by inulin supplementation. The Meijer et al. results are more consistent with the lack of significant effects in our study.

5.3 Limitations

This trial was limited to subjective reporting of clinical signs in study diaries completed by participants. Participants' symptoms were not corroborated by histological or endoscopic examinations. Since the ultimate goal of this research is to improve quality of life of patients who suffer from chronic pouchitis, the researchers did not feel it was appropriate to perform invasive procedures such as pouchograms or biopsies to determine if inflammation of the pouch was present.

The population of patients suffering from pouchitis in Saskatoon is small (n= 93), which subsequently limited the sampling.

The dietary behaviors and lifestyle habits of the participants were not evaluated in this clinical trial, thus it is possible that these factors may have influenced gastrointestinal symptoms, such as fecal frequency. However, it was felt that a lengthy baseline and supplement period would provide sufficient data to account for minor dietary and lifestyle fluctuations. Any supplements and medications that a participant was taking at baseline were permitted and reported during the treatment period. Other supplements and medications could confound the findings and therefore, make it difficult to isolate the effects of inulin that could be attributed to this study. However, the first objective of this study was to determine if inulin supplementation is a practical and safe nutritional recommendation for patients with chronic pouchitis; it could be harmful and impractical if participants were required to stop taking their preventative medications and treatments for acute onsets of pouchitis. Therefore, participants were permitted to use supplements and medications throughout the study.

5.4 Future Research

This pilot study has pointed to the potential problems associated with inulin supplementation; however, our findings appear to conflict with the other reported studies. Specifically, larger randomized trials are needed. Future research should involve determining a dose and method of delivery of inulin that is acceptable and that produces significant bifidogenic effects in specifically in patients with IPAA. Further exploration of synbiotic therapy for pouchitis may be warranted, based on the many positive results of the probiotic trials in UC and IPAA. The Friedman and George (2002) study of *Lactobacillus GG* and FOS in IPAA patients was successful; however larger, randomized trials have not yet been conducted.

Allowance for other supplements and medications and not evaluating dietary and lifestyle habits made it difficult to isolate the effects of inulin in our study, therefore future studies would need to strictly regulate and control for confounding factors. Any future studies of prebiotics or synbiotics for inulin should use the Pouchitis Disease Activity Index (PDAI) to evaluate efficacy, as this index is very sensitive and specific in diagnosing pouchitis and was used by Welter et al. (2002). It is interesting that bloody bowel movements occurred in both our prebiotic trial and two probiotic trials. Future research may wish to examine the heme content of stools during prebiotic and probiotic trials of IPAA patients.

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APPENDICES

APPENDIX 1.1

CERTIFICATE OF APPROVAL

University of Saskatchewan
Biomedical Research Ethics Board (Bio-REB)

24-May-2006

Certificate of Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Wendy J. Dahl	Pharmacy	06-65

INSTITUTION (S) WHERE RESEARCH WILL BE CARRIED OUT

Royal University Hospital

103 Hospital Drive

Saskatoon SK S7N 0W8

SUB-INVESTIGATOR(S)

S. Chandra-Kanthan

Natasha Haskey

Nadia Rodych

SPONSORING AGENCIES

ROYAL UNIVERSITY HOSPITAL FOUNDATION

TITLE:

The Effect of Inulin Supplementation on Relapse Rates and Quality of Life in Patients with Pouchitis

ORIGINAL APPROVAL DATE	CURRENT EXPIRY DATE	APPROVAL OF
24-May-2006	01-May-2007	Revised Researcher's Summary Form Participant Information and Consent Form, Version 2 (inclusive of Appendix I: The Short Inflammatory Bowel Disease Questionnaire)(16-May-2006)

CERTIFICATION

The University of Saskatchewan Biomedical Research Ethics Board has reviewed the above-named research project at a full-board meeting (any research classified as minimal risk is reviewed through the expedited review process). The proposal was found to be acceptable on ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research project, and for ensuring that the authorized research is carried out according to governing law. This Approval is valid for the above time period provided there is no change in experimental protocol or in the consent process.

ONGOING REVIEW REQUIREMENTS/REB ATTESTATION

In order to receive annual renewal, a status report must be submitted to the Chair for Committee consideration within one month of the current expiry date each year the study remains open, and upon study completion. Please refer to the following website for further instructions: http://www.usask.ca/research/ethics.shtml. In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. This approval and the views of this REB have been documented in writing.

APPROVED.

Michel Desautels, Ph.D., Chair

University of Saskatchewan

Biomedical Research Ethics Board

Please send all correspondence to:

Ethics Office
University of Saskatchewan
Room 305 Kirk Hall, 117 Science Place
Saskatoon, SK S7N 5C8
Phone: (306) 966-4053   Fax: (306) 966-2069

APPENDIX 1.2

NOTICE OF ETHICAL REVIEW

University of Saskatchewan
Biomedical Research Ethics Board (Bio-REB)

19-Apr-2006

Notice of Ethical Review

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Wendy J. Dahl	Pharmacy and Nutrition	06-65

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
Royal University Hospital
103 Hospital Drive
Saskatoon SK S7N 0W8

SUB-INVESTIGATOR(S)
S. C. Kanthan, Nadia Rodych

SPONSORING AGENCIES
ROYAL UNIVERSITY HOSPITAL FOUNDATION

TITLE
The Effect of Inulin Supplementation on Relapse Rates and Quality of Life in Patients with Pouchitis

Thank you for submitting the above protocol to the Biomedical Research Ethics Board for review. The REB has reviewed the protocol for your proposed study, and has withheld issuing a Certificate of Approval until the following conditions have been satisfied or information provided:

(Please highlight or underline changes made to the consent form when resubmitting)

This protocol describes studies in patients who have undergone colon surgery and resection of the colon. The study will examine the utility in supplementing the diet of such patients with Inulin (Fruitafit®) a preblotic on quality of life and relapse rates related to pouchitis.

The study is acceptable on ethical ground. The consent form is poorly drafted and requires revisions.

Researcher's Summary Form
1. Page 3 of 4, last line under "Procedures": Is something missing between "SIBDQ" and "every two months" (e.g. "will be done every two months...")?
2. Page 3 of 4, under "Subjects", (a) it is indicated that patients "subsequently" diagnosed with Crohn's disease will be excluded. Subsequent to what? In (b), who will approach the subjects for recruitment into the study?
3. Page 4 of 4, under "Data Storage": Please confirm that the data will be stored for 5 years, as per University of Saskatchewan regulations.

Consent Form

1. Page 1 of 2: The contact information for the Principal Investigator is required on page 1 of the consent, inclusive of his/her affiliation and address. The name(s) and affiliation(s) of the sub-investigator(s) and/or student researcher(s) should also be listed on the first page, as should the name of the study sponsor.

2. Page 1 of 2: The paragraph beginning with "You are being invited" should be titled "Introduction" and needs to be written in lay language.

3. Page 1 of 2, 3rd paragraph: In layman's terms, please provide an accessible definition of "pouchitis" and of "prebiotic".

4. Page 1 of 2: Prior to the "Procedures" section, there should be a section titled "Description of the Research." In that section, there should be an explanation of the rationale and research hypothesis for this study. The random placement into one of two groups (control or placebo) should be clearly explained to study subjects. This should also help clarify #1 under "Procedures."

5. Page 1 of 2, under "Procedures": For those subjects selected into the control group an alternate or rescue medication should be described or detailed so that should they suffer a relapse they will know what medical care is available. Study subjects should also be informed what other alternate medications or treatments might be available for their condition. These medications/treatments should be listed under the heading "Alternative Treatments."

Please send all correspondence to:

Ethics Office
University of Saskatchewan
Room 305 Kirk Hall, 117 Science Place
Saskatoon SK S7N 5C8
Telephone: (306) 966-4053   Fax: (306) 966-2069

PRINCIPAL INVESTIGATOR   DEPARTMENT   Bio #
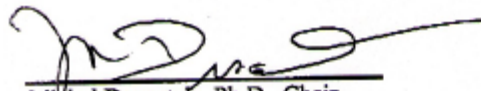
Wendy J. Dahl   Pharmacy and Nutrition   06-65

6. Page 1 of 2, #1, it should be indicated that the blind may be broken in an emergency.

7. Page 1 of 2, #5 under "Procedures": Are the questions provided? Please confirm and provide the questions to the REB, if applicable.

8. Page 1 of 2, #6 under "Procedures": This paragraph needs to be more fully developed, and in layman's language. First, how would the patient know if he/she had pouchitis? Please provide a description of the symptoms the research subject may experience if developing pouchitis. What is the research subject to do in the event he/she is unable to reach Dr. Kanthan? The second sentence should begin "With your consent, he may carry out...". In the last line, will the results of the tests not made available to the research subject as well?

9. Page 1 of 2, #7 under "Procedures": Please explain why subjects' medical charts will be reviewed six months into and at the end of the study and what information is to be obtained from the charts.

10. Page 2 of 2, under "Research Related Injury": At the end of the paragraph, please add the statement "By signing this document you do not waive any of your legal rights."

11. Page 2 of 2, under "Contacts": Who are these four contacts? Please provide the requisite information.

Suggested Formatting, Typographical and Grammatical Corrections

1. Page 1 of 2: The paragraph beginning with "Participation in this study is voluntary" should be titled "Voluntary Participation."
2. In a header/footer, please provide the proper date and version number of the consent form. Also, the REB asks that you number the pages as "Page 1 of 3, Page 2 of 3," etc.

If you have any questions regarding these requirements, please call:

Michel Desauteis, Ph.D., Chair

University of Saskatchewan

Biomedical Research Ethics Board

Please send all correspondence to: Ethics Office
University of Saskatchewan
Room 305 Kirk Hall, 117 Science Place
Saskatoon SK S7N 5C8
Telephone: (306) 966-4053   Fax: (306) 966-2069

TOTAL P.02

APPENDIX 1.3
SASKATOON HEALTH REGION APPROVAL

Saskatoon Health Region

Research Services Unit
Strategic Health Information & Planning Services (SHIPS)
Joanne Franko, Manager
Suite 300 Saskatoon Square
410 22nd St E
Saskatoon, SK   S7K 5T6
Phone: 306.655.3356 Fax: 306.655.3373

DATE: July 27, 2006

TO: Dr. Wendy Dahl, Food & Nutrition Services, RUH

FROM: Joanne Franko
               Manager, Research Services Unit
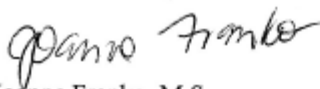
RE: **RESEARCH PROJECT ETHICS COMMITTEE (EC)#: 2006-65**
               PROJECT NAME: The Effect of Inulin Supplementation on Relapse Rates and
               Disease Activity Index Scores in Patients with Pouchitis
               PROTOCOL #: N/A

Saskatoon Health Region is pleased to provide you with operational approval of the above-mentioned research project.

Please advise me when the data collection phase of the research project is completed. I would also appreciate receiving a summary of the results for this research project. As well, any publications or presentations that result from this research should include a statement acknowledging the assistance of Saskatoon Health Region.

I would like to wish you every success with your project. If you have any questions, please contact our office at 655-3351.

Yours truly,

Joanne Franko, M.Sc.
Manager, Research Services Unit

cc: Chris Arnold, Professional Leader, Food & Nutrition, SPH
      Yvette Lyster, Manager, Health Records, RUH
      Laura Wiwchar, Health Records, RUH

APPENDIX 2

PARTICIPANT INFORMATION AND CONSENT FORM

Study Title: The Effect of Inulin Supplementation on Relapse Rates and Quality of Life in Patients with Pouchitis.

Principal Investigator for this study:

Wendy Dahl RD PhD Adjunct Professor
College of Pharmacy and Nutrition, University of Saskatchewan.
Ph: 655 1310 Fax: 966 6377
Email: wendy.dahl@saskatoonhealthregion.ca

Sub-investigators:

Dr. S. C. Kanthan FRCSC, FRCS, Associate Professor, General and Colorectal Surgery, Royal University Hospital
Lindsay Hauser, Graduate Student, College of Pharmacy and Nutrition, University of Saskatchewan
Natasha Haskey, Pediatric Dietitian, Royal University Hospital
Nadia Rodych, Nutritional Support Services Dietitian, Royal University Hospital

Study Sponsor: Royal University Hospital Foundation

Introduction: You are invited to participate in this research study because you have a surgically-created pouch, following the removal of your large intestine. Participation in this study may help to determine if inulin, a fibre ingredient, improves pouch health and reduces infections of the pouch (known as pouchitis). Inulin is known as a prebiotic, a food ingredient that increases the number of good bacteria in the gut.

Voluntary Participation: Participation in this study is voluntary and you have the right to refuse participation or withdraw from the study at anytime. If you do not wish to participate, you do not have to provide any reason for your decision, nor will you lose the benefit of any care to which you are entitled or are presently receiving.

Purpose of the Study: The purpose of this study is to determine if consuming inulin, a fibre ingredient, will decrease pouch infections and improve quality of life in patients with pouches.

Benefits: There may not be direct benefits to you for participating in this study. Knowledge gained from this study may help to improve care for people living with a pouch.

Description of the Research: This study may help us to determine if consuming inulin will reduce pouch infections and improve quality of life for people with pouches. Consuming inulin may increase the numbers of good bacteria in the pouch and result in improved pouch health. We will be enrolling up to 60 people with pouches into this study. Participants will be placed into one of two groups at random (determined with a randomization table) -- each participant will take a supplement for six months.

The treatment group will receive the inulin supplement and the control group will receive a maltodextrin (sugar) supplement. It is expected that those participants consuming the inulin will have improved pouch health while those consuming the maltodextrin will have no change in pouch health. Neither the researchers nor the participants will know what group the participants are placed into until the end of the study.

Participants will be asked to record when they take the supplement and any pouch problems that they may have in a study diary that will be provided. Participants will be interviewed about their pouch health

and their quality of life by a graduate student four times, once at the beginning of the study and every second month for 6 months.

Procedures: If you choose to participate in this study:

1. You will be randomly placed into either the control group or the treatment group and receive a supplement. You will not know which group you were placed or which supplement you were given until the end of the study.

2. You will be given a two-month supply of either inulin (a fibre) or maltodextrin (a sugar), provided in daily 10 gram plastic packages.

3. You will be asked to consume the contents of one package of inulin or maltodextrin each day for 6 months. At the beginning of the study, the graduate student will teach you how to mix the inulin or maltodextrin into your usual beverages and food.

4. You will be given a study diary to record your intake of the inulin or maltodextrin and to record pouch symptoms.

5. You will be interviewed by the graduate student four times, once at the beginning of the study and every second month for 6 months. You will be asked questions about symptoms and quality of life (see Short Inflammatory Bowel Disease Questionnaire attached).

6. If you do develop any symptoms of pouchitis such as abdominal pain, diarrhea, urgency, rectal bleeding or fever, please contact Dr. Kanthan's office – 966-8174. Dr. Kanthan (or other physician) will provide you with the standard medical treatment for pouchitis such as antibiotics. With your consent, he may carry out endoscopic (visual observation of the pouch using a scope) and/or histologic (lab) tests. The results of these tests will be made available to you and the researchers. If emergency medical problems arise that require Dr. Kanthan (or other physician) to know which supplement you are taking, he or she will be informed. If you are unable to reach Dr. Kanthan, please contact your family physician or go directly to emergency depending on the degree of your symptoms.

7. Your medical chart (at Royal University Hospital only) will be reviewed at the end of the study to assess any relevant medical information, symptoms or treatments not accounted for in your self-report study diaries.

Confidentiality: While absolute confidentiality cannot be guaranteed, every effort will be made to ensure that the information you provide for this study is kept entirely confidential. Your name will not be attached to any information, nor mentioned in any study report, nor be made available to anyone except the research team. It is possible that the research team may wish to present results from this study in scientific journals or at related conferences and workshops, but your identity will not be revealed.

Voluntary Participation: Your participation in this study is entirely voluntary. You have the right to refuse participation and to withdraw from the study at any time, for any reason. Early withdrawal from the study will not result in any sort of penalty.

Potential Risks: There are no known risks associated with study. Some individuals may experience increased gas production and increased stool frequency. As with any intervention, there may be unforeseen risks.

Research Related Injury: There will be no costs to you for your participation in this study. You will not be charged for any research procedures. In the event that you become ill or injured as a

result of participating in this study, necessary medical treatment will be made available at no cost to you. By signing this document, you do not waive any of your legal rights.

Compensation: There will be no compensation for participation in this study.

Contacts: If you have any questions, please contact:

Wendy Dahl RD PhD Adjunct Professor
College of Pharmacy and Nutrition, University of Saskatchewan.
Ph: 655 1310 Fax: 966 6377
Email: wendy.dahl@saskatoonhealthregion.ca

In addition, you may contact the following sub-investigators:

Dr. S.C. Kanthan, Surgeon, Royal University Hospital. Ph: 966-8174

Natasha Haskey, Dietitian, Royal University Hospital. Ph: 655-6512

Lindsay Hauser, Graduate Student, College of Pharmacy and Nutrition, University of Saskatchewan.
Ph: 978-4250 or 221-7853. Email: lindsay.hauser@usask.ca

This study has been approved, on ethical grounds, by the Biomedical Research Ethics Board (Bio-REB) of the University of Saskatchewan. If you have any questions about your rights as a research subject, you may contact the chair of the Biomedical Ethics Board, c/o the Office of Research Services, University of Saskatchewan at (306) 966-4053.

The contents of this consent form have been explained to me. I have been able to ask questions about the study and these questions have been answered to my satisfaction. I have received a copy of the consent form for my own records. I freely consent to participate in this study. By signing this document, I am not waiving any of my legal rights by signing this consent form.

SIGNATURES

Study Volunteer: _____Date: _____

Please clearly print your name here: _____

Research Coordinator: _____ Date: _____

UNIVERSITY OF SASKATCHEWAN

S.C. Kanthan, FRCSC, FRCS, Associate Professor
General and Colorectal Surgery

Royal University Hospital
103 Hospital Drive
Saskatoon SK S7N 0W8
Telephone: (306) 966-8174
Facsimile: (306) 966-8102

February 1, 2007

Dear _____,

I would like to invite my patients who have had a surgically-created pouch to participate in a study of inulin supplementation. Inulin is a fibre found in certain foods that increases good bacteria in the gut. It is our hope that inulin supplementation will reduce infections of the pouch (a condition called pouchitis).

The study will be coordinated by Ms. Lindsay Hauser, a dietitian and graduate student at the University of Saskatchewan. Starting on November 20, 2006, Ms. Hauser will be contacting you by phone to invite you to participate in this research project. If you decide to take part in the study, she will set up a convenient time for you to review the consent form and ask any questions you may have. Participation in this study is voluntary. You have the right to refuse participation and you may withdraw from the study at anytime. If you do not wish to participate, you do not have to provide any reason for your decision, nor will you lose the benefit of any care to which you are entitled or are presently receiving. Your participation in this study is strictly confidential. If you are concerned about Ms. Hauser calling your home, please contact her directly within one week of your receiving this letter at 978-4250 or 221-7853.

We will be enrolling up to 60 people into the study. As a participant, you will be placed into one of two groups at random. One group will receive the inulin supplement and the other group will receive a maltodextrin (sugar) supplement for a one year period. Neither the researchers nor the participants will know in which group they are placed in until the end of the study. You will be asked to record when you take the supplement and any pouch problems that you might experience over the course of the study period. Ms. Hauser will contact you by phone six times throughout the study to ask you about bowel health and problems that you may be having, once at the beginning of the study and every second month for 12 months.

I have included a copy of the study consent form for you to review. Should you have any questions or concerns, please feel free to contact Ms. Hauser at 978-4250 or cell: 221-7853. You may also contact her supervisor, Dr. Wendy Dahl, Adjunct Professor of the College of Pharmacy & Nutrition, at 655-1310.

Ms. Hauser looks forward to speaking with you and we hope you will consider participating in this project. Your involvement would be appreciated.

Sincerely,

S. C. Kanthan, M.D., FRCSC, FRCS
Associate Professor
General and Colorectal Surgery

SYMPTOM DIARY POUCHITIS STUDY

Month _____ (date)	Did you take the powder?	How would you rate your overall health today?	How many bowel movements did you have today?	Please check the boxes if you experienced these symptoms today. You may write any additional comments on the back of this page.
Monday _____ **(date)**	❑ Yes ❑ No	❑ Excellent ❑ Very Good ❑ Good ❑ Fair ❑ Poor		❑ Blood in feces ❑ Urgency of bowel movements ❑ Abdominal cramps ❑ Fever (oral temp > 37.5 º C) ❑ Other_____
Tuesday _____ **(date)**	❑ Yes ❑ No	❑ Excellent ❑ Very Good ❑ Good ❑ Fair ❑ Poor		❑ Blood in feces ❑ Urgency of bowel movements ❑ Abdominal cramps ❑ Fever (oral temp > 37.5 º C) ❑ Other_____
Wednesday _____ **(date)**	❑ Yes ❑ No	❑ Excellent ❑ Very Good ❑ Good ❑ Fair ❑ Poor		❑ Blood in feces ❑ Urgency of bowel movements ❑ Abdominal cramps ❑ Fever (oral temp > 37.5 º C) ❑ Other_____
Thursday _____ **(date)**	❑ Yes ❑ No	❑ Excellent ❑ Very Good ❑ Good ❑ Fair ❑ Poor		❑ Blood in feces ❑ Urgency of bowel movements ❑ Abdominal cramps ❑ Fever (oral temp > 37.5 º C) ❑ Other_____
Friday _____ **(date)**	❑ Yes ❑ No	❑ Excellent ❑ Very Good ❑ Good ❑ Fair ❑ Poor		❑ Blood in feces ❑ Urgency of bowel movements ❑ Abdominal cramps ❑ Fever (oral temp > 37.5 º C) ❑ Other_____
Saturday _____ **(date)**	❑ Yes ❑ No	❑ Excellent ❑ Very Good ❑ Good ❑ Fair ❑ Poor		❑ Blood in feces ❑ Urgency of bowel movements ❑ Abdominal cramps ❑ Fever (oral temp > 37.5 º C) ❑ Other_____
Sunday _____ **(date)**	❑ Yes ❑ No	❑ Excellent ❑ Very Good ❑ Good ❑ Fair ❑ Poor		❑ Blood in feces ❑ Urgency of bowel movements ❑ Abdominal cramps ❑ Fever (oral temp > 37.5 º C) ❑ Other_____

APPENDIX 5:
THE SHORT INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you are having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one option from the following:

☐All of the time

☐Most of the time

☐A good bit of the time

☐Some of the time

☐A little of the time

☐Hardly any of the time

☐None of the time

2. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem?

☐All of the time

☐Most of the time

☐A good bit of the time

☐Some of the time

☐A little of the time

☐Hardly any of the time

☐None of the time

3. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done over the last 2 weeks?

☐A great deal of difficulty, activities made impossible

☐A lot of difficulty

☐A fair bit of difficulty

☐Some difficulty

☐A little difficulty

☐Hardly any difficulty

☐No difficulty; the bowel problems did not limit sports or leisure activities

4. How often during the last 2 weeks have you been troubled by pain in the abdomen?

☐All of the time

☐Most of the time

☐A good bit of the time

☐Some of the time

☐A little of the time

☐Hardly any of the time

☐None of the time

5. How often during the last 2 weeks have you felt depressed or discouraged?

☐All of the time

☐Most of the time

☐A good bit of the time

☐Some of the time

☐A little of the time

☐Hardly any of the time

☐None of the time

6. Overall, in the last 2 weeks, how much of a problem have you had passing large amounts of gas?

☐A major problem

☐A big problem

☐A significant problem

☐Some trouble

☐A little trouble

☐Hardly any trouble

☐No trouble

7. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be?

☐A major problem

☐A big problem

☐A significant problem

☐Some trouble

☐A little trouble

☐Hardly any trouble

☐No trouble

8. How often during the last 2 weeks have you felt relaxed and free of tension?

☐None of the time

☐A little of the time

☐Some of the time

☐A good bit of the time

☐Most of the time

☐Almost all of the time

☐All of the time

9. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the toilet even though your bowels were empty?

☐All of the time

☐Most of the time

☐A good bit of the time

☐Some of the time

☐A little of the time

☐Hardly any of the time

☐None of the time

10. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem?

☐All of the time

☐Most of the time

☐A good bit of the time

☐Some of the time

☐A little of the time

☐Hardly any of the time

☐None of the time

Participant	P-02	P-05	P-06	P-09	P-01	P-03	P-04	P-07	P-08
Assigned Treatment	Placebo	Placebo	Placebo	Placebo	Inulin	Inulin	Inulin	Inulin	Inulin
Baseline 4 weeks No Treatment									
Low Dose 5 g 2 weeks				DO-3					
High Dose 10g 6 weeks					DO-1		DO-2	C	C
High Dose 10 g 8 weeks	C	C	C			C			
High Dose 10 g 8 weeks									

Legend:

⬛➤ = Placebo Treatment Period

▭▷ = Inulin Treatment Period

DO-1= Participant dropped-out of study because he was experiencing very uncomfortable gas.

DO2= Participant dropped out of study because she was experiencing bleeding and cramping

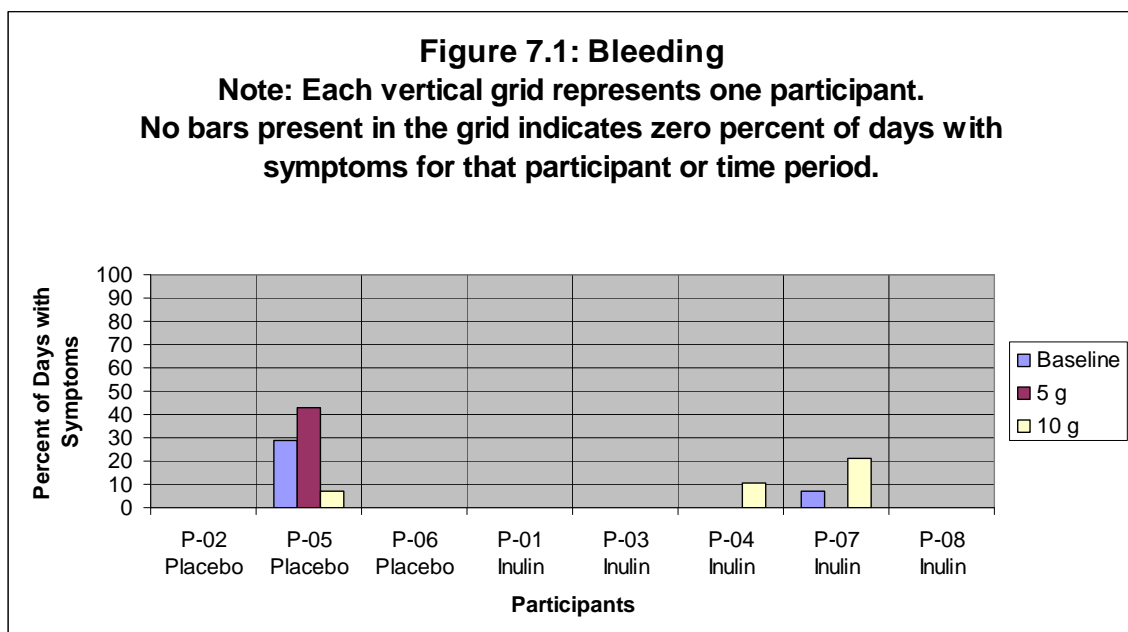**DO-3**= Participant dropped-out of study because he was diagnosed with Crohn's disease

C= Early cessation of the study

APPENDIX 7:

DETAILED INDIVIDUAL SYMPTOM DATA AND ANALYSIS
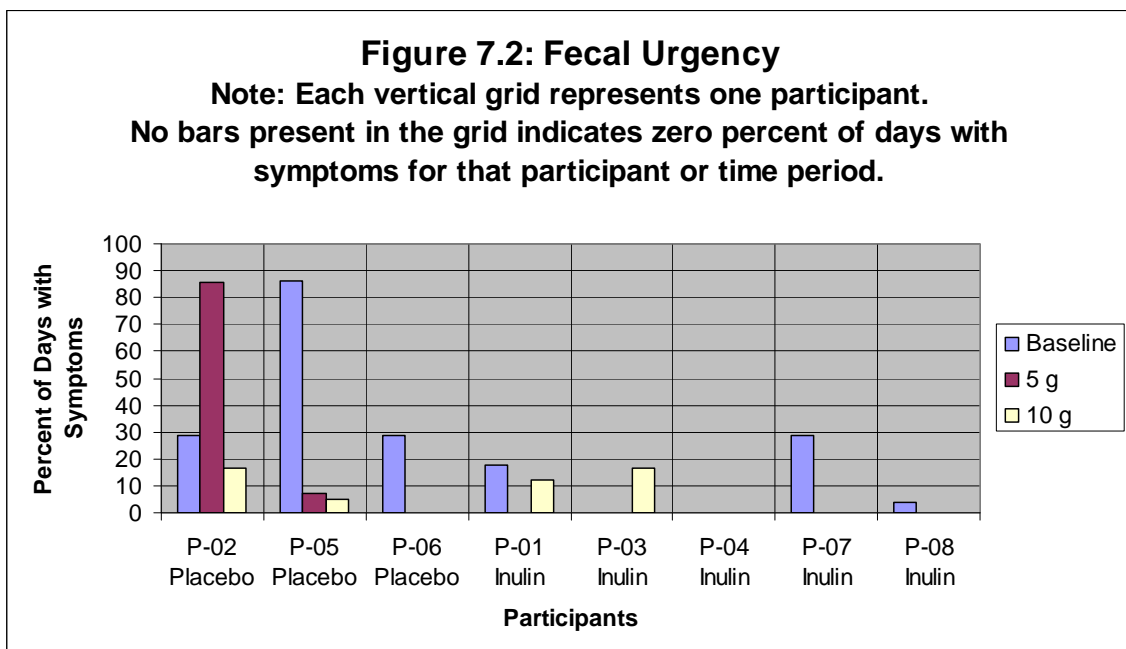
Appendix 7.1 Bleeding

As depicted in Figure 7.1, the symptom of blood in feces and blood upon wiping occurred in 3 of 9 participants. One participant in the placebo group (P-05) had this symptom at baseline, and the bleeding increased at 5 g dose and decreased at 10 g dose. Two participants in the inulin group (P-07 and P-04) experienced this symptom as well. P-04 did not experience bleeding at baseline or at the 5 g dose, but experienced bleeding at the 10 g dose and subsequently dropped out of the study. P-07 had bleeding at baseline, decreased bleeding at 5 g dose, and increased bleeding at 10 g dose.

Figure 7.1: Bleeding
Note: Each vertical grid represents one participant.
No bars present in the grid indicates zero percent of days with symptoms for that participant or time period.
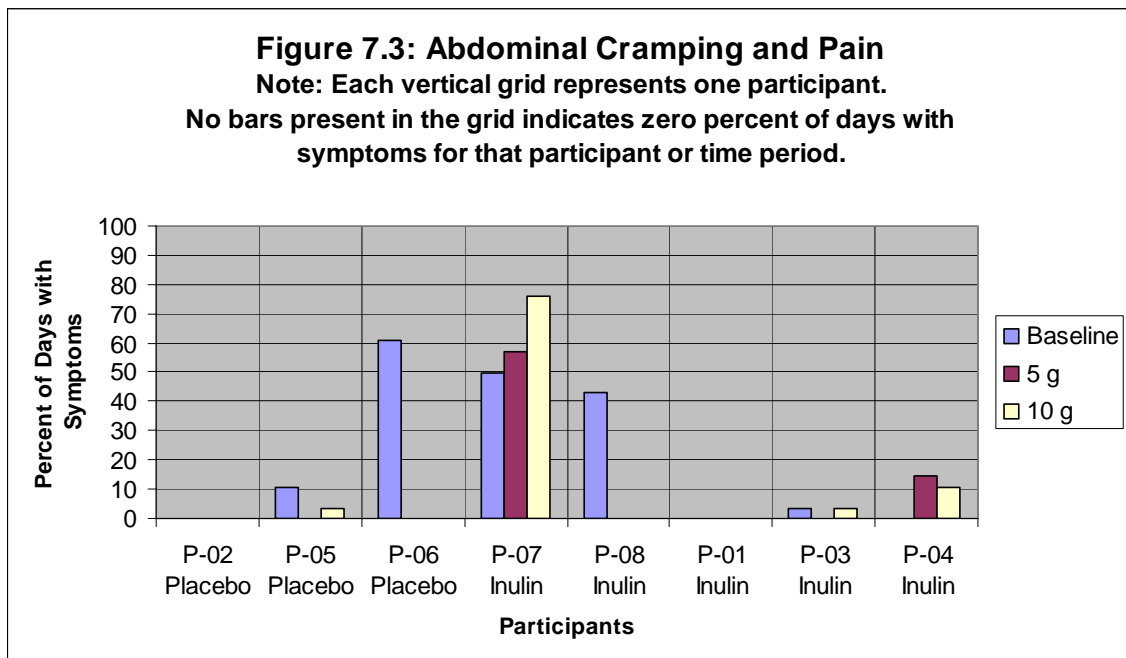
Appendix 7.2 Fecal Urgency

The symptom of fecal urgency is examined in Figure 7.2. Participant P-05 of the placebo group experienced fecal urgency 82.6% of days at baseline, dropping dramatically to 7.1 % at the 5 g dose of the placebo. Participant P-02 of the placebo group experienced fecal urgency 28.6 % of days at baseline, increased dramatically at the 5g dose to 85.7 %, then dropped to 16.7 % at the 10 g dose.

Two participants in the inulin group experienced fecal urgency at baseline, and experienced no symptoms at the 5 g dose. However, upon increasing to the 10 g dose, the symptom of urgency returned.
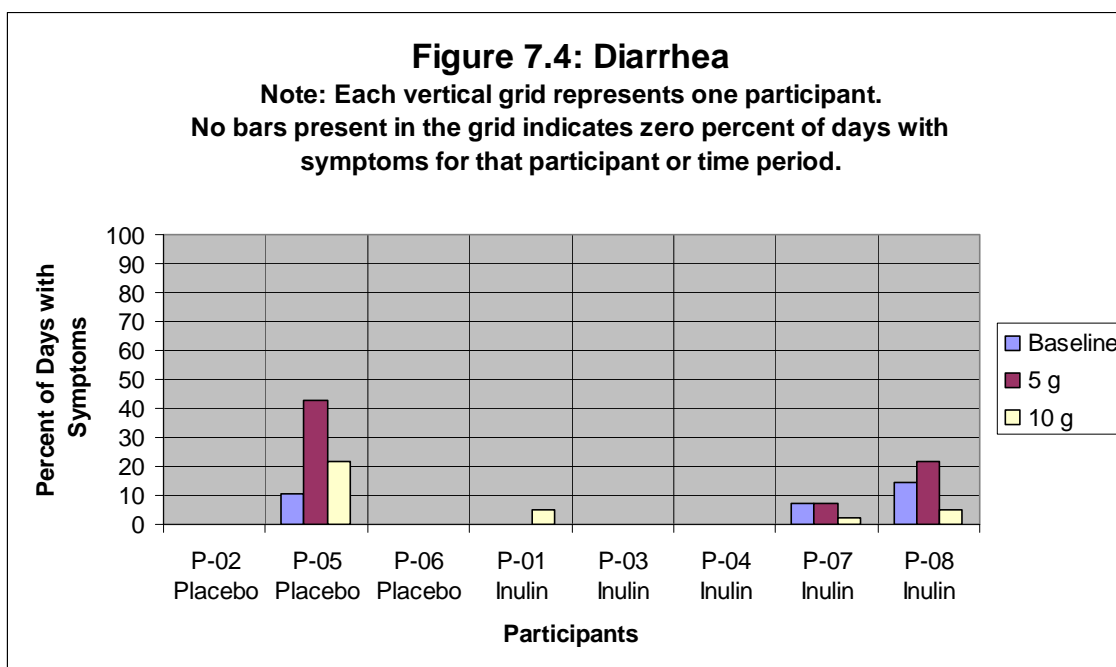

Figure 7.2: Fecal Urgency
Note: Each vertical grid represents one participant.
No bars present in the grid indicates zero percent of days with symptoms for that participant or time period.

Appendix 7.3 Abdominal Cramping & Pain

Figure 7.3 shows how one participant (P-07) in the inulin group experienced an increase in abdominal cramping and pain upon supplementation, increasing from 50% at baseline to 76.2% at the 10 g dose. Another participant in the inulin group (P-04) did not experience any abdominal pain or cramping at baseline, but reported an increase in abdominal cramping upon supplementation (14.3 % at 5 g and 10.7 % at 10 g). This participant cited this abdominal cramping as a reason for dropping out of the study. Participants in the placebo group who experienced abdominal pain or cramping at baseline reported a decrease in abdominal pain upon supplementation (60.7 % for P-06, 7.1 % for P-05).
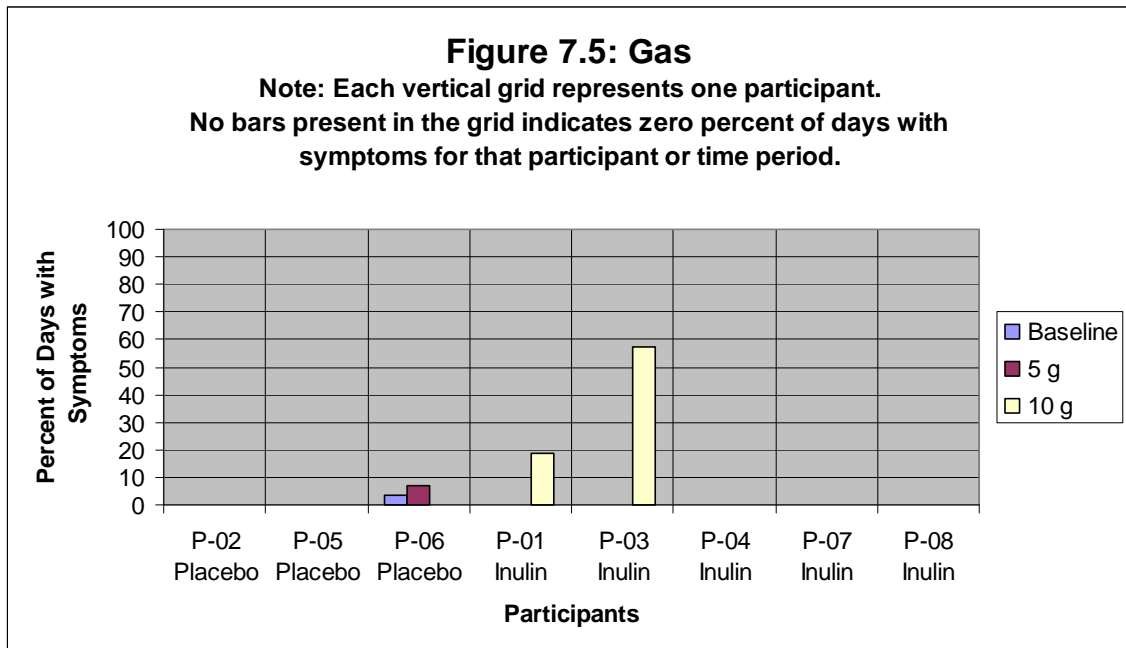

Figure 7.3: Abdominal Cramping and Pain
Note: Each vertical grid represents one participant.
No bars present in the grid indicates zero percent of days with symptoms for that participant or time period.

Appendix 7.4 Diarrhea

Two participants, one from the inulin group (P-08) and one from the placebo group (P-05) experienced increased diarrhea at the 5 g dose. One participant in the inulin group (P-01) who did not report diarrhea at baseline or the 5 g dose experienced diarrhea at the 10 g dose. One participant in the inulin group showed no change at the 5 g dose, but showed a decrease in diarrhea on the 10 g dose.

Figure 7.4: Diarrhea
Note: Each vertical grid represents one participant.
No bars present in the grid indicates zero percent of days with
symptoms for that participant or time period.

Appendix 7.5 Gas

Two participants (P-01 and P-03) in the inulin group experienced gas at the 10 g dose Figure 7.5. P-01 felt his gas was so severe that he had to discontinue taking the supplement, despite halving his dose to 5 g. This participant dropped out of the study due to this severe gas he experienced. One participant in the placebo group experienced a mild increase in gas, but the gas decreased at the 10 g dose.

Figure 7.5: Gas
Note: Each vertical grid represents one participant.
No bars present in the grid indicates zero percent of days with symptoms for that participant or time period.

Appendix 7.6 BM Frequency

Eight participants were plotted on Figure 7.6 (P-09 was excluded because he only completed baseline). The figure represents mean bowel movement (BM) frequency at three time periods: at the baseline period, at the 5 g supplementation period and at the 10 g supplementation period.

100
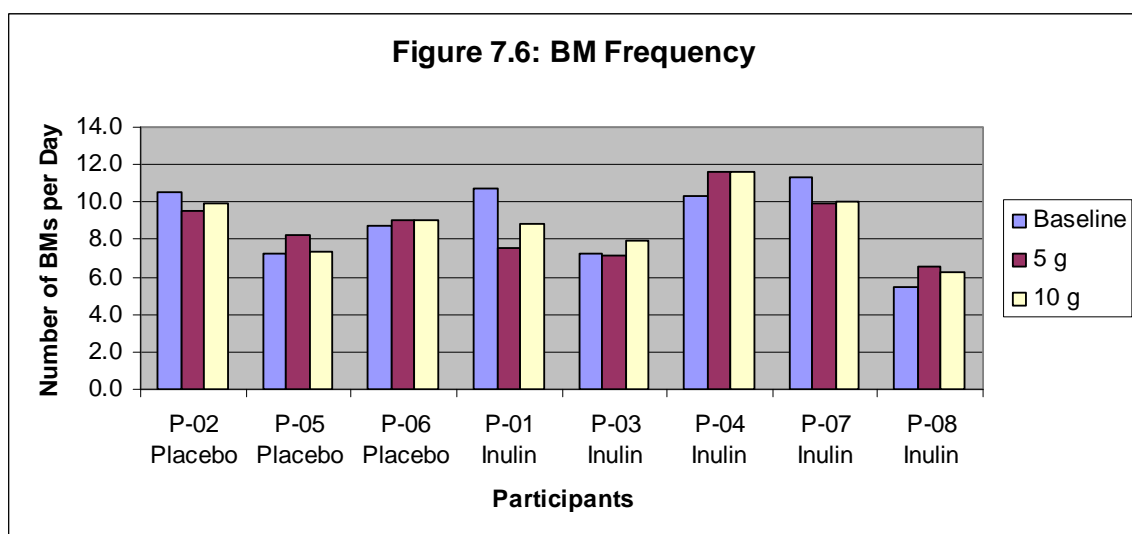
APPENDIX 8:

MEDICATIONS

Please list any medications or supplements that you are currently taking (including vitamins, minerals, probiotics, etc.).

APPENDIX 9:
RESEARCHER'S NOTES ON POTENTIAL EFFECTS OF MEDICATIONS

1. Participant: P-01
Treatment: Inulin
   ➢ Participant took a low dose (3.4 g of psyllium/day) of Metamucil during baseline and treatment periods.
Researcher's note: A relevant adverse effect is bloating, abdominal pain, flatulence and diarrhea. However, the participant tolerated Metamucil before taking the inulin. It could be the combined effect, as discussed in the results section.

2. Participant: P-02
Treatment: Placebo
   ➢ This participant took the Flagyl at baseline and 3 times while taking the placebo at full dose to decrease his BM frequency.
Researcher's note: Flagyl (Metronidazole) - is an antibacterial against anaerobic bacteria. A relevant adverse effect is diarrhea

3. Participant: P-03
Treatment: Inulin
   ➢ Lomotil (Anti-diarrheal): bloating and cramps
   ➢ Imodium (anti-diarrheal): abdominal cramping
   ➢ "Jade Windscreen" herbal formula for Respiratory health
   ➢ Multivitamin
   ➢ Vitamin C 1 tablet per day: can be abdominal cramps
   ➢ Acidophilus and Bifidus
   ➢ UNDA # 3, 37, 50 (Herbal Supplements)
   ➢ Replete Probiotic Formula: 130 billion CFU of L. acidophilus, B. bifidum, B. lactis, and L. salivarius in each packet.
   ➢ Flovent and Solvent for asthma:
   ➢ * Flagyl taken 2 weeks into 10 g dose: adverse effect could be diarrhea
Researcher's note: Uncontrolled mix of medications and herbal formulas and probiotic formulations makes it difficult to determine isolated effects of Inulin

4. Participant: P-04
Treatment: Inulin
"Every Sunday" took these medications for Rheumatoid Arthritis:
   ➢ Methotextrate: Diarrhea and GI ulceration/bleeding
   ➢ Gravol: shouldn't affect GI symptoms
   ➢ Enbrel
Researcher's note: ** The bleeding experienced by this patient could potentially be linked to her use of Methotextrate; perhaps the inulin aggravated potential ulcerations

5. Participant: P-05
Treatment: Placebo
   ➢ Advil once during 5 g dose
   ➢ Tylenol once during 10 g dose

Researcher's note: These small doses and frequencies of medications mot likely linked to any interaction with inulin or side effect.

6. Participant: P-06
Treatment: Placebo
  ➢ No medications listed.
Researcher's note: No interactions or side effects due to medications

7. Participant: P-07
Treatment: Inulin
  ➢ Metronidazole (Flagyl) at baseline and 1 week into 5 g dose
  ➢ Salofalk: (Lower GI anti-inflammatory) at baseline and 1 week into 5 g dose: flatulence is uncommon side effect

8. Participant: P-08
Treatment: Inulin
  ➢ Throughout baseline and treatment, took an iron supplement
  ➢ Apo- metronidazole (Flagyl): could cause diarrhea took for 10 days during baseline
Researcher's note: iron not likely to cause interaction or side effect since taken continuously
Flagyl should be taken into consideration as a drug that may have caused a side effect during baseline.

9. Participant: P-09
Treatment: Placebo (but never started placebo due to Crohn's diagnosis)
  ➢ Nu-Cephalex: 500 mg for 1 week during baseline
Researcher's note: Diarrhea and cramping could be related to use of Nu-Cephalex, however it was only taken during baseline.