THE EFFECTS OF POLYDEXTROSE AND SOLUBLE CORN FIBER ON LAXATION AND SATIETY IN HEALTHY HUMAN SUBJECTS

A DISSERTATION
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
OF THE UNIVERSITY OF MINNESOTA
BY

Derek Allen Timm

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

Dr. Joanne Slavin

September 2012

Acknowledgements

I would like to thank my parents Dan and Brenda since without them I wouldn't have had an opportunity to complete my project and for all the lessons and hard work they instilled in me growing up. I would also like to thank my brother Matt for living with me during school and putting up with my freak outs and harassing me when I needed motivation. Next I want to thank my advisor Dr. Joanne Slavin for her wisdom and support during my graduate school journey. Next I would like to thank Abby Klosterbuer for always being a wonderful person to bounce ideas off and help solve problems with. My past and present lab mates including Hilary, Michelle, Jackie, Katie, Renee, Snow, Jen, and Melinda have been great company and helpers along the way. A special thanks to Maria Stewart and Holly Willis, who helped train and set up many of the assays I used in my research. I would like to thank those who participated in my studies and were willing to share so much information about their bowels habits since without them I could not have completed my research.

Dedication

I want to dedicate this to all the scientists that came before me and laid the groundwork for all of the analyses and knowledge I drew upon in order to conduct my research.

Abstract

Dietary fiber from whole foods has long been known to regulate bowel function; however it is essential to confirm this in isolated or synthesized fibers. Stool weight, gastrointestinal transit time, and stool consistency are all ways to measure changes in bowel function in humans and can be used to evaluate the efficacy of dietary fibers. Gastrointestinal tolerance is also of great concern since consumer acceptability of dietary fiber is related to intolerance issues. Furthermore, since observational and epidemiological data suggests dietary fiber reduces energy intake, which may be modulated by changes in postprandial satiety, we also investigated acute satiety using visual analog scale (VAS) and food intake via food diaries. Therefore, we investigated the influence of 20 grams per day for 10 days of the functional fibers Polydextrose (PDX) and Soluble Corn Fiber (SCF) compared a low fiber control on bowel function. Thirty-six healthy men and women completed this randomized, double-blind, placebo-controlled study. A two-week washout period was completed between each treatment period. Results show both PDX and SCF significantly increased stool weight compared to the control treatment. In contrast, whole gut transit time was not difference among the treatments. Stool pH was significantly lower for PDX compared to the control treatment. PDX caused a significantly looser stool than SCF and control. Flatulence and stomach noises were significantly increased by the fiber treatments compared to the control. Satiety was not difference among the treatments as measured by a VAS. No differences were observed in energy intake among the treatments.

Table of Contents

List of Tables

Chapter 2

Chapter 3

Chapter 4

List of Figures

Chapter 3

Chapter 1 Background on Dietary Fiber Definitions, Laxation, Satiety, Polydextrose, and Soluble Corn Fiber

Section 1: Dietary Fiber Definition and Average Intake

The term dietary fiber was coined by Hipsley in 1953 as the nondigestible constituents of plant walls (1). In 1972 Trowell expanded the definition of dietary fiber to include beneficial physiological effects (2). Since then, many discussions have occurred pertaining to the definition of dietary fiber. Currently, three definitions of dietary fiber are widely accepted and were created by three separate organizations - Codex Alimentarius Commission, American Association of Cereal Chemists (AACC), and the Institute of Medicine (IOM).

The Codex Alimentarius Commission definition is important worldwide because it is recognized by the World Trade Organization. The Codex Alimentarius Comission defines dietary fiber as "carbohydrate polymers[1] with ten or more monomeric units[2], which are not hydrolysed by the endogenous enzymes in the small intestine of humans and belong to the following categories:

- Edible carbohydrate polymers naturally occurring in the food as consumed,
- carbohydrate polymers, which have been obtained from food raw material by physical, enzymatic or chemical means and which have been shown to have a physiological effect of benefit to health as demonstrated by generally accepted scientific evidence to competent authorities,
- synthetic carbohydrate polymers which have been shown to have a physiological effect of benefit to health as demonstrated by generally accepted scientific evidence to competent authorities

[1] When derived from a plant origin, dietary fibre may include fractions of lignin and/or other compounds when associated with polysaccharides in the plant cell walls and if these compounds are quantified by the Association of Official Analytical Chemists (AOAC) gravimetric analytical method for dietary fibre analysis : Fractions of lignin and the other compounds (proteic fractions, phenolic compounds, waxes, saponins, phytates, cutin, phytosterols, etc.) intimately "associated" with plant polysaccharides are often extracted with the polysaccharides in the AOAC 991.43 method. These substances are included in the definition of fibre insofar as they are actually associated with the poly- or oligo-saccharidic fraction of fibre. However, when extracted or even re-introduced into a food containing non digestible polysaccharides, they cannot be defined as dietary fibre. When combined with polysaccharides, these associated substances may provide additional beneficial effects

[2] Decision on whether to include carbohydrates from 3 to 9 monomeric units should be left to national authorities."

The AACC describes dietary fiber as "the edible parts of plants or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine. Dietary fiber includes polysaccharides, oligosaccharides, lignin, and associated plants substances. Dietary fibers promote beneficial physiological effects including laxation, and/or blood cholesterol attenuation, and/or blood glucose attenuation" (3).

The IOM definition divides fiber into two classes: *dietary fiber* and f*unctional fiber* (4). *Dietary fiber* includes "carbohydrates and lignin that are intrinsic and intact in

plants that are not digested and absorbed in the small intestine" (4). *Functional fiber* is "isolated, nondigestible carbohydrates that confer beneficial physiological effects in humans" (4). The sum of *dietary fiber* and *functional fiber* is termed *total fiber*. The rational for creating two different classes of dietary fiber is that intact *dietary fiber* may have different physiological effects than isolated or artificially synthesized *functional fiber*.

The Codex method relies upon methods developed by the AOAC, which uses analytical techniques for the determination of total dietary fiber, soluble fiber, and insoluble fiber. The AOAC method has also been adopted by the Food and Drug Administration for the purposes of classifying dietary fiber on the nutrition facts labels (4). Despite the acceptance of the AOAC method of fiber quantification, there has been trend to move away from this definition. The reason for the shift is because the solubility of a dietary fiber does not always predict its physiochemical properties. Instead viscosity and fermentability have been suggested as better descriptors for dietary fiber; however no consensus on how to characterize dietary fiber has been agreed upon to date (4).

Regardless of definition, fibers must demonstrate physiological benefits in order to be classified as dietary fiber. These benefits include laxation, blood glucose attenuation, and serum cholesterol reduction. Therefore newly discovered or synthesized fiber-like compounds must be investigated for their physiological effects.

Dietary Fiber Intake

The Dietary Reference Intake (DRI) committee recommends consumption of 14 grams of dietary fiber per 1000 kcal, which translates into a recommended level of 25

g/day for women and 38 g/day for men. A recommendation of 19-25g/d has also been made for children over the age of 2. Previously no dietary recommendation existed for dietary fiber because it was not considered a nutrient (4). Despite the recommendations, dietary fiber consumption in the United States is low. Intake of dietary fiber in large cohorts of adult men and women is 21g/day and 18 g/day (5,6). Fiber intake in a cohort of older men and women between the age of 50 and 71 was 10.3 g/day (7). Another cohort of older people found consumption of 12 g/day (8). These cohorts show that adults in the United States are consuming significantly less than the recommended levels of dietary fiber.

Section 2: Laxation Mechanisms, Methods, and Effects of Wheat Bran

Laxation is a term that refers to the elimination of waste via stools. The frequency of laxation is highly individualized and the normal frequency can vary from 3 stools a day to 3 stools a week. Generally constipation is defined as less than 3 stools a week; whereas diarrhea is more than 3 stools a day (9). Clinically diarrhea has also be reported as a stool weight exceeding 200 g/day (10). This second definition of diarrhea is likely inappropriate for all populations since it has been reported that the average stool weight ranges from 72-470 g/day worldwide (11). This fact highlights that a normal stool weight is likely a function of diet and culture due to the wide range of stool weights reported worldwide.

Laxative mechanisms of dietary fiber as a whole are well established, but those of individual fibers may not be clear and warrant research. Fibers may exert a laxative effect by increasing fecal weight, altering gastrointestinal transit time, increasing the

frequency of defecation, changing stool consistency, or a combination of all the aforementioned effects.

One common way to compare laxative effects of different fibers is to look at the increase of stool weight. It is important that the fiber be given time to pass through the gastrointestinal tract prior to collecting. Also at least a 4-day stool collection and preferably 5-7 day collection should be done to account for intra-individual stool weight differences. Comparison of fecal weight changes are best accomplished in a crossover design study so that the control period can be compared to a fiber treatment within each subject. Then the fecal weight during the control period can subtracted for the stool weight during the fiber treatment and divided by the amount of fiber supplemented during the collection period yielding grams of fecal weight increase per gram of fiber supplemented. This number is relatively robust and is useful for comparing results between studies.

Increases in stool weight are one of the most notable effects of dietary fiber. Measuring stool weight is one of the easiest and least invasive ways to examine the effects of dietary fiber on laxation. The composition of the stool can be investigated in a number of different ways. The most basic way is to simply weigh the sample. Differences in stool weight are generally related to dietary fiber intake, but not always due to differences in fermentability or water binding capacity of fibers. It has been shown that some highly fermentable fibers such as pectin or inulin do not increase stool wet as much as other less fermentable fibers. However, highly fermentable fibers do influence stool weight by increasing the bacterial mass of the stool (12). In contrast, non-

fermentable fibers like cellulose increase stool weight by directly contributing to the stool after they pass through the gastrointestinal tract (12). Psyllium fiber exerts a laxative effect by binding water, which in turn increases the weight of the stool (13,14). The previous three examples are the extremes of how dietary fiber functions as a laxative, but in reality, dietary fibers exert their laxative effect by a combination of the aforementioned mechanisms.

Another way to investigate the mechanism of laxation is by drying the fecal sample, which allows the researcher to examine the contribution of dry matter to the total fecal weight. Determining the dry weight is useful for investigating the laxative mechanism of a new fibers; however drying the sample is that it is very labor intensive. Many studies have demonstrated increased fecal dry weight after a dietary fiber intervention as a result of unfermented fiber (15). An interesting study compared the laxative effects of WB to plastic particles of similar size to WB. This study found plastic particles had similar affects on stool weight and WGTT as WB demonstrating a similar mechanism between the two substances (16).

Another mechanism of laxation involves the water-binding capacity of the dietary fiber. An *in vitro* study conducted by Stephen and Cummings investigated the water binding capacity of 17 different dietary fiber components (17). Pectin had the greatest water binding ability at 56 g water/g fiber, but the smallest change in fecal weight, whereas WB had the lowest water binding at 4 g water/g fiber and largest increase in fecal weight (17,18). A notable exception to this relationship is psyllium, which produces a laxative effect due to its ability to bind water and form a gel (19,20). Xylose

and arabinose account for a high percentage of the gel fraction of the feces and are thought to account for the laxative mechanism of psyllium (19). Furthermore, particle size influences water binding capacity of fibers with smaller particle sizes significantly increasing water binding (17). In addition, the particle size of inert plastic pieces has been shown to influences the laxative effects (21). This indicates particle size may also play an independent role in laxation of fibers since plastic particles do not bind water and are not fermentable.

Apart from directly bulking the stool, some fibers increase fecal weight due to proliferation of bacteria during fermentation as indicated by an increase in muramic acid content of stool, a component of the bacterial cell wall (22). This mechanism is supported by highly fermentable oat bran increasing fecal weight to a similar degree as WB (23). It has been observed that alive and dead bacteria comprise between 55-60% of human feces by weight (23,24). Overall, the physiochemical properties, particle size, and fermentability of dietary fiber all influence their laxative effects.

Measurement of Gastrointestinal Transit Time

The ability of dietary fiber to alter gastrointestinal transit time has been measured for many years. Investigators have used many different methods to determine transit time including colored dyes, colored glass beads, ^{51}Cr-labeled sodium chromate, cobalt-ethylenediamine-tetraacetic acid, and terbium oxide; however currently the most commonly used methods are radioopague markers (ROM) and scintigraphy. The newest technology used to measure transit time is a wireless motility device called the SmartPill®.

ROM

The ROM technique has its origin with the 1969 study by Hinton. This study examined the influence size and specific gravity on ROM passage finding that 5mm solid pellets were the most consistent. The specific gravity of these pellets are similar to the specific gravity of the gut contents, hence it is believed they pass at approximately the same rate as the gut contents. Also the repeatability and variance of the method was examined 5 times within 6 different subjects. One of the conclusions of this study was WGTT is best defined by the time required to pass 80% of the pellets since the last couple pellets may be disproportionally delayed (25). Furthermore, this study compared ROM to ^{51}Cr-labeled sodium chromate and found in general ROM was the same or faster than the sodium chromate (25). A study by Wyman aimed to examine the variability of colonic function using the Hinton 80% transit time. Ten men and women completed repeated ROM determination of transit time on their basal diet. This study found a large variability in transit time, fecal output, and the size of individual stools in both men and women (26). Unfortunately transit time was only repeated twice and dietary intake was not recorded or controlled; therefore it is difficult to determine in the differences are due to biological processes or confounding factors.

The ROM methodology was expanded by Cummings by introducing multiple doses of differently shaped ROM to examine the mixing of gut contents (27). The continuous method involves subjects swallowing 5 ROM pellets with each meal for one week; thereafter each fecal sample was collected, frozen, and x-rayed. The continuous mean transit time (C-MTT) determines gastrointestinal transit based on the turnover time

of ROM (27). The same study also created an equation to determine WGTT after a single dose of ROM (S-MTT) (27). This equation is based on the number of pellets passed multiplied by the time interval after swallowing divided by the number of total pellets passed (27). Additionally this study examined the simultaneous swallowing of 4 distinctly-shaped ROM and found no differences based on the shape of the ROM (27). When comparing 80% transit time (63.1 h) with C-MTT (54.2 h) a significant difference was observed; whereas the S-MTT method was similar to the C-MTT (27).

Based on the results of the previous study, Cummings and Wiggins set out to validate the single stool method as an acceptable alternative to the tedious continuous marker method in 15 healthy men (27). They observed a significant correlation between the two methods of ($R = 0.78$ $p < 0.001$), hence showing that a single stool method is an acceptable method of determining transit time (27). Another study examined S-MTT, 80% ROM, and colored dye transit time methods on low and high fiber diets. It was observed that S-MTT was shorter than the 80% method on both the low and high fiber diet (28). Also, the dye method produced a significantly shorter transit time than both ROM methods (28). Regardless of method, the high fiber diet reduced variability of transit time measurements (28). Another study used repeated measures of transit time using ROM and found no differences between the same subject on 4 separate occasions, indicating a relatively low variablitity of repeated measures using the ROM technique (29).

Based on the series of studies on the gastrointestinal transit time methods it is clear each method is slightly different and may yield significantly different results.

Therefore, when comparing studies of gastrointestinal transit time one must look at the ROM technique used and take this into account while making conclusions due to the variation between methods.

Scintigraphy

Scintigraphy involves the consumption of a radio-labeled meal followed by abdominal scans to determine the concentration of the radio-labeled meal in each part of the gastrointestinal tract. Most commonly a ^{99m}Tc sulfur radio-labeled egg sandwich is used as a test meal (30). However, other radioisotopes are used including ^{111}In that is used to determine liquid gastric emptying time (GET) time (31). Traditionally scintigraphy methodology has been mired by a lack of a standardized procedure. In recent years, there has been an effort to standardize this methodology. In 2000, a large multicenter study established a radio-labeled low fat egg meal with abdominal scans at 0, 1, 2, and 4 hours as the standard procedure (32). GET was defined as the time required for half of the radioactivity to exit the stomach (32).

Scintigraphy can also be used to determine colonic transit time (CTT). It utilizes regions of interest to help aid in determination of regional CTT based on the progression of isotope in each region of interest (31). The center of mass of the radioisotope is used to determine the progression of the radio-labeled meal through the large intestine. The frequency of abdominal scans varies between studies ranging from one to three times daily (31,33). The requirement for abdominal scans cause increased burden on the subjects and investigators; hence ROM are more often used for WGTT studies. Overall,

despite the burden on subjects and investigators scintigraphy is widely regarded as the gold standard for GET measurement (30).

Physiological Influences on Transit Time

Menstrual cycle, gender, and exercise are three factors thought to influence transit through the gut. Menstrual cycle has been extensively investigated for its influence on transit through various sites of the gastrointestinal tract. An early study examined GET, as measured by dual isotope scintigraphic techniques, and found no difference between the follicular and luteal phase in the 10 women measured (34). In contrast, a more recent study found the follicular phase significantly slows GET as measured by a 3D ultrasonography method (35). Examination of the effect of menstrual cycle on CTT has yielded no differences when measured by scintigraphic methodology (36). Likewise, two studies found no difference in WGTT between the menstrual cycle using ROM (26,37). In contrast, a study using ROM along with an abdominal radiograph showed a significant difference in CTT between phases of the menstrual cycle with the luteal phase CTT being longer (38). Likewise, a study using ROM found the MTT to be significantly longer for women during the luteal phase (39).

Three studies that examined GET, SBTT, and CTT using scintigraphic methods found conflicting results on effect of gender on transit time (40-42). A study using ROM found women have significantly longer GET, SBTT, and CTT than men (43). Another study found no statistical difference in CTT between men and women, but women did have an average of 7 hours longer CTT (38). Other studies have found that women have significantly slower WGTT compared to men (44-46); whereas others do not (26).

Exercise has also been investigated as a potential influence on gastrointestinal transit time. Different levels of participant fitness, type of exercise, and transit time measurement methodology all complicate interpretations of this literature. A crossover study of sedentary people compared daily running, biking, and rest for an hour with other physical activity not being permitted and dietary fiber and fluid intake were controlled. WGTT was measured by a single dose of ROM and results show a significant reduction in WGTT from 51.2 h on the control to 36.6 and 34.0 h for biking and running respectively (47). In contrast, a study examining the effects of daily brisk walking compared to no exercise showed no differences in CTT in men (48). These two studies show that the effect of exercise is likely proportional to the intensity of exercise.

It is apparent that apart from diet, gender, menstrual cycle, and exercise all influence transit time, making it is important to control for their effects during any clinical trial. The effect of menstrual cycle on transit time remains controversial so it is best to control for menstrual cycle as a best practice to reduce variability since the luteal phase tends to slow gastrointestinal transit time. Gender can be taken into account during statistical analysis as a covariant, but also by designing a study for either exclusively men or women or by having a gender balanced study. Lastly, exercise should be maintained at the same level during all phases of a clinical trial and investigators should try to recruit relatively sedentary people since high intensity exercise reduces transit time.

Stool Consistency

A stool consistency can vary greatly from within and between individuals from small hard pellets to completely liquid. Generally the extremes in stool consistency are

associated with either constipation or diarrhea. These differences in stool form are a function of gastrointestinal transit time since transit can alter the amount of water absorbed in the colon (39,49). Also, it has been shown that stool consistency and water content are directly related (50). The same study found that healthy adults had a near constant stool water content despite wide ranges in stool weight (50). Since dietary fiber tends to regulate bowel function by altering transit time it can, depending on the person, either slows transit to produce a harder stool or speeds transit to soften the stool. Moreover, it has been shown that stool form and colonic transit time are correlated (49,51). Therefore, stool consistency is essentially an auxiliary measure of gastrointestinal transit and can be used to approximate transit time when it is not measured (49).

Throughout the years several different ways of determining stool form have been used. Common scales involve a numeric scale with accompanying descriptions that are rated by either subject or investigators. As the scales have evolved, pictures of stool samples have been combined with descriptions to increase the continuity between the people rating the stool. The most common scale is the 7 point Bristol Stool Form Scale that utilizes pictures with descriptions ranging from hard pellets to completely liquid. This scale is relatively robust since experimentally it was correlated with both fast and slow transit times (49). Another popular scale is the Kings Stool Chart. This scale forms a matrix with stool weight ranges (>100g, 100-200g, >200g) and 4 different descriptors with pictures (52). This scale has been validated; however it was done in hospital patients with diarrhea and the modal rating was liquid (52). Besides these two pictorial

scales other more basic scales are still in common use since no standard stool form scale has been established. The major drawback of various scales is that there is no guide for each investigator to make reference to and this may account for inconsistent stool form results between studies apart from subject differences.

Laxation Studies Examining WB

WB is widely considered the gold standard of laxative fibers and has a wealth of literature to support its effect. One of the earliest was conducted by Eastwood and associates found no difference in transit time after 3 weeks of WB or cellulose consumption using ROM (53). This study did, however, observe significant increases in both wet and dry fecal weight as a result of both fibers (53). Payler and colleagues and examined the effects of a 20 g dose of WB on 20 men using ROM. When compared to the basal diet, 20 g of WB decreased WGTT from 2.75 ± 1.6 to 2.0 ± 0.9 days (54). Cummings and associates examined the effect of WB in 6 male subjects in a metabolic ward. They consumed a tightly controlled diet that only varied by substituting 30 grams of WB for white flour. A significant decrease in WGTT was observed on the WB treatment from 57.8 ± 8.3 h to 40.3 ± 8.9 h using the C-MTT method (55). Also a significant increase in fecal weight from baseline 79.3 ± 6.6 g to 228.0 ± 29.9 g observed on the WB treatment (55).

Cummings also investigated the effect of concentrated fiber extracted from carrot, cabbage, WB, and guar gum (56). WGTT and stool weight was determined on a controlled low fiber diet followed by a randomly assigned fiber treatment. Fecal weight was significantly increased by all fibers except guar gum (56). WGTT was significantly

decreased by WB, cabbage fiber, and apple fiber, however no change was observed on the carrot and guar gum treatments (56). A study fed 16g/day of course ground WB for 3 weeks compared to a control period. The results show significantly increased fecal wet and dry weight, but no difference in WGTT as measured by the Hinton method (18). Another study investigated the effect of WB enriched bread on laxation. Twelve young men completed both a low fiber (9 g) treatment and a high fiber treatment (22 g). The high fiber diet significantly decreased WGTT from 88 h to 52 h and significantly increased fecal wet weight from 77 g/d to 140 g/d (57). A similar gender-balanced crossover study compared the laxative effects of 21 g/day of WB to a low-fiber control. WGTT was determined by 80% recovery of ROM after a 4-day fecal collection. Results show no difference in WGTT despite the control having significantly lower insoluble and total fiber consumption (58). However fecal wet weights were significantly increased by WB compared to the control (58).

A high-fiber diet (45 g) composed of dietary fiber from primarily fruit and vegetable fiber resulted in a significant reduction in WGTT of approximately 18 hours and a significant increase in fecal wet weight of 115 grams when compared to a low fiber diet (12 g) (59). Another study by this group investigated WB, citrus pectin fiber, and fruit/vegetable fiber on several biomarkers including fecal output and transit time. WGTT as determined by ROM found significant reductions of 13 and 19 hours on the fruit/vegetable fiber and WB respectively as well as an increase in stool frequency (60). Fecal wet weight was also increased as a result of the fruit/vegetable fiber and WB, but not the citrus pectin (60).

In order to clarify the effect of particle size, two clinical trials were conducted investigating fine, medium, and course ground WB. The first study compared 19 grams of fine or medium ground WB to a low-fiber control while the second study compared medium or course ground WB to a low-fiber control. Both WB treatments significantly increased fecal weight compared to the control, but were not different from each other (61). However, the medium ground WB had a significantly higher frequency of bowel movements compared to the fine ground WB (61). Similarly, results of the second study showed significantly increased fecal weights for the medium and course ground WB treatments compared to the control with no differences between the WB treatments (61). In contrast, no difference in frequency of bowel movements was observed between the medium and course ground WB (61).

Another crossover study examined WB, psyllium, or a low fiber control in twelve women. This study found WB was most effective at decreasing WGTT with psyllium having an intermediate effect between WB and control (29). In contrast, psyllium was more effective at increasing fecal wet weight than WB (29). Overall, WB is considered the gold standard for laxation because it has been repeatedly shown to decrease gastrointestinal transit time and increase fecal weight. These classical studies examined dietary fiber from natural sources or extracted from natural sources. Therefore it is imperative to determine the physiological effects of newly synthesized or chemically modified dietary fibers because without proof of physiological benefits indigestible carbohydrates may not be considered dietary fiber.

Section 3: Fermentation of Dietary Fiber

Gut Microbiota

The human gastrointestinal tract harbors a total of approximately 100 trillion bacterial cells (62). Each gram of feces contains approximately 10^{12} -10^{14} bacteria (63). These bacteria belong to 500-1000 distinct species (64-66); however the Bacteroidetes and Firmicutes familes account for proximately 90% of all bacteria (67). Several different techniques are used to detect the microbiota including culturing techniques, 16s RNA, terminal restriction fragment polymorphism, fluorescent in situ hybridization, and DNA microarray chips (68). Currently, no standard way of analyzing gut microbiota exist so different group's use one of the techniques, which makes comparing results difficult between studies. As techniques improve and standardization occurs the large intestinal ecosystem will become clearer and easier to understand the complex relationships between microbial metabolism and large intestinal function. In the meanwhile it is well known that colonic bacteria play a large role in the function of the gastrointestinal tract through fermentation of dietary fiber and protein supply energy for the coloncytes and the body.

Prebiotics/Probiotics

Prebiotics are a class of dietary fibers described as "a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and activity of one or a limited number of bacteria in the colon that have the potential to improve host health" (69). Inulin-type fructans and resistant starches are the most

common prebiotics. The beneficial bacteria that prebiotics stimulate the growth are termed probiotics. A definition of probiotics is "any living microorganisim which upon ingestion in certain numbers, exert health benefits beyond inherent general nutrition" (70). Probiotic bacteria generally consist of lactic acid producing bacteria in the Lactobacillus and Bifidobacterium genera (71,72). Probiotics have the characteristics of being non-toxic, non-pathogenic bacteria that are also resistant to low pH. Both prebiotics and probiotics have beneficial effects including alterations of the metabolic activity of intestinal bacteria, SCFA production, and enhancement of intestinal immunity (71).

SCFA

When dietary fiber reaches the large intestine, resident bacteria ferment the fiber producing SCFA at a concentration around 100 mM (73). The three main SCFA produced in the colon are acetate, propionate, and butyrate at a ratio of approximately 60:25:10 (73). Branched-chain fatty acids such as isobutyrate, valerate, and isovalerate and are produced in the colon as a result of protein fermentation (74). Collectively SCFAs provide energy for the body in the range of 1.5 – 2.5 kcal/g (75). SCFA production is influenced by several factors such as the number and type of microflora present in the colon, the fermentative substrate, and transit time through the large intestine (76,77).

The large intestine efficiently absorbs SCFA with an overall rate of 95-99% (78). SCFAs are absorbed by three mechanisms: bicarbonate SCFA exchange, nonionic diffusion of protonated SCFA and anion exchange (79-81). Bicarbonate appearance is

linked to SCFA disappearance (81). Nonionic diffusion of protonated SCFA involving hydration of luminal carbon dioxide accounts for 60% of SCFA absorption (81). Anion exchange occurs through sodium-coupled monocarboxylate transport (SLC5A8) transporter in the colon (82). Sodium is absorbed with SCFA causing a net absorption of water because of osmotic pressure. This may have implications in the prevention of diarrhea (83). Between 5-10% of SCFAs are not absorbed and excreted in the feces. Due to the noninvasive nature of stool collection, many researchers collect stool samples for analysis of SCFAs assuming fecal SCFA are similar to colonic levels. This practice has obvious drawbacks, but until a better noninvasive method is developed this practice will likely continue.

Acetic acid is the most prevalent SCFA. After absorption it is primarily metabolized for energy by peripheral muscles and the liver (77).

Propionate, after absorption, is transported to the liver where it can undergo gluconeogenesis (77). In addition, propionate has been found to inhibit cholesterol synthesis by some (84-86), but not others (87,88). A proposed mechanism for decreased cholesterol biosynthesis involves inhibition of the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase, which is required in the first step in cholesterol biosynthesis (89). These results were observed with addition of physiologically relevant concentrations of 2 mM propionate and 5 mM butyrate using Caco-2/TC-7 enterocyte cell lines (89). However, until consistent results are observed in humans, the impact of propionate on cholesterol synthesis will remain controversial.

The third main SCFA is butyrate and can be formed directly or from the conversion of lactic acid by several bacterial species (90). Butyrate is the preferred energy sources for colonic mucosal cells, supplying as much as 60-70% of energy needs (91,92). Butyrate also has been shown to induce apoptosis in colon cancer cell lines and animal models, thereby eliminating cancerous cells before they further progress to malignancy and spread (93). Butyrate has been found to decrease coloncyte proliferation, increase coloncyte differentiation, and decrease the risk of developing colon cancer (94-98).

SCFA production is assumed to be directly related to dietary fiber intake; however a recent study put this into question. McOrist and colleagues examined free living individuals on their habitual diets for 12 weeks and found fecal SCFAs to be highly variable within and between individuals (99). This study also found that dietary fiber intake from diet records did not correlate with fecal butyrate or total fecal SCFA concentrations (99). This study puts into question the utility of measuring fecal SCFAs and if changes in levels are due to a dietary intervention or simply natural variation.

Collectively fermentation and SCFA production reduce the pH of the large intestine due to release of hydrogen ions from acetate, propionate, butyrate, lactate, succinate, and bicarbonate. The bulk of fermentation occurs in the cecum; therefore the cecum has a lower pH than the distal colon. Changes in pH alter the competitive balance of various different bacteria and it is generally assumed that a decrease in colonic pH is beneficial for the host. Furthermore, it has been suggested that high colonic pH may promote colon cancer through the conversion of bile acids to secondary bile acids (100).

This is simply a hypothesis and is virtually impossible to prove experimentally due to the long progression of colon cancer, but highlights the potential importance of fermentation in the gut.

Gas Production

In addition to SCFA production, gases are formed during fermentation of dietary fibers. The three main gases produced during fermentation are carbon dioxide, hydrogen gas, and methane. About 10% of these gases can diffuse into circulation where they are exhaled through the lungs and detected in the breath (101). The rest of the unabsorbed gases are passed through the anus as flatus.

Hydrogen gas is assumed to be ubiquitously produced in humans as the result of dietary fiber fermentation, however some studies report that up to 27% of people are non-producers (102). The bacteria family responsible for hydrogen gas production appears to be the Clostridia (101). Hydrogen gas production can also be used as a proxy for fiber fermentation and can be used to predict transit time from the mouth to terminal ileum (103).

Methane is produced from hydrogen and carbon dioxide by methanogenic bacteria particularly *Methanobrevibacter smithii* (104,105). Only a relatively small subset of Western population produce methane gas with the reason being variations in the *Methanobrevibacter smithii* population levels within the colon (106). Only approximately 30-38% of the Western populations produce detectable concentrations of methane gas in expelled air (107). Methane is a non-toxic gas that is thought to consume hydrogen so it may not be converted to toxic hydrogen sulfide gas (104). Interestingly,

when examining rural African populations, which have long been noted for low colon cancer rates, it was observed that between 80-91% of the population were methane producers indicating that it might play a role in colon cancer prevention (108).

One theory of the role of methane in colon cancer is that it outcompetes sulfate-reducing bacteria (109,110). This is because sulfate-reducing bacteria produce hydrogen sulfide, which is a genotoxin and causes DNA damage through generation of free radicals (111,112). Interestingly, Gibson has shown that a decrease in pH from 7 to 6 caused a 50% reduction in hydrogen sulfide formation (113), which shows a potential link between low pH, high methane production, and low colon cancer rates in native Africans.

Gastrointestinal Tolerance

Gastrointestinal tolerance is an umbrella term used to for a variety of digestive maladies. Dietary fiber is just one component of the diet that may negatively affect tolerance and is generally assumed to be caused by excessive gas formation in various sections of the gastrointestinal tract. Some commonly reported issues are bloating, excessive flatulence, cramping, stomach noises, burping, gastroesphogeal reflux, and nausea. These complaints are highly individualized and vary widely between people so a crossover study design is best so baseline tolerance can be compared to an intervention within each subject.

The volume of gas usually present in the human intestinal tract is estimated to be between 100 and 200 mL (114). Increases in gas can lead to several undesirable side effects such as flatulence, bloating, or abdominal pain which may decrease the acceptability of a high fiber diets. The volume of gas produced from dietary fiber

fermentation is dependent upon dose as well as the type of substrate. Research provides insights into how and why these side effects affect some individuals and not others.

One way to examine gas dynamics is done by infusing gas and lipids into the intestines and observing the resulting physical symptoms. As expected, this type of study has established a link between increased gas infusion and increased number of gas evacuations (115). Also, some individuals retain more gas than infused, while others evacuate more gas than was infused (115). Serra and colleagues reported that neither gas infusion rate nor volume of gas evacuated was correlated with abdominal discomfort. A high proportion of individuals retaining 400 mL or more of gas reported more discomfort, which suggests that gas retention may be a good indicator of discomfort (115-117). The reason for gas retention may be the result of dysfunction in reflex controls of gas transit (117). In addition, the site of gas infusion influences the perception of abdominal pain. When comparing gas infusion into the jejenum or rectum, significantly higher abdominal discomfort was observed with the jejenal infusion (118). As a result, it is assumed that the colon is better able to tolerate high gas volumes compared to the small intestine, which may account for the differences observed in the previous study. Overall, the literature shows that gas volume is not the cause of the majority of abdominal discomfort, but rather an inability of patients to pass gas. Gas produced from dietary fiber may not be the root cause of abdominal discomfort, but would contribute to discomfort in susceptible individuals.

Investigators use self-reported questionnaire completed by the subjects during a dietary intervention are used to assess tolerance. Tolerance questionnaires typically use a

numeric scale with or without descriptive anchors to quantify tolerance. These scales range from 4 point to 10 point scales (119,120). To date no standard questionnaire has been developed for gastrointestinal tolerance, which makes comparison of tolerance between studies somewhat difficult, but nonetheless the heart of all tolerance questionnaires is to assess the subjects' gastrointestinal wellbeing.

Section 4: Satiety and Food Intake

Measurement of Satiety and Food Intake

Satiety is the perception or state of being satisfied following a meal and is related to the amount of time before initiating eating again (121). Satiation is a term used for the satisfaction of appetite throughout a meal, which leads to a stopping of an eating experience (121). Many different scales have been developed in order to assess this subjective measure (122). Scales range from bipolar hunger-fullness scale, unipolar hunger scale, unipolar fullness scale, unipolar prospective food consumption scale, and a 7-point bipolar hunger-fullness scale. The diversity of satiety scales is great; however satiety is usually assessed using four validated satiety-related questions pertaining to hunger, fullness, satisfaction, and prospective food consumption (123). Satiety questions are evaluated on a 100 mm line anchored statements such as "I am not hungry at all" on one end and "I have never been more hungry" on the other end (123). Subjects are repeatedly asked to mark their perceptions of each question on the continuum of 100 mm line and their responses are then hidden to prevent earlier responses from influencing prospective responses. Numerous studies have found these ratings to be correlated with

subsequent food intake (123-125). The results of these measures are best used for within-subject comparisons due to variability between subjects (123).

Traditionally VAS scales were completed using pen and paper; however the recent development of electronic systems has facilitated a trend away from pen and paper. Several studies have compared the two types of VAS scales simultaneously and found favorable correlations between them (125-127). It is important to that these two scales should not be used interchangeably (125,127,128). Overall, the electronic VAS has the advantage of instant measurement, ease of use, and reduced data entry time.

Dietary fiber is thought to influence satiety due to its low calorie density, which allows it to displace other more caloric macronutrients. Many studies have investigated the relationship between dietary fiber and satiety. A review of satiety studies on dietary fiber from 1984 to 2000 found that the majority of studies had positive effects on energy intake (129). More recent studies have shown mixed results on the effect of dietary fiber on satiety as measured by VAS with many supporting satiety (130-134,134,135)and some refuting it (136-139). Different dietary fibers, doses, and study populations influence the results of these studies, but overall dietary fiber has shown to have an effect on satiety despite mixed results.

Another way to evaluate satiety is through *ad libitum* meals, where investigators are able to measure exactly how much a subject consumed at a given meal. These meals usually consist of either a buffet or a single food and subjects are given a set time in order to consume the meal. *Ad libitum* lunches given precise measures of energy intake, but

have the disadvantage of being labor intensive and rarely show differences in consumption. An easier, albeit, less precise method involves completion of self-reported food diaries by subjects who are instructed to record all the foods and beverages along with the amount they consumed during a given period of time. This method is most commonly used in chronic research studies to track longer term energy consumption. The disadvantage of food diaries is they require accurate recording by the subjects and foods need to entered into a diet analysis software program. Nonetheless, these methods are the most commonly used in dietary intervention trials.

The effects regarding dietary fiber on *ad libitum* food intake or energy consumption are mixed with several studies supporting it (132,134,140-142), but many do not (119,130,135-139). Despite the common believe that dietary fiber reduces food intake, few studies actually support this belief and further research must be done to elucidate these effects.

Section 5: Test Fibers

Polydextrose

Polydextrose (PDX) is a water soluble fiber with a low viscosity formed from random polymerization of glucose with sorbitol and citric acid (143). The result of this reaction produces several types of glycosidic linkages including α(1,3), (1,4), (1,6) and β(1,2), but the predominate linkage is α(1,6) (143,144). PDX has a highly branched structure with an average degree of polymerization of 12 and average molecular weight of 2000 daltons (143). Very little PDX is absorbed in the small intestine and only about

50% is fermented in the large intestine (143). PDX yields approximately 1 kcal/g through bacterial fermentation and SCFA production (143,145,146).

In vitro data suggests PDX is slowly fermented significantly increases bifidobacteria (147,148). Further evidence for its fermentation is the breath hydrogen response of a 11 g dose of PDX (149). This study showed each g of PDX resulted in a breath hydrogen response of 9 ppm/hour (149).

Feeding PDX at a dose of 30 g/day has yielded conflicting results for stool weight. One study demonstrated significant increases in fecal weight compared to the control (150), whereas another study found no statistically significant differences in fecal wet and dry weight despite increases in fecal weight in 5 of the 6 subjects (145). A recent study of 21 healthy men found that a 21 g/day dose of PDX resulted in significant increases in 5 day fecal dry weight compared to the control (120). Interestingly this study found no difference in fecal wet weight, stool consistency, or ease of stool passage for the PDX compared to the control (120). Results from a study feeding 30 g PDX daily found approximately 33% of PDX in the fecal dry matter (145). Another study found increased self-reported stool volume at a daily dose of 15 g of PDX (151). No differences in WGTT have been found when feeding PDX (145,150).

The Vester-Boler study found no difference in stool pH and significantly lower concentrations of propionate, butyrate, and total SCFA compared to the control (120). They also reported reduced concentrations of harmful and putrefactive compounds like ammonia and branched chain fatty acids after PDX consumption (120). The Vester-Boler study also examined microbiota levels of *Bifidobacterium*, *Lactobacillus*, and

Escherichia coli. Increased, but non-significant levels of *Bifidobacterium* were reported, while no changes were seen for *Lactobacillus*, and *Escherichia coli* levels (120).

One side effect of PDX is flatulence, which is observed at doses as low as 10g/day (150). Also significant increases in self-reported diarrhea have been seen with PDX at a dose of 15 g/day (151). Mild, but significantly increased levels of self-reported flatulence and distension was found after 21 g of PDX per day (120).

Few studies have examined the effects of PDX on satiety. A study by King and associates found significant decrease in net energy intake between a 25 g dose of PDX and a control at an *ad libitum* lunch, whereas subjective hunger and fullness did not differ between PDX and the control (144). Willis also found no difference in subjective satiety between a dose of 9.5 g PDX and a low-fiber control (133). A study looked at the effects of a 190 kcal and 24 g PDX preload compared to an isoenergetic and low calorie preloads and found no difference in hunger, fullness, or desire to eat between PDX and the isoenergetic treatment (152). Furthermore, no difference was observed in energy intake at an *ad libitum* lunch between the PDX and isoenergetic or low calorie preloads (152). A recent study again examined the impact of 12 g of PDX compared to a low-fiber, isocaloric control and found no differences in subjective hunger, fullness, and desire to eat between the treatments (153). However, the same study observed a significant 100 kcal reduction in *ad libitum* lunch energy intake for the 12 g PDX treatment compared to the control (153). Overall, mixed results have been found in the few studies that have examined the effects of PDX on satiety energy intake; however further investigation is needed to make a well informed conclusion.

Soluble Corn Fiber

Soluble corn fiber (SCF) is produced from the hydrolysis of corn starch followed by random polymerization and has an average degree of polymerization of 10 (119). SCF consists of a mixture of α(1,4), α(1,6), α(1,2), and α(1,3) glycosidic linkages, with α(1,4) predominating (119,154). SCF is water soluble with a low viscosity that is considered GRAS, which make it easy to incorporate into various foods (155). Standard SCF contains >70% dietary fiber based on the AOAC 2001.03 method along with <20% simple sugars (155). The energy value of SCF is approximately 2 kcal/g (120).

An *in vitro* digestion model showed that SCF approximately 17% digestible by human digestive enzymes including pancreatic enzymes and amyloglucosidase in a method similar to the AOAC method 2002-02 (156). This study then subjected SCF to the TNO *in vitro* model of the proximal large intestine for 72 hours, which was designed to mimic the human proximal large intestine. This model showed that SCF is readily fermented by intestinal bacteria derived from 20 healthy donor consuming a Western diet and produced a SCFA ratio of acetate:propionate:butyrate of 60:17:23 (156). Also this study used a microarray chip to investigate any changes in the microbiota as a result of SCF fermentation. These preliminary microbiota results were inconclusive in regards to a potential prebiotic for SCF (156).

SCF also has been investigated using rat and mice models. The first study examined the potential relationship between SCF fermentation and increased calcium absorption and bone strength (155). Fifteen male Sprague-Dawley rats were assigned to the SCF group were fed AIN93 chow with 4% SCF and 1% cellulose and the control

group was fed the unaltered AIN93 chow. After the rats were sacrificed, cecal SCFA concentrations were determined and found acetate, propionate and, total SCFA were significantly higher to the control group (155). When looked at as a ratio SCFAs were 61:24:9 acetate, propionate, and butyrate respectively (155). When compared to the *in vitro* data, acetate levels were similar (61 v 60), propionate levels are higher (17 v 24), and butyrate levels were much lower (23 v 9) (155,156).

Overall, there are very few studies published in the literature on the gastrointestinal effects of SCF in humans. An early crossover study fed 20 healthy men and women SCF at a dose of 12 g/day then examined laxation, fecal chemistry, and gastrointestinal tolerance (119). This study found no differences after a four-day fecal collection on the number of stools, total stool weight, stool consistency, stool pH, or total SCFA concentration between SCF and the control treatment (119). This study also found significantly higher flatulence and stomach noises compared to the control (119). Another crossover study fed 21 g/day of SCF to 21 healthy men and examined effects on laxation, fecal chemistry, and gastrointestinal tolerance (120). This study found SCF caused a significant increase in fecal wet and dry weight compared to the control (120). Other laxation related outcomes stool consistency and ease of stool passage were not different from the control (120). No differences in acetate, propionate, butyrate, or total SCFA concentrations were found compared to the control; however, SCF significantly decreased stool pH (120). Similar to the Stewart study, this study found significantly higher flatulence on the SCF treatment compared to the control while all other tolerance questions were similar (120). Another study examined breath hydrogen and methane,

indicators of fermentation, after a 11 g dose of SCF and showed significantly higher hydrogen and methane 240 minutes after consumption (157). These findings combined with previous findings of increased flatulence show that SCF is rapidly fermented in the gut.

A unique finding of the Vester-Boler study was that *Bifidobacterium* levels significantly increased compared to the control, whereas no differences in *Lactobacillus* levels were observed in this study (120). These findings suggest a potential prebiotic effect of SCF, which requires further investigation. In all, the limited literature on SCF related to laxation and fecal chemistry show some inconsistencies that warrant further research along with the potential probiotic effect.

The literature on the effects of SCF on satiety and energy intake is sparse, but suggests SCF may have a significant effect on energy intake. A satiety study looked at the effects of a 190 kcal and 24 g SCF preload compared to an isocaloric and low calorie preloads. This study found no difference in hunger, fullness, or desire to eat between SCF and the isocaloric treatment (152). In contrast, the SCF preload caused a significant decrease in energy intake at an *ad libitum* lunch compared to the low calorie preload, but was not different from the isocaloric preload (152). Another satiety study examined the effects of 11 g SCF compared to a low fiber isocaloric control on satiety, *ad libitum* lunch intake, and 24 hour intake. This study found no differences in the AUC for the satiety perceptions, lunch intake, or 24 hour energy intake (157). Lastly, no differences in energy consumption between SCF and the control based on three-day food records (119).

In all, the results are mixed on whether or not SCF influences satiety and energy intake, however any reduction in energy intake is beneficial.

Other miscellaneous findings in humans regarding serum lipid, glucose, or hormone levels show nominal effects on these values. Studies feeding 12 g/d SCF or low-fiber placebo found no effect of SCF on fasting glucose, insulin, or ghrelin levels (119,158). Also no differences were observed in total triglycerides, total cholesterol, LDL cholesterol, or HDL cholesterol compared to the control (119).

Chapter 2: Polydextrose and soluble corn fiber increase fecal wet and influence fecal chemistry in healthy men and women.

Dietary fiber is a hot topic in the nutrition world and is being added to many commercially produced products. As a result, many new functional fibers are being developed with positive sensory properties. Two such fibers are polydextrose (PDX) and soluble corn fiber (SCF). We conducted a randomized, placebo-controlled crossover study on the laxative effects of PDX and SCF at a dose of 20 g/day compared to a low fiber control in 36 healthy men and women. Each treatment period was 10 days with a two week washout period. Subjects collected fecal samples during the last five days of each treatment and completed food diaries and gastrointestinal tolerance questionnaires on days 1, 2, and 10 of each treatment period. Five day fecal weight was significantly higher ($p < 0.0001$, $p = 0.0007$) for PDX and SCF compared to the control. Likewise, the number of stools and daily fecal output per day significantly increased on the PDX and SCF treatments. No differences were seen for whole gut transit time using radio-opaque pellets (ROM). PDX caused a significantly softer stool ($p = 0.0018$) than the SCF and control treatments. Fecal pH was significantly lowered ($p = 0.02$) by the PDX treatment, whereas SCF trended ($p = 0.07$) toward a lower pH compared to the control. Subjects consuming PDX and SCF reported mild, yet significantly higher flatulence and borborygmi compared to the control. PDX and SCF clearly show a laxative effect for these fibers with minimal gastrointestinal tolerance issues.

Introduction

Dietary fiber has several well-noted physiological effects including improved laxation, plasma glucose attenuation, and blood lipid reduction (4). Despite these benefits, the average dietary consumption remains low at approximately 12-18 g/day, substantially lower than the recommended levels of 25 g/day for women and 38 g/day for men (4). A possible way to reduce this gap is by incorporating functional fibers into commercially produced products. With many new functional fibers being developed, it is imperative to examine their physiological effects. Two such functional fibers are polydextrose (PDX) and soluble corn fiber (SCF), which are not broken down in the small intestine, but partial fermented in the colon (144,145,156). PDX is formed from random polymerization of glucose with sorbitol and citric acid with the predominate linkage being α-1,6 (144). SCF is produced from the hydrolysis of corn starch and consists of a mixture of α-1,4, α-1,6, α-1,2, and α-1,3 glycosidic linkages (119).

Laxation studies of novel fibers, including PDX and SCF are somewhat limited. Laxation is typically described as changes in stool weight, stool frequency, whole gut transit time (WGTT), or changes in fecal chemistry. Stool weight studies of PDX are conflicting with some show significantly increases while others show no difference (120,145,150,159). To date, no difference in WGTT was found with PDX compared to a control (145,150). Some studies find a significantly softer stool with consumption of PDX, whereas some results are conflicting (119,120,159). Little *in vivo* data are available on SCF, but it increases SCFA production *in vitro* (156). Only two crossover studies have been conducted on SCF to date and one found no differences after a four-

day fecal collection in the number of stools, total stool weight, stool pH, or total SCFA concentration (119). The other study found a significant increase in five-day fecal dry matter, a significant decrease in stool pH, but no difference in total SCFA concentration compared to a control (120). Both studies found significantly higher flatulence compared to the control (119,120).

Since relatively little research exists regarding the gastrointestinal effects these fibers; we designed a study to examine the laxative effects of PDX and SCF compared to a no fiber control. Laxation was examined by five day fecal wet weights, gastrointestinal transit time, and stool consistency. Fecal chemistry was investigated by fecal short chain fatty acids (SCFA) and pH. Additionally, a self-reported gastrointestinal tolerance questionnaire was used to measure flatulence, bloating, cramping, borborygmi, nausea, diarrhea, and constipation.

Methods

Subjects

Thirty-six subjects (18 males, 18 females) were recruited from the University of Minnesota by fliers posted on campus and screened by telephone. The participants were required to be age 18 or older, have a BMI between 18.5 and 30, be free of medication use, have no chronic diseases, and consume an approximately 15 grams of fiber per day. All subjects had to be free of antibiotic use for at least 3 months prior to study enrollment. Exclusion criteria included diagnosis of heart, liver, or kidney disease, diabetes, any gastrointestinal conditions, taking anti-diarrheal or constipation

medications, vegetarians, consumption of prebiotic or probiotic supplements, and non-breakfast eaters. Data on the subject population can be found in table 1.

Study Design

The study protocol was approved by the University of Minnesota Institutional Review Board and all subjects gave informed consent prior to beginning the study. Subjects were randomly assigned into a Williams designed double-blind, placebo-controlled cross-over study with six different treatment orders that balances for crossover effects. Each subject completed three treatment periods where they consumed either 20 g/day of PDX (STA-LITE® Polydextrose; Tate and Lyle Ingredients, Decatur, IL, USA), SCF (PROMITOR™ Soluble Corn Fiber; Tate & Lyle Ingredients, Decatur, IL, USA) or a no fiber control in the form of a breakfast cereal and a muffin. The cereal and muffins were formulated and produced by General Mills Inc. (Minneapolis, MN, USA) and matched for calories and macronutrient content. The nutritional information of the test products can be found in Table 2. The cereal and muffins were analyzed for total fat, protein, dietary fiber, and weight. Total dietary fiber was assessed along with soluble and insoluble fiber. Resistant oligosaccharides were determined according to the Association of Official Analytical Chemists methods. Carbohydrate was calculated by subtraction. Subjects consumed one packet of cereal and one muffin each day for the 10-day treatment period. A minimum of a 2-week washout period was completed between each treatment period.

Stool Collection and Analysis

Subjects maintained a stool diary during each treatment period. On the morning of the 6th day of each treatment period subjects swallowed a single dose of 20 radioopaque markers (ROM) and recorded the time at which this was done. The time at which the pellets were swallowed served as the baseline for transit time calculations. Participants then collected all their fecal samples over the next 5 days of each treatment period using a Commode Specimen Collection System (Sage Products, Crystal Lake, IL, USA). Each fecal sample was then placed on ice until it could be returned to our laboratory and frozen at -20°C. The fecal samples were weighed individually in a bag, the average weight of an empty bag was subtracted, and total 5 day stool weight calculated. Whole gut transit time (WGTT) was investigated by x raying each sample to observe the passage of the ROM pellets. The 80% transit time method of Hinton was used to calculate WGTT, where the time to pass 80% of ROM pellets approximates WGTT (25).

The final fecal sample of each treatment period was used for determination of stool consistency, pH, and SCFAs. The investigators assigned stool consistency using the Bristol stool consistency chart, which quantitatively assigns each stool a number based on comparison to the chart (49). Stool pH was assessed using an electrode pH meter (PerpHecT_ LogR_ meter model 350, Orion Research, Inc., Beverly, MA, USA). SCFA extraction was completed using diethyl either with ethyl butyrate serving as an internal standard as described earlier (119). SCFA concentrations were determined using a Hewlett-Packard 5890 Series gas chromatograph (Palo Alto, CA, USA) with Stabilwax-DA fused silica column (30m long; inner diameter, 0.52 mm; film thickness, 1 mm;

Restek, Bellefonte, PA, USA). Helium served as the carrier gas with a flow rate of 30 ml/min. The oven, injector, and detector temperatures were 110, 220 and 240°C respectively.

Gastrointestinal Tolerance

Subjects completed self-reported gastrointestinal tolerance survey on days 1, 2, and 10 of each treatment period. Each survey consisted of 7 questions regarding levels of flatulence, bloating, cramping, stomach noises, nausea, constipation, and diarrhea they experienced each day. Subjects ranked each symptom based on a 0-10 scale where 0 corresponds to no symptom and 10 correspond to the worst imaginable symptom. This scale was based on an earlier published study from our lab group (119). The sum of these 3 days was used to determine the tolerance of each treatment. In addition, we asked a quality of life question regarding how changes in bowel function may have influenced the subject's daily life ranging from not at all to always. This quality of life question was adapted from a longer validated bowel function instrument created for rectal cancer patients (160).

Dietary Intake

Participants completed food diaries on days 1, 2, and 10 of each treatment period. All caloric foods and beverages except test products were recorded and entered into Nutrition Data System for Research (NDSR, Minneapolis, MN). Total calories, protein, fat, carbohydrates, and dietary fiber of the background diet were averaged between the 3 days and compared between treatments.

Statistical Analysis

Differences between treatments were compared for all study endpoints using a mixed effects linear model by SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA). A general linear model was used for each outcome variable with a random intercept for each subject. This model was also used to examine period and carryover effects. Statistical significance was achieved at $p < 0.05$ and a p value between 0.01 and 0.05 was considered a trend.

Results

All thirty-six of the study participants finished the study and completed all of the study measurements. The background dietary information shows no differences between the treatment periods for dietary fat, protein, CHO, dietary fiber, or energy (Table 3). The background diet consisted of about 14 grams of dietary fiber per day with no differences between the treatment groups. Therefore, dietary fiber intake of the background diet is similar to a typical American diet and changes in fecal parameters can be attributed to the supplemental dietary fiber and not the background diet.

Stool weight for the PDX and SCF treatments was significantly higher compared to control period ($p <0.0001$, $p = 0.0007$) (Table 4). Likewise, the number of stools passed during the PDX and SCF periods was significantly higher than during the control period ($p < 0.0001$, $p = 0.0005$). However, significant treatment period interaction was observed for the number of stools ($p = 0.0052$). In contrast, no differences in the average weight per stool were observed between treatments. PDX had a significantly higher daily output compared to the control ($p = 0.02$); whereas SCF showed a trend of increased fecal output compared to the control ($p = 0.08$). Fecal wet weight increased compared to

control per gram of supplemental fiber during the 5 day collection period showed PDX increased fecal weight by 2.07 g/g and SCF produced an increase of 1.62 g/g.

All ROM pellets passed during the 5 day collection indicating excellent compliance to the study protocol. Despite this, we did not observe any difference in WGTT between the fiber treatments and the control (Table 4).

The stool consistency determined by the investigators based on the 7-point Bristol Stool Consistency Chart showed that PDX had a significantly softer stool ($p = 0.0018$) than both SCF and the control (Table 4). Additionally, fecal pH was significantly lower ($p = 0.02$) in the PDX treatment compared to the control, whereas SCF trended ($p = 0.07$) toward a lower pH compared to the control.

Total SCFA concentration was higher in the control than the PDX but the same as the SCF treatment (Table 5). SCF and control had higher acetate concentrations than PDX. Propionate concentrations were significantly different for all treatments with in the control being highest, followed by SCF, and PDX had the lowest concentration. The control had a significantly higher butyrate concentration than PDX, but was not different from SCF. When examined as ratios actate:proptionate:butyrate of the total the control treatment was (33.6:31.5:34.9), PDX was (33.8:32:34.2) and SCF was (35.3:30.9:33.8). SCF had a significantly higher acetate ratio than the control and tended to be higher than PDX. Propionate and butyrate ratios were not different between the treatments.

The subjective tolerance scores were all minimal, indicating that the fiber treatments were well-tolerated by the study participants (Table 6). Significant differences were observed with flatulence and stomach noises being higher for both treatments

compared to the control. All other questions showed no difference between the treatments.

Discussion

Although the laxative effects of fiber are generally accepted, few studies exist on the ability of novel fibers to affect laxation. No one indicator of laxation is accepted, but objective measures including stool weight and transit time are needed to determine if fibers improve laxation. Our study clearly shows laxative effects of both PDX and SCF. Five-day fecal weight and stool frequency was greater for both PDX and SCF compared to the control treatment. PDX and SCF were tolerated at a dose of 20 grams per day. This was in addition to the usual fiber intake of our subjects, suggesting that both SCF and PDX can be added to usual American diets and will increase stool weight without causing gastrointestinal tolerance issues.

Previous studies have found inconsistent results of PDX and SCF on stool weight, but these studies fed these fibers in doses of 8-12 g/day (119,159,161). The recent Vester-Boler study investigated the laxative effects of 21 g/day of PDX and SCF in adult men and found PDX and SCF increased fecal wet weight compared to the control (120). Interestingly they found a greater laxative effect of SCF than PDX, whereas we found no differences in stool weight between the fibers. It is worth noting that not all fibers affect stool weight equally. Cummings compared the increase in stool weight among different fibers and expressed results as grams of increase in stool weight per gram of fiber fed (15). Of course, these studies were conducted in different ways and fiber measured by different methods, so these values should be used as estimates. Still, large differences

were found among fibers. The laxative effects of some other common fibers such as wheat bran (~5.0-5.5 g wet weight/g), cellulose and cellulose derivatives (~3-4 g wet weight/g), psyllium (~3-4 g weight weight/g), pectin (~1-2 g wet weight/g) suggest that fibers that survive gut transit, i.e. wheat bran and cellulose, are more effective at increasing stool weight than fibers that are extensively broken down in the gut, i.e. pectin. We observed increases of 2.07 and 1.62 increases in fecal weight per gram of PDX and SCF respectively. The Vester-Boler study noted a similar trend, but with lesser increases of 1.4 and 0.9 fecal weight/g of PDX and SCF (120). Taken together our study and the Vester-Boler study clearly show laxative effects of PDX and SCF at a dose of 20 g/day.

PDX and SCF increased fecal output to 166 and 157 g/day compared to 125 g/day on the control treatment. This is a noteworthy finding since it has been observed that a stool output of greater than 150 g/day may reduce the incidence of colon cancer (11,162). Spiller has discussed the optimal stool weight and it is well known that populations consuming diets high in resistant carbohydrates have stool weights above 500 g/day (163).

We did not observe significant differences in WGTT in this study. Previous results in PDX and transit time are mixed with one study finding no change in transit time with 30 g/day (150); whereas another study found 8 g/day PDX decreased orofecal transit time; however this study used colored dyes to examine transit time (159). Changes in WGTT are most important when examined in the context of diarrhea (fast transit) or constipation (slow transit); however since we screened these populations out it may not be a surprise that we did not see a difference in transit time. Furthermore, in the absence

of a functional bowel disorder, changes in WGTT have little tangible benefit. It is worth noting that a faster WGTT is related to a higher stool weight is thought to be linked to a reduced chance of developing colon cancer due to decreased exposure of cytotoxic compounds to the colonic epithelial cells (11).

The fecal pH of PDX was significantly lower than the control treatment, which is an indicator of fermentation. SCF was similar to the control treatment in this study and has been noted in a previous study (119). In contrast, the Vester-Boler study found SCF to have a significantly lower pH compared to the control, whereas the PDX was similar to the control and SCF (120). A randomized non-crossover study of 120 Chinese men and women showed a dose response decrease is stool pH with doses of PDX of 0, 4, 8, and 12 grams (161). Therefore, it is difficult to establish a consistent trend between our study and the Vester-Boler study for PDX and SCF. Nonetheless, any decrease in fecal pH is important because a more acidic pH may inhibit the growth of some pathogenic bacteria including *Clostridium perfringens,* decrease conversion of bile acids to carcinogenic secondary bile acids, and may make minerals more soluble thereby increasing absorption (92,100).

A significantly softer fecal consistency for the PDX was observed in our study, with the SCF and control being similar. Other recent studies on PDX and SCF did not observe any differences in stool consistency compared to the control (119,120,164). It is worth noting that we used the 7 point Bristol stool consistency scale to determine the consistency, whereas the other studies used 4 or 5 point scales that may not have been as sensitive to changes in stool consistency as the 7 point scale we used.

The benefits of SCFAs on gut health are well-noted, especially the role of butyrate as an energy source for the colonocytes and cell proliferation and differentiation (77). Contrary to what we would expect, total SCFA concentration was significantly lower for PDX compared to the control while SCF was similar to both treatments. With the consumption of 20 grams of fermentable fiber, one would expect higher SCFA concentrations compared to a low fiber control; however it is possible that the increased fecal weight may have diluted the SCFA concentrations. Interestingly, a dilution effect has been suggested in other recent studies examining PDX and SCF (120,164). Also it should be noted that the majority of SCFA are produced in the proximal colon and approximately 95% of SCFA are absorbed soon after production; therefore, fecal SCFAs are more representative of distal colon concentrations rather than the proximal colon (92). Furthermore, the *in vitro* data on PDX shows it produces low SCFA concentrations compared to other fibers; therefore supporting our current findings (147,165).

Apart from looking at concentrations, ratios of SCFA are a useful way to compare SCFA across studies. Comparing our SCFA ratio results with previous studies shows a marked difference in the SCFA ratios. The Vester-Boler study found a higher acetate ratio and lower propionate and butyrate ratio for PDX and SCF of (68:18:15) and (67:19:15) respectively; whereas our results were (33.8:32:34.2) for PDX and (35.3:30.9:33.8) for SCF (120). Our SCFA ratios compare more favorably with an earlier study by our lab group that showed SCF had a ratio of (43:26:31) (119). These differences in ratios may be due to differences in gut microflora or extraction method. The Vester-Boler study extracted SCFA from the fecal dry matter, whereas our study and

the Stewart study extracted SCFA from the wet stool. This highlights the need for a standardized SCFA extraction method so that results can be compared among studies. Nonetheless, measurement of fecal SCFA is still important since there currently is not a better way to non-invasively measure them in humans.

The increase in flatulence on the fiber treatments is expected due to an increase in fermentable substrate in the colon. Although this increase in flatulence was statistically significant; the absolute level on the scale was still relatively mild with an average of 3 out of 10. Recent studies indicate that a significant increase in flatulence is common for both fibers (119,120,164). Likewise, the significant increase in stomach noises was relatively mild with an average of 1.25 and 1.3 on the PDX and SCF respectively. Overall, the PDX and SCF did have significant increases in tolerance symptoms; however no serious incidences were reported indicating that a split 20 gram dose of PDX and SCF is well tolerated.

Thus, both PDX and SCF increase stool weight in healthy subjects when the fibers are added to cereal and muffins. An increase in stool weight is accepted as a biomarker of improved laxation. The addition of these fibers to processed foods and beverages should improve bowel health.

Table 1. Subject Data (Mean values ± SD)

	Age	Height (in)	Weight (lb)	BMI
Total	25.8 ± 9.1	68.0 ± 3.4	153.4 ± 24.8	23.3 ± 2.9
Men	25.4 ± 8.7	70.4 ± 2.4	163.7 ± 20	23.1 ± 1.9
Women	26.2 ± 9.9	65.6 ± 2.3	143.2 ± 3.7	23.4 ± 3.7

Table 2. Nutritional Composition of Study Cereal and Muffin

Study Product	Serving size (g)	Fat (g)	Protein (g)	Sugar (g)	Soluble Fiber (g)	Insoluble Fiber (g)	RO	Total Fiber (g)	Energy (kcal)
Control Cereal	45	1.3	2.2	10.1	0.3	0.6	0.5	1.4	175
PDX Cereal	53	1.5	2	10	0.3	0.7	10.2	11.2	174
SCF Cereal	51	1.4	1.8	10.1	0.3	0.6	10.5	11.4	171
Control Muffin	79.1	4.8	3.6	12.6	0.6	1.2	0.5	2.3	191
PDX Muffin	89.8	4.8	3.6	12.5	0.9	1.3	9.5	11.7	186
SCF Muffin	86.8	4.9	3.6	12.7	0.8	1.2	9.7	11.7	188

*Diet records were analyzed using NDSR
*RO stands for Resistant Oligosaccharide

Table 3. Daily Food Intake from Three Day Food Diary (Mean ± SD)

	Control	PDX	SCF
Fat (g)	78.9 ± 45.2	76.4 ±35.4	76.8 ± 38.0
Protein (g)	81.6 ± 37.9	79.0 ± 30.6	77.5 ± 34.0
CHO (g)	222.1 ± 104.6	222.8 ± 93.7	212.7 ± 92.5
Soluble Fiber (g)	4.1 ± 2.5	4.3 ± 2.5	4.3 ± 2.3
Insoluble Fiber (g)	9.2 ± 5.9	9.0 ± 4.8	10.2 ± 7.0
Total Fiber (g)	13.5 ± 8.1	13.4 ± 6.9	14.6 ± 8.8
Energy (kcal)	1959 ± 907	1908 ± 668	1900 ± 720

* Data displayed as mean values ± SD within each row treatments with unlike letters are significantly different ($p < 0.05$)

Table 4. Stool Weight and Characteristics (Mean ± SD)

	Control	**PDX**	**SCF**
WGTT	52 ± 22	50 ± 23	56 ± 24
5 day fecal wet weight	623 ± 342[b]	830 ± 443[a]	785 ± 364[a]
Number of stools	4.4 ± 2.1[b]	5.5 ± 2.3[a]	5.3 ± 2.1[ab]
Fecal wet weigh/stool	150 ± 59	163 ± 73	155 ± 66
Stool wet weight/day	125.2 ± 68.1[b]	166.1 ± 88.7[a]	157.0 ± 73.0[ab]
Fecal Weight increase/ g fiber supplemented	-	2.07	1.62
Fecal pH	6.55 ± 0.36[b]	6.37 ± 0.39[a]	6.41 ± 0.50[ab]
Stool Consistency	3.86 ± 1.38[b]	4.64 ± 1.31[a]	3.89 ± 1.47[b]

* Data displayed as mean values ± SD within each row treatments with unlike letters are significantly different ($p < 0.05$)

Table 5. SCFA concentration in µmol/g stool wet weight (Mean ± SD)

	Control	PDX	SCF
Acetate	18.65 ± 4.79a	15.55 ± 4.92b	17.67 ± 5.34a
Propionate	17.50 ± 5.36a	14.68 ± 4.70c	15.48 ± 5.12b
Butyrate	19.37 ± 9.86a	15.70 ± 7.98b	16.95 ± 7.08ab
Total SCFA	55.52 ± 17.31a	45.93 ± 16.30b	50.09 ± 16.10ab

*Data displayed as mean values ± SD within each row treatments with unlike letters are significantly different ($p < 0.05$)

Table 6. Gastrointestinal Tolerance (Mean ± SD)

	Control	PDX	SCF
Flatulence	2.06 ± 1.81[b]	2.86 ± 1.89[a]	2.99 ± 1.96[a]
Bloating	1.19 ± 1.59	1.23 ± 1.17	1.12 ± 1.37
Cramping	0.49 ± 1.04	0.58 ± 0.95	0.74 ± 1.22
Borborygmi	0.74 ± 0.67[b]	1.25 ± 1.2[a]	1.30 ± 1.17[a]
Nausea	0.15 ± 0.45	0.08 ± 0.22	0.13 ± 0.41
Constipation	0.47 ± 1.10	0.34 ± 0.65	0.36 ± 0.70
Diarrhea	0.09 ± 0.27	0.24 ± 0.51	0.26 ± 0.67

*Data displayed as mean values ± SD within each row treatments with unlike letters are significantly different ($p < 0.05$)

Chapter 3 Assessment of acute satiety and food intake of polydextrose and soluble corn fiber in healthy adults.

High intakes of dietary fiber are associated with lower body weight and body fat. It is thought that this relationship exists since dietary fiber can enhance satiety and decrease energy intake. We conducted a randomized placebo-controlled crossover study to investigate the effects of the functional fibers polydextrose and soluble corn fiber on satiety and food intake. Thirty-six men and women consumed 10 grams of fiber or a low fiber control with 10 oz of 2% milk and completed 4 satiety related questions for 4 hours. After the acute visit, subjects consumed 20 grams of fiber per day or a low fiber control for 10 days while completing a food diary on 3 of those days. No differences in the 4 satiety related questions were observed between the PDX, SCF, and control treatments. Likewise, dietary intake from the food diaries showed no difference in energy intake between the treatments. In conclusion, PDX and SCF at a dose of 20 g/d do not affect acute satiety or energy intake in healthy humans.

Background

Dietary fiber is thought to influence satiety by three different mechanisms as suggested by Heaton (166). The first potential mechanism involves a decreased energy density since fiber displaces more energy dense nutrients. The second mechanism is the increased mastication and secretion of saliva that can expand the stomach and increase satiety. The third involves decreased or slowed absorption of nutrients in the small intestine that may alter hormone levels. In addition to potential mechanisms, it is has been observed that individuals with higher intakes of fiber has lower body weights and body fat (167-169). Many review articles also suggest that dietary fiber plays a role in satiety and weight management (129,170,171). Nonetheless, due the wide array of dietary fibers it is imperative to study each specific type of dietary for potential effects on satiety. Two novel fibers, which can be incorporated into commercial products to close the fiber gap are polydextrose (PDX) and soluble corn fiber (SCF). PDX is a soluble fiber formed from random polymerization of glucose with sorbitol and citric acid, with the predominate linkage being α-1,6 (144). SCF is a soluble fiber produced from the hydrolysis of corn starch and consists of a mixture of α-1,4, α-1,6, α-1,2, and α-1,3 glycosidic linkages (119). These fibers have shown promise as functional ingredients by promoting laxation and attenuating glycemic responses (144).

Unfortunately, the literature is sparse on the effects of PDX and SCF in regards to satiety and food intake. Several studies have examined PDX and have found conflicting results on its affects on satiety with some showing a significant effect (144), while others do not (120,133,152,153). However, despite no difference in subjective feelings of

satiety, some differences in energy intake have been noted (144,153). The effects of SCF on acute satiety have not been well-studied with only two studies examining SCF acutely. One study showed suppressed hunger, increased fullness, and decreased desire to eat for a 12 g/day dose of SCF compared to a low calorie control, but no differences to an isocaloric low fiber control (152). In contrast, a recent study found no difference in acute satiety between 11 grams of SCF and a low fiber control (157). Monsivais and colleagues found SCF decreased energy intake at an *ad libitum* lunch compared to a low energy control, but did not significantly decrease energy intake compared to the isocaloric low-fiber control (152). Three previous studies have examined energy intake by diet records after SCF consumption; however neither study saw a difference between the fiber and control treatments (119,120,157).

Overall, the literature on PDX and SCF is sparse and conflicting in regards to satiety and energy intake; therefore it is imperative to study the effects of each individual fiber. As a result, we conducted a clinical trial to examine the potential effect of the functional fibers PDX and SCF on satiety using the standardized visual analog scale (VAS) questions and measured food intake via food diaries.

Methods

Study Design

The study used a randomized crossover design with 2 week washout periods between 10-day treatment periods. Each subject completed three treatment periods where they consumed either 20 g/day of PDX (STA-LITE® Polydextrose; Tate and Lyle Ingredients, Decatur, IL, USA), SCF (PROMITOR™ Soluble Corn Fiber; Tate & Lyle

Ingredients, Decatur, IL, USA) or a no fiber control in the form of a breakfast cereal and a muffin. Subjects were instructed to consume one packet of cereal and one muffin each day for the 10-day treatment period. Three men and three women were randomly assigned to each of the six sequences for the three treatments, balancing any carryover effects.

Subjects

Thirty-six participants (18 men and 18 women) were recruited from the University of Minnesota community and screened via telephone. Inclusion criteria were as follows: age 18-65, weight stable, BMI 18.5-30, free of chronic diseases or significant medical history. Exclusion criteria included use of tobacco products, recent antibiotic use (<3 months), chronic diseases affecting metabolic processes, currently dieting, pregnant, lactating, or had irregular menstrual cycles, taking medications that influence gastrointestinal transit, vegetarian diet, consuming fiber supplements, prebiotics, or probiotics, breakfast non-consumer, and high-intensity athletes. Subjects were randomly assigned into a treatment order in the order, which they entered the study. Characteristics of the study participants can be found in **Table 1**. Informed consent was attained prior to beginning the study and the study protocol was approved by the Institutional Review Board at the University of Minnesota.

Study Protocol

Prior each study visit, subjects were instructed to fast for 12 hours and refrained from strenuous physical activity and alcohol. Women participated in the study during the follicular phase of their menstrual cycle (35). Subjects were required to participate in the

study at the same time for each study visit. Upon arriving for their study visit, height and weight recorded and adherence to the fasting protocol was confirmed. Acute satiety was assessed before and after a standard breakfast containing one packet of breakfast cereal and 10 oz of 2% milk. Subjects were given 10 minutes to consume the breakfast cereal and milk, which provided approximately 325 kcal and 10 grams of supplemental fiber. The nutritional composition of the cereal and muffins can be found in **Table 2**. A computerized 100 mm visual analog scale (VAS) was used to assess four validated satiety-related questions: How hungry do you feel? How satisfied do you feel? How full do you feel? How much do you think you can eat? These questions were asked at baseline, 15, 30, 45, 60, 90, 120, 180, and 240 minutes after consuming the standard breakfast and were previously validated (123). VAS ratings were quantified by measuring in millimeters the distance between the left end of the scale and the marked point. In between rating satiety, participants were held in a quiet room and permitted to read. A breath sample was taken for hydrogen analysis at baseline and 240 minutes. The following characteristics were used to assess the palatability of the cereal: visual appeal, smell, taste, aftertaste, and overall pleasantness at 30 minutes after consuming the cereal. Each palatability question was rated on a 100 mm line where 0 is good and 100 is bad, except aftertaste was rated the opposite with 0 being good and 100 being bad.

At the end of the each acute satiety visit, participants were given a 10 day supply of cereal and muffins and were instructed to consume a muffin later on day one and then one packet of cereal and one muffin on subsequent days. Subjects were required to

consume the test product, but were allowed to consume other foods and beverages in addition to the test products.

Breath Hydrogen Collection and Analysis

To determine breath hydrogen concentrations at baseline and 240 minutes, breath samples were analyzed using a Quintron model DP microlyzer (Quintron Instrument Company, Milwaukee, WI). After calibration, the concentration of hydrogen was analyzed by injecting 20 mL of expelled gas into the MicroLyzer. Each sample was analyzed in triplicate with the accuracy of the detector for a single sample being 3–4 ppm hydrogen.

Food Intake

Subjects recorded all the food and beverages they consumed on days 1, 2, and 10 of each treatment period. Food records were entered into Nutrition Data System for Research (NDSR, Minneapolis, MN). Total calories, protein, fat, carbohydrates, soluble fiber, insoluble fiber, and dietary fiber were averaged between the 3 days and compared between treatments.

Statistical Analysis

Subject demographic data is presented as mean ± SD. Treatments were compared using mixed-effects linear models with treatment and visit as fixed effects and with a random intercept for each subject to model correlation between repeated measurements from the same subject. For each outcome, equal carryover and treatment-visit interaction were checked by these mixed-effects models. The VAS responses were used to calculate the area under the curve (AUC) for each question using the trapezoidal rule then the

baseline level was subtracted from all subsequent responses. Statistical significance was achieved at $p < 0.05$ and a p value between 0.1 and 0.05 was considered a statistical trend. Data analysis was performed by SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Visual Analog Scale

No differences were seen for any of the four satiety questions at baseline in **Table 3**. The change from baseline AUC for hunger, satisfaction, fullness, and prospective food intake also did not differ between the treatments in **Figure 1**.

Food Intake

Dietary intake on days 1, 2, and 10 were pooled and averaged and can be found in **Table 4**. No differences ($p > 0.05$) in energy, protein, fat, carbohydrate, soluble fiber, insoluble fiber, and total fiber were seen among the treatments.

Palatability of Test Cereal

The analysis of palatability showed some variation between the treatments. No significant differences in visual appeal, aftertaste, and overall pleasantness were seen among treatments (data not shown). SCF had a significantly worse smell than PDX ($p = 0.01$) and tended to be worse than the control ($p = 0.07$). A statistical trend ($p = 0.06$) was identified between the PDX and SCF treatments for taste. Taken together the palatability rating may suggest a lower acceptability of SCF compared to PDX.

Breathe Hydrogen

No differences in breath hydrogen levels at baseline were observed and can be found in **Table 5**. Breath hydrogen levels were significantly higher at 240 minutes for

both fiber treatments compared to the control ($p < 0.05$). Furthermore, the absolute change from baseline showed significant increases in breath hydrogen for PDX and SCF compared to the control ($p < 0.05$).

Discussion

One commonly held belief is that dietary fibers reduce hunger and increase fullness. This notion is largely the result of observational and epidemiological studies that show people with high dietary fiber intakes tend to weigh less than those who have low fiber intakes (167-169). These studies generally clump all types of dietary fiber together, so it is especially important to examine the effect of novel dietary fibers with unique structures or properties on satiety. Fiber type and doses influence the effect of fiber on satiety. The literature shows that large doses of dietary fiber are needed to illicit differences in satiety cues. However such large doses of dietary fiber are not practical and can cause gastrointestinal discomfort. To date there is little information regarding the effects of PDX or SCF on satiety and food intake using practical doses in the literature.

PDX and SCF did not alter the sensations of hunger, satisfaction, fullness, or prospective food intake compared to control in the current study. Our results corroborate an earlier study that found 9.5 g of PDX in the form of a muffin did not increase the AUC of hunger, satisfaction, fullness, or prospective food intake compared to a low fiber control (133). Furthermore, PDX only decreased hunger below baseline for 15 minutes, whereas all other treatments including the control did so for at least 60 minutes indicating that PDX is not very satiating; unfortunately, this study did not measure *ad libitum* food intake so that a relationship with energy intake could be observed (133). Another study

found feeding 25 g of PDX resulted in no difference in hunger or fullness compared to a low fiber control treatment (144). PDX did result in a significant ($p = 0.002$) 9.9% reduction in energy intake at an *ad libitum* lunch compared to the control treatment (144). A third study examined the effects of a 17 g of PDX added to a smoothie compared to a low fiber control, after eating a standard breakfast, on satiety sensations and *ad libitum* lunch intake (153). This study found no difference between PDX and control for hunger, fullness, satisfaction, or desire to eat sensations (153). However, this study did observe a significant reduction in energy intake of approximately 100 kcal at an *ad libitum* lunch intake for PDX compared to the control (153). Similar to previous studies, a double preload design found no difference in mean VAS ratings for hunger, fullness, and desire to eat for 24 grams of PDX and SCF compared to a isoenergentic and low energy controls; however, it did find the SCF preloads resulted in a significantly lower energy intake at an *ad libitum* lunch compared to a low calorie preload, but not the isoenergic preload (152). Neither the PDX or SCF preloads reduced the energy intake at an a*d libitum* lunch compared to an isoenergetic control (152). Taken together, the current study and previous research shows a negligible effect of PDX or SCF on the appetite sensations however may reduce energy consumption as evidenced by decreased intake at *ad libitum* lunches. This may be due to a lack of attention to conscious hunger and fullness sensations, yet increased satiation in free living populations that is a potential explanation for the discrepancy between epidemiological weight data and acute satiety studies. This is supported by study conducted by Parnell and Reimer, which reported no differences in acute satiety ratings yet decreased energy intake during a 12 week

intervention of 21 g/day of fructooliogosaccharide in overweight subjects (172). Therefore, the lack of changes in satiety as a result of PDX and SCF may not be as important as once thought.

In the current study, we did not observe a difference in macronutrient intake of the background diet between any of the treatments based on diet records completed on days 1, 2, and 10. Two previous studies feeding PDX and SCF have taken diet records. Stewart and associates completed a crossover, placebo-controlled clinical trial that fed 12 g/day of SCF for 14 days and had subjects complete diet records on the last 3 days of each treatment period. This study found significantly increased levels of soluble and total fiber on the SCF treatment compared to the control, but this is only because the additional fiber from the test product is included in the comparison (119). If the 12 grams of SCF were removed from the diet records, the amount of total fiber would be almost identical (29g to 18g) for the SCF and control treatments (119). More recently Vester-Boler conducted a crossover study compared the effects of PDX and SCF fed 21 g/d to a low fiber control. This study had the subjects complete food diaries during the entire study and compared the average daily macronutrient intake. They found no differences in the amount of protein, fat, carbohydrate, or total dietary fiber between the treatments excluding the test products (120). Combining our results with the previous findings it is clear that PDX and SCF did not statistically reduce energy intake based on food diaries, however our study did show a non-significant decrease in caloric intake of 59 and 51 calories on the SCF and PDX treatments compared to the control. This decrease in

caloric intake on SCF and PDX, if this maintained over a long period of time, may aid in weight loss and/or maintenance.

Some research suggests the increased palatability of a meal may affect satiation compared to a less palatable meal (124); whereas others do not (173,174). Since palatability may play a role in satiety, we measured the visual appeal, smell, taste, aftertaste, and overall pleasantness 30 minutes after consumption of the test product and found a trend toward a better taste for the PDX cereal compared to the SCF cereal. Also we observed that the SCF had a worse smell than the PDX cereal. Little data exists on the palatability of SCF, but no direct comparisons are available in the literature; however an earlier study saw no difference in nausea between SCF and control (152). Studies show PDX incorporated into a muffin resulted in a significantly better taste compared to other muffins (133), whereas another study found that PDX incorporated into a smoothie didn't not significantly affect the taste or pleasantness compared to control (153). Likewise, 25 g PDX added to yogurt did not affect the taste of the product (144). Therefore, our study seems to corroborate the earlier studies that PDX is highly palatable and suggests SCF is equally palatable as a low fiber control.

Assessment of breath hydrogen is done as a proxy for fermentation in the gut since they are related. Also breath hydrogen is influenced by meals; therefore our results show no difference in baseline breath hydrogen levels point toward adherence to the 12 hour fast, in addition, to verbal conformation. We clearly showed an increase in breath hydrogen as a result of PDX and SCF over the 240 minute study period. Our results confirm earlier findings showing significantly increased breath hydrogen after PDX and

SCF consumption (149,157). Breath hydrogen is an indicator of gastrointestinal fermentation, which produces short-chain fatty acids (SCFA). Some researchers have hypothesized that a second meal affect may be modulated by SCFA (175). The mechanism for this effect involves the activation of the ileal brake, which delays GET, increases SBTT, reduces energy intake, and increases satiety (176). SCFAs in particular propionate and butyrate may play a role in satiety by triggering the release of peptide YY (PYY), a mediator of the ileal brake. The SCFA receptors FFA2 and FFA3 are found in the colon near the same enteroendocrine L-cells as the ileal brake (177-179). Investigation into the activation of these SCFA receptors showed increased PYY concentrations in the blood after administration of SCFA in rat, rabbit, and pig models (180-182). Several studies have investigated the potential satiety-inducing mechanism of SCFA and have found increases in satiety sensations following orally-delivered acetate and propionate (183-187). It is thought that the decreased palatability of the orally given SCFA probably cause the increased satiety. A recent review has examined the relationship between SCFAs and satiety and concluded that no significant relationship exists between the two (188). Nonetheless, this remains an area of active research and could ultimately prove to be an important modulator of appetite.

One limitation of our study is that we did not measure food intake an *ad libitum* lunch; however we did have subjects record their dietary intake for the rest of the first day. Another drawback is that we only measure satiety once at the beginning of the study. Additionally, in an effort to reduce participant burden only a 3-day food diary was recorded instead of during the entire study. Despite the drawbacks of the study our

findings are relatively consistent with the limited published data regarding PDX and SCF and satiety and food intake. In conclusion, the current study does not support PDX and SCF as inducing satiety and reducing food intake; however further research should be conducted to confirm this observation.

Table 1. Subject Characteristics

	N	Age	Height (in)	Weight (lb)	BMI
Total	36	25.8 ± 9.1	68.0 ± 3.4	153.4 ± 24.8	23.3 ± 2.9
Men	18	25.4 ± 8.7	70.4 ± 2.4	163.7 ± 20	23.1 ± 1.9
Women	18	26.2 ± 9.9	65.6 ± 2.3	143.2 ± 3.7	23.4 ± 3.7

*Values are means ± SD.

Table 2. Nutritional composition of study cereal and muffin[a]

Study Product	Serving size (g)	Fat (g)	Protein (g)	Sugar (g)	Soluble TDF[b] (g)	Insoluble TDF (g)	RO[c] (g)	TDF + RO[d] (g)	Energy (kcal)
Control Cereal	45	1.3	2.2	10.1	0.3	0.6	0.5	1.4	175
PDX Cereal	53	1.5	2	10	0.3	0.7	10.2	11.2	174
SCF Cereal	51	1.4	1.8	10.1	0.3	0.6	10.5	11.4	171
Control Muffin	79.1	4.8	3.6	12.6	0.6	1.2	0.5	2.3	191
PDX Muffin	89.8	4.8	3.6	12.5	0.9	1.3	9.5	11.7	186
SCF Muffin	86.8	4.9	3.6	12.7	0.8	1.2	9.7	11.7	188

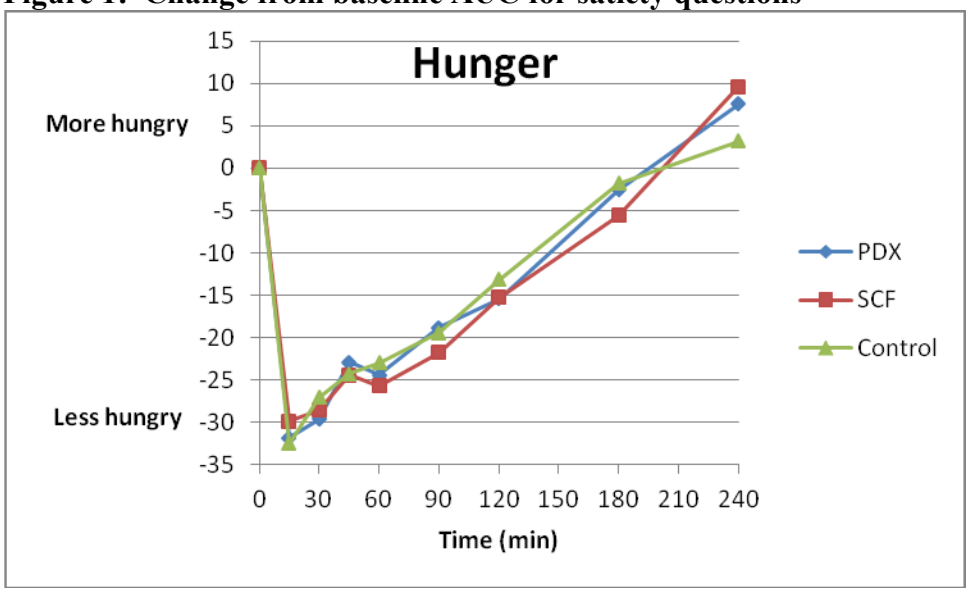
[a] Values listed are means of analytics after product preparation.
[b] TDF, total dietary fiber.
[c] RO, Resistant Oligosaccharide.
[d] TDF and RO was analyzed by AOAC method 2001.03.

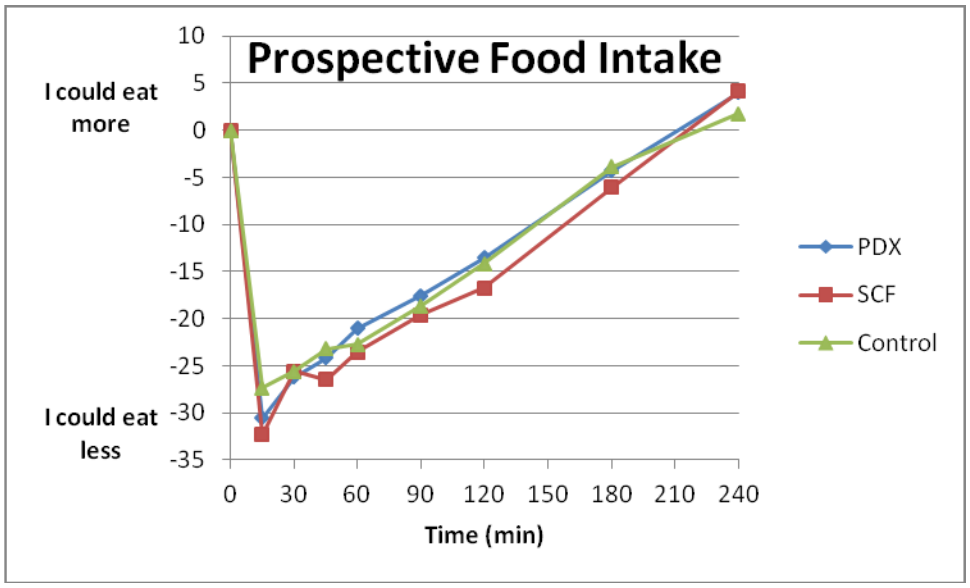
Table 3: Baseline Satiety

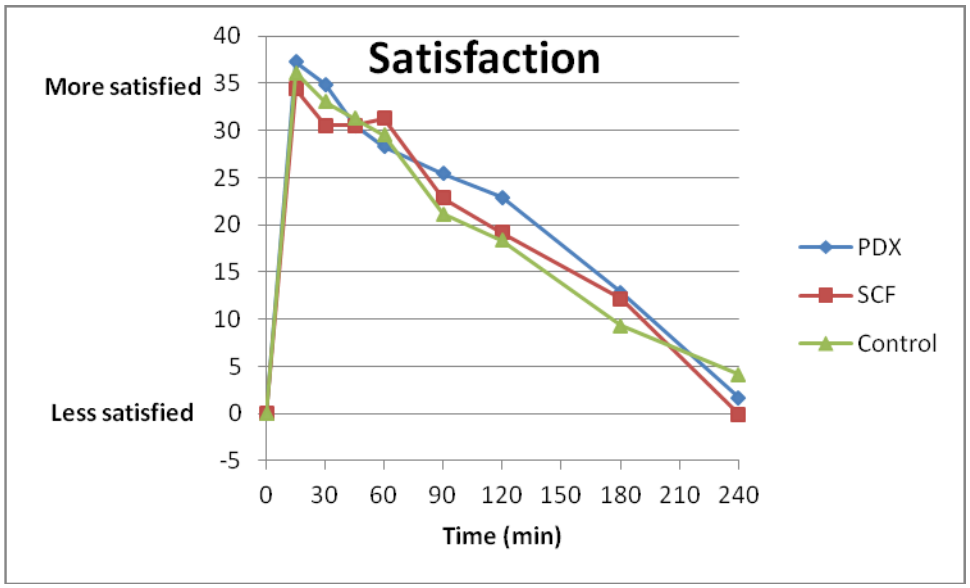
Treatment	Hunger (mm)	Satisfaction (mm)	Fullness (mm)	Prospective Food Intake (mm)
PDX	66.8 ± 3.3	20.9 ± 2.4	15.5 ± 2.5	72.0 ± 2.8
SCF	68.3 ± 3.3	18.5 ± 2.4	16.4 ± 2.5	75.6 ± 2.8
Control	68.5 ± 3.3	19.4 ± 2.4	16.5 ± 2.5	74.1 ± 2.8

***** Data are means values ± SEM. Within each row, treatments with no letters in common are significantly different ($p < 0.05$).

Figure 1: Change from baseline AUC for satiety questions






Satisfaction
More satisfied
Less satisfied
40
35
30
25
20
15
10
5
0
-5
0 30 60 90 120 150 180 210 240
Time (min)
PDX
SCF
Control

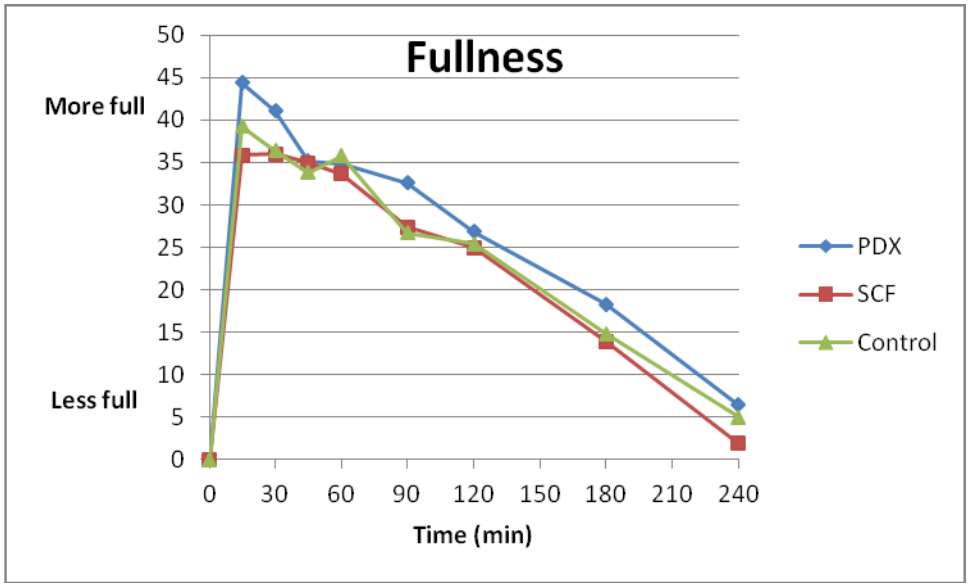

Fullness
More full
Less full
50
45
40
35
30
25
20
15
10
5
0
0 30 60 90 120 150 180 210 240
Time (min)
PDX
SCF
Control

Table 4. Daily Food Intake from Three Day Food Diary

Nutrient	Control	PDX	SCF
Fat (g)	78.9 ± 45.2	76.4 ±35.4	76.8 ± 38.0
Protein (g)	81.6 ± 37.9	79.0 ± 30.6	77.5 ± 34.0
CHO (g)	222.1 ± 104.6	222.8 ± 93.7	212.7 ± 92.5
Soluble Fiber (g)	4.1 ± 2.5	4.3 ± 2.5	4.3 ± 2.3
Insoluble Fiber (g)	9.2 ± 5.9	9.0 ± 4.8	10.2 ± 7.0
Total Fiber (g)	13.5 ± 8.1	13.4 ± 6.9	14.6 ± 8.8
Energy (kcal)	1959 ± 907	1908 ± 668	1900 ± 720

* Data displayed as mean values ± SD. Within each row, treatments with no letters in common are significantly different ($p < 0.05$).

Table 5: Breath hydrogen concentration (ppm)

Treatment	Baseline	240 Minutes	Difference
Polydextrose	8.2 ± 8.2	16.0 ± 13.1a	7.8 ± 13.9a
Soluble Corn Fiber	9.6 ± 10.9	15.7 ± 13.8a	6.1 ± 17.4a
Control	8.2 ± 6.5	9.1 ± 10.6b	0.9 ± 10.5

* Data displayed as mean values ± SD. Within each row, treatments with no letters in common are significantly different ($p < 0.05$).

Chapter 4: The use of a wireless motility device (SmartPill®) for measurement of gastrointestinal transit time after dietary fiber intervention, as published in the British Journal of Nutrition

Title The use of a wireless motility device (SmartPill®) for measurement of gastrointestinal transit time after dietary fiber intervention

Authors Derek Timm[1], Holly Willis[1], William Thomas[2], Lisa Sanders[3], Thomas Boileau[4], Joanne Slavin[1]

[1] University of Minnesota, Department of Food Science and Nutrition, St. Paul, MN 55108

[2] University of Minnesota, Division of Biostatistics, School of Public Health, Minneapolis, MN 55414

[3] Tate & Lyle Health & Nutrition Sciences, Decatur, IL 62521

[4] General Mills Inc, Minneapolis, MN 55427

Although it is generally accepted that one of the beneficial health effects of dietary fiber is decreasing gastrointestinal transit time, few recent studies have measured transit time with diet intervention. Historically, measurement of gastrointestinal transit time has required collection and x-raying of fecal samples for up to 7 days after swallowing radio-opaque markers (ROM); a tedious, labor-intensive technique for both subjects and investigators. Recently, a wireless motility capsule (SmartPill®) capable of measuring gut pH, pressure, and temperature in real time was developed. The SmartPill® device is able to measure gastric emptying time by pH change and whole gut transit time by temperature change. Intestinal transit time is the difference between whole gut transit time and gastric emptying time. This device, however, has not been validated with dietary interventions. Therefore, we conducted a crossover trial to determine if the device could detect a significant difference in gastric emptying, intestinal, and whole gut transit time after subjects consumed 9 grams of wheat bran (WB) or an equal volume, low-fiber control for three days. This dose of WB has previously been shown to decrease whole gut transit time using traditional methods. In this study, ten healthy subjects (5 men, 5 women) swallowed the SmartPill® after consuming a standard breakfast with or without 10 grams of WB. A paired t-test was used to determine differences in transit times. Colonic transit time decreased by 10.8 hours ($p = 0.0062$) on the WB treatment. Whole gut transit time also decreased by 8.9 hours ($p=0.0243$) after consumption of the WB. This decrease was due entirely to changes in colonic transit time as gastric emptying time and small bowel transit time did not differ between the treatments. In addition, no differences were observed between

genders. Results show, with minimal participant burden, the SmartPill technology appears to be a useful tool for assessing transit time after dietary intervention. In conclusion, WB significantly reduces transit time and the SmartPill technology shows promise for digestive studies with novel fibers and other ingredients that are promoted for gut health.

Introduction

Traditional methods for determining gastrointestinal transit time are cumbersome and labor-intensive both for subjects and investigators. The two most commonly used methods are radio-opaque markers (ROM) and scintigraphy. ROM can be used to determine gastric emptying time (GET), colonic transit time (CTT), or whole gut transit time (WGTT). Measurement of GET or CTT is achieved through use of abdominal x-rays; whereas WGTT is measured by collecting and x-raying fecal samples for 5 to 7 days (25,27). The ROM WGTT methodology involves a large amount of participant burden and requires exceptional compliance because missing stool samples affects results.

Measurement of GET or CTT by scintigraphy requires consumption of radioactive isotopes followed by frequent x-rays of the participant's abdomen (189). Scintigraphy has been used in a number of studies; but results of these studies have been mired by no universally accepted method (189). Recently, a multicenter study designed to standardize the GET scintigraphic method was able to find similar gastric retention between each center (32). Whole gut scintigraphy can be used to determine GET, small bowel transit time (SBTT), CTT, and WGTT; however, this method requires the subject to undergo frequent abdominal scans and requires a 3-day stay in an inpatient facility (190). Another disadvantage of scintigraphic methods is that the results must be examined by a gastroenterologist and are subject to interpretation errors (189). Nonetheless, these methods are acceptable measures of gastrointestinal transit time.

Recently a wireless motility device called the SmartPill was developed that simplifies the determination of GET, SBTT, CTT, and WGTT. The SmartPill is a cylindrical capsule with dimensions of 26.8 mm long by 11.7 mm in diameter, which measures pH, pressure, and temperature in real time. Subjects swallow the SmartPill, after consuming a standard meal; data is then wirelessly transmitted to a data receiver that is attached to the participant's clothing. The pH sensor has a range of 0.5 - 9 units with accuracy ± 0.5 units. The pressure sensor has a range of 0 - 350 mmHg with accuracy of 5 mmHg below 100 mmHg and 10% at or above 100 mmHg. The temperature sensor has a range of 25-49°C with an accuracy of ± 1°C. The data measured by the SmartPill device can be used to determine GET, SBTT, CTT, and WGTT.

Previous studies have compared gastrointestinal transit time using the SmartPill technology to ROM and scintigraphy (191-195). These studies show favorable correlations between scintigraphy gastric retention and SmartPill GET at 120 minutes ($r = 0.95$; $p < 0.01$) and 240 minutes ($r = 0.70$; $p = 0.024$) (194,195). Scintigraphic meals exit the stomach prior to the SmartPill capsule because indigestible objects empty the stomach with the phase 3 migrating motor complex, initiated in the fasting state; thereby making direct comparisons of GET between the two methods impractical (191). On the other hand, SBTT was found to be different between scintigraphy and SmartPill while WGTT was found to be similiar (194). ROM and SmartPill correlate well for CTT and WGTT in healthy and constipated individuals (192). Overall, this series of studies show favorable comparisons between the SmartPill and the traditional methodologies.

The purpose of this study was to determine if the SmartPill technology is able to detect a significant difference in transit time between a low-fiber and high-fiber treatment in a healthy population.

Methods

Ten healthy subjects aged 18 to 65 were recruited from the University of Minnesota community by fliers posted on campus. Subjects were screened via telephone to determine eligibility. Exclusion criteria included contraindicated conditions for the SmartPill: dysphasia, gastric bezoar, strictures, fistulas, bowel obstructions, diverticulitis, previous gastrointestinal surgery, implanted electro-mechanical medical devices, and medications shown to influence gastrointestinal transit time. Exclusion criteria also includes diagnosis of cardiovascular disease, diabetes, cancer, Crohns disease, ulcerative colitis, irritable bowel disease, BMI of <18.5 or >30, pregnant or lactating, irregular menstrual cycle, smoke or chew tobacco, high dietary fiber intake, consumption of probiotics or fiber supplements, vegetarian diet, taken antibiotics less than 3 months earlier, and food allergies to the test products.

Descriptive data of the study participants can be found in **Table 1.**

Gastrointestinal transit time was measured on two separate occasions in each of the subjects. Subjects consumed a modified breakfast of earlier SmartPill studies, which included 120g of Egg Beaters®, and either a low-fiber hot cereal or a high-fiber hot cereal with 250 ml of water (191-195). The high fiber hot cereal contained wheat bran as the primary fiber component and was utilized due to the extensive literature on wheat bran's influence on transit time. The serving sizes and volume of the meals were the

same; however, the control (low fiber) breakfast had 250 kcals while the test (high fiber) breakfast had 215 kcals. **Table 2** describes the nutrient composition of the breakfast. The control cereal consisted of 52 grams of Cream of Wheat® (B&G Foods, Inc.) providing 2 grams of dietary fiber. The test cereal consisted of 30 grams of Cream of Wheat® and 22 grams of course-ground red WB (SunOpta, Inc. Brampton, Ontario, Canada) that provided 11 grams of dietary fiber; a dose previously shown to significantly decrease WGTT using ROM (196).

The MotiliGI software (SmartPill, Inc, Buffalo, NY) was used to determine GET, SBTT, CTT, and WGTT based on pH and temperature changes. GET is defined as the time between capsule ingestion and an abrupt rise in pH above gastric baseline pH. This rise in pH corresponds with the transition from the acidic stomach to the alkaline duodenum (197). SBTT is the time between duodenum entry and cecum entry (192-194). Cecal entry is defined as the first sustained drop in pH of more than 1 unit that occurs at least 30 minutes after entry into the small bowel (192). The decrease in pH is thought to be the result of fermentation of digestive residue by the large intestine (192,197,198). CTT is the difference between entry into the cecum and exit from the body, which is indicated by an abrupt decrease in temperature (192). WGTT is the time between the SmartPill ingestion and exit from the body.

Dietary Intake Analysis

Twenty-four hour food diaries were analyzed using the dietary analysis program, Nutrition Data System for Research (NDSR, version 2007, Nutrition Coordinating

Center, Minneapolis, MN). NDSR provided detailed nutrient information including: total energy, carbohydrate, fat, protein, and fiber intake.

Study Protocol

Participants consumed one serving of either the control or the WB cereal for 3 days prior to each study visit. During this time, subjects also completed one 24-hour food diary prior to each treatment; this was done in order to quantify usual dietary habits, specifically dietary fiber intake. Participants completed the control treatment first followed by the WB treatment. Women participated in the study during the follicular phase of their menstrual cycles. On the morning of each study visit, subjects arrived after fasting for 12 hours. They consumed a standard breakfast consisting of 1 cup of Egg Beaters® eggs, test cereal, and ½ cup of water. This is a departure from the standardized meals in previous SmartPill studies because the test cereal replaced two pieces of toast and jelly (192). Subjects were given 10 minutes to consume the breakfast and immediately afterwards swallowed the SmartPill capsule. The SmartPill was activated and calibrated prior to swallowing as described elsewhere (194). After swallowing the capsule, the subjects were allowed to resume normal activities, with the exception of strenuous physical activity and alcohol consumption. Subjects were instructed to refrain from eating for 6 hours in order to determine GET. The test cereals were consumed once a day in the morning until the capsule passed. In addition, subjects were instructed to complete a gastrointestinal tolerance survey the day the SmartPill was swallowed. The tolerance survey was adapted from a previous study and investigated flatulence, bloating, abdominal cramps, stomach noises, nausea, diarrhea, and constipation using a 10-point

scale with 0 being no symptom and 10 being the worst imaginable symptom (119). When subjects had a bowel movement they were instructed to allow the stool to remain in the toilet for 5 minutes allowing the capsule to detect a temperature decrease or visually confirm the SmartPill had passed.

Data Analysis

Data was analyzed using SAS 9.1 (SAS Institute, Cary, NC). A paired t-test procedure was used to determine differences in transit times and dietary intake. Statistical significance was achieved at $p < 0.05$.

Results

All 10 subjects completed both treatments and transit times are shown in **Table 3**. The WB treatment significantly decreased CTT ($p = 0.0062$) and WGTT ($p = 0.0243$) compared to the control, however it had no effect on GET ($p = 0.23$) or SBTT ($p = 0.83$). We conclude that the -8.9 h decrease in WGTT is due to decreased CTT (-10.8 h) since GET (+0.6 h) and SBTT (-0.1 h) did not change. A comparison of the current study with previous crossover studies that examined WGTT with a WB intervention using ROM can be found in **Table 4**. Men and women had similar GET ($p = .0817$), SBTT ($p = 0.5197$), CTT ($p = 0.0965$), and WGTT ($p = 0.0948$).

Mean dietary intake not including the test cereals is shown in **Table 5.** There was no difference in background total fiber intake between the control and WB treatment ($p > 0.60$). In contrast, women had a significantly higher total fiber intake ($p = 0.03$), but did not have different transit times compared to men. Total calories and the percentage of

calories from carbohydrate and fat were similar between treatments; however protein intake was higher ($p = 0.0099$) on the WB treatment.

Tolerance

There were no adverse events reported as a result of consuming the cereals or swallowing the SmartPill. There were no differences in gastrointestinal tolerance between the control and WB treatment with the exception of significantly higher flatulence with the WB treatment, ($p = 0.03$).

Discussion

Recent SmartPill studies have been conducted primarily for the purposes of comparing gastrointestinal transit times between the wireless device and other methods such as ROM or scintigraphy (191,192,194,195). Additional studies have used the SmartPill for evaluating transit times in individuals with various motility disorders including gastroparesis and constipation (192,193,199,200). Our study was the first to use the SmartPill technology for determination of gastrointestinal transit time with a dietary fiber intervention.

Our results show the SmartPill technology is able to detect a significant decrease in CTT and WGTT after a high-fiber intervention. These results were not confounded by usual dietary fiber intake between treatments and were clearly a result of the intervention. The ability to detect significant decreases in CTT and WGTT demonstrates the utility of the SmartPill technology in dietary intervention studies

The SmartPill did not detect differences in either GET or SBTT in our study. Our results are inconsistent with an earlier study showing 15 g of WB significantly delays

GET and reduces SBTT (201). However, this study had an older population than our study (60 years versus 25 years) and used scintigraphy. GET was defined as 50% gastric retention of the radio-labeled meal while SBTT was defined as the difference between GET and 50% colonic arrival of the radio-labeled meal. Therefore, due to different definitions of GET and SBTT, direct comparisons may not be appropriate. Moreover, the SmartPill empties the stomach with the phase 3 migrating motor complex, which is initiated during the fasting state (191). Subjects are allowed to resume eating 6 hours after swallowing the SmartPill; therefore, if GET is longer than 6 hours, a subsequent meal would skew GET by a returning the subject to the fed state. Our results suggest WB does not affect SBTT; however different fibers with different physiochemical properties may influence SBTT.

Earlier research examined the effect of gender on transit time and yielded conflicting results (36,40,42-46,202). Generally women have longer transit times compared to men (36,42-46). Additional research has examined the influence of the phase of the menstrual cycle on transit time. The majority of research has found no difference between the follicular phase and luteal phase (26,34,36,37,202); however some do (35). A previous study using the SmartPill found women have significantly longer CTT compared to men; however this study did not control for menstrual cycle (192). Due to the inconsistencies in the literature, we decided to control for menstrual cycle in this study by having women complete both study visits during the follicular phase. Since subjects consumed the low-fiber control treatment first, there was no need for washout

period before starting the WB treatment. In contrast to the previous findings, we did not observe any differences in transit times between men and women.

Since this study is the first of its kind, we wanted to determine how the SmartPill passes through the gastrointestinal tract when consuming a low-fiber hot cereal since the substitution of the bread and jam for hot cereal was a deviation from previous SmartPill studies. Therefore, subjects completed the control and then the WB treatment. The lack of randomization is a limitation of this study. Another limitation is the relatively small sample size of this study. However, the ability to detect significant differences in CTT ($p = 0.0062$) in such a sample demonstrates the sensitivity of this new technology and strength of the treatment effect.

While the SmartPill is promising for diet intervention studies due to its ease of use and sensitivity, there are certain limitations that may have an impact on future studies. The SmartPill capsule is relatively large at 13 mm x 26 mm making it not suitable for people with swallowing problems. Also, the data receiver must be kept within 5 feet of the subject at all times and failure to do so results in missing data. The battery life of the data receiver is only 5 days and after the battery runs low the data is no longer considered reliable. Lastly, the data receiver is generally worn on the belt and is therefore sensitive to physical damage. However, none of our subjects reported problems with these limitations.

Overall, the capacity to non-invasively measure GET, SBTT, CTT, and WGTT gives the SmartPill an advantage over both ROM and scintigraphy. Using the SmartPill eliminates the need for subjects to: consume radio-labeled meal, have repeated x-rays,

and collect fecal samples. This is clearly less burdensome for both subjects and investigators. In conclusion, the ability to detect significant differences in CTT and WGTT after a dietary intervention makes the SmartPill technology a useful new tool for measuring gastrointestinal transit; however, further research should confirm the findings of this study.

Table 1. Study Participant Data

	All (n = 10)	Males (n = 5)	Females (n = 5)
Age (years)	24.5 (20 – 32)	24.2 (20 – 32)	24.8 (23 – 29)
BMI (kg/m^2)	26 (22 – 29.5)	27.1 (23.6 – 29.5)	24.9 (22 – 27.5)

Table 2. Composition of Breakfast Components

Cereal	**Serving (g)**	**Energy (kcal)**	**Carbohydrate (g)**	**Dietary Fiber (g)**	**Protein (g)**	**Fat (g)**
Control Cereal (Cream of Wheat®)	52	190	40	2	4	0
Test Cereal (30 g Cream of Wheat® + 22 g red WB)	52	154	39	11	6	1
Egg Beaters®	120	60	2	0	12	0

Table 3. Mean Transit Times in Hours ± SEM

	Control	**WB**	**Difference**	**P value of Difference**
GET (n = 8)*	3.2 ± 0.4	3.8 ± 0.3	0.6	0.2337
SBTT (n = 10)	4.9 ± 0.4	4.8 ± 0.4	-0.1	0.8313
CTT (n = 10)	23.1 ± 2.1	12.7 ± 2.1	-10.8	0.0062
WGTT (n = 8)*	31.4 ± 2.2	22.5 ± 2.2	-8.9	0.0243

* Two subjects were excluded from analysis of GET and WGTT due to extremely delayed GET

Table 4. Previous Crossover Studies Measuring WGTT after WB Treatment using ROM

Study	**Population**	**Intervention**	**WGTT ± SEM**
Cummings 1978	5 healthy men	Control 20 g WB	73 ± 11 h 43 ± 4 h
Stevens 1988	12 healthy women	Control 23 g WB	70 ± 6 h 47 ± 3 h
Vuksan 1999	24 healthy subjects	Control 21 g WB	31 ± 3 h 32 ± 3 h
Muir 2004	20 healthy subjects	Control 12 g WB	48 ± 4 h 37 ± 2 h
Current Study	10 healthy subjects	Control 9 g WB	31 ± 2 h 23 ± 2 h

Table 5. Mean Dietary Intake

	Control	**WB**	**P value of Difference**
Soluble Fiber	5 ± 0.4 g	4 ± 0.4 g	0.30
Insoluble Fiber	11 ± 2 g	9 ± 2 g	0.42
Total Fiber	15 ± 1.5 g	14 ± 1.5 g	0.44
% Carbohydrate	43.4 ± 2.1 %	42.4 ± 2.1 %	0.7435
% Protein	15.2 ± 0.87 %	19.2 ± 0.87 %	0.0099
% Fat	38.6 ± 2.26 %	36.0 ± 2.26 %	0.4372
Total Kcal	1904 ± 190 Kcal	1668 ± 190 Kcal	0.13

Works Cited

(1) Hipsley EH. Dietary "fibre" and pregnancy toxaemia. Br Med J 1953 Aug 22;2(4833):420-422.

(2) Trowell H. Crude fibre, dietary fibre and atherosclerosis. Atherosclerosis 1972 Jul-Aug;16(1):138-140.

(3) American Association of Cereal Chemists. The Definition of Dietary Fiber. CFW 2001;46(3):112-126.

(4) Institute of Medicine. Dietary, Functional, and Total Fiber. Dietary Reference Intakes For Energy, Carbohydrate,Fiber,Fat,Fatty Acids,Cholesterol,Protein, and Amino Acids. 2005th ed. Washington, DC: The National Acedemies Press; 2005. p. 339-421.

(5) Jensen MK, Koh-Banerjee P, Hu FB, Franz M, Sampson L, Gronbaek M, et al. Intakes of whole grains, bran, and germ and the risk of coronary heart disease in men. Am J Clin Nutr 2004 Dec;80(6):1492-1499.

(6) Lin J, Zhang SM, Cook NR, Rexrode KM, Liu S, Manson JE, et al. Dietary intakes of fruit, vegetables, and fiber, and risk of colorectal cancer in a prospective cohort of women (United States). Cancer Causes Control 2005 Apr;16(3):225-233.

(7) Schatzkin A, Mouw T, Park Y, Subar AF, Kipnis V, Hollenbeck A, et al. Dietary fiber and whole-grain consumption in relation to colorectal cancer in the NIH-AARP Diet and Health Study. Am J Clin Nutr 2007 May;85(5):1353-1360.

(8) McCullough ML, Robertson AS, Chao A, Jacobs EJ, Stampfer MJ, Jacobs DR, et al. A prospective study of whole grains, fruits, vegetables and colon cancer risk. Cancer Causes Control 2003 Dec;14(10):959-970.

(9) Lederle FA, Busch DL, Mattox KM, West MJ, Aske DM. Cost-effective treatment of constipation in the elderly: a randomized double-blind comparison of sorbitol and lactulose. Am J Med 1990 Nov;89(5):597-601.

(10) McRorie J, Zorich N, Riccardi K, Bishop L, Filloon T, Wason S, et al. Effects of olestra and sorbitol consumption on objective measures of diarrhea: impact of stool viscosity on common gastrointestinal symptoms. Regul Toxicol Pharmacol 2000 Feb;31(1):59-67.

(11) Cummings JH, Bingham SA, Heaton KW, Eastwood MA. Fecal weight, colon cancer risk, and dietary intake of nonstarch polysaccharides (dietary fiber). Gastroenterology 1992 Dec;103(6):1783-1789.

(12) Cummings JH. The effect of dietary fiber on fecal weight and composition. In: Spiller GA, editor. CRC Handbook of Dietary Fiber in Human Nutrition. 2nd ed. Boca Raton, FL: CRC Press; 1993. p. 263-349.

(13) Marlett JA, Kajs TM, Fischer MH. An unfermented gel component of psyllium seed husk promotes laxation as a lubricant in humans. Am J Clin Nutr 2000 Sep;72(3):784-789.

(14) Marlett JA, Fischer MH. A poorly fermented gel from psyllium seed husk increases excreta moisture and bile acid excretion in rats. J Nutr 2002 Sep;132(9):2638-2643.

(15) Cummings JH. The Effect of Dietary Fiber on Fecal Weight and Composition. CRC Handbook of Dietary Fiber in Human Nutrition. 2nd ed. Boca Raton, FL: CRC Press; 1993. p. 263-315.

(16) Lewis SJ, Heaton KW. The intestinal effects of bran-like plastic particles: is the concept of 'roughage' valid after all? Eur J Gastroenterol Hepatol 1997 Jun;9(6):553-557.

(17) Stephen AM, Cummings JH. Water-holding by dietary fibre in vitro and its relationship to faecal output in man. Gut 1979 Aug;20(8):722-729.

(18) Eastwood MA, Robertson JA, Brydon WG, MacDonald D. Measurement of water-holding properties of fibre and their faecal bulking ability in man. Br J Nutr 1983 Nov;50(3):539-547.

(19) Marlett JA, Kajs TM, Fischer MH. An unfermented gel component of psyllium seed husk promotes laxation as a lubricant in humans. Am J Clin Nutr 2000 Sep;72(3):784-789.

(20) Marteau P, Flourie B, Cherbut C, Correze JL, Pellier P, Seylaz J, et al. Digestibility and bulking effect of ispaghula husks in healthy humans. Gut 1994 Dec;35(12):1747-1752.

(21) Lewis SJ, Heaton KW. Roughage revisited: the effect on intestinal function of inert plastic particles of different sizes and shape. Dig Dis Sci 1999 Apr;44(4):744-748.

(22) Sharon N. The bacterial cell wall. Sci Am 1969 May;220(5):92-98.

(23) Chen HL, Haack VS, Janecky CW, Vollendorf NW, Marlett JA. Mechanisms by which wheat bran and oat bran increase stool weight in humans. Am J Clin Nutr 1998 Sep;68(3):711-719.

(24) Stephen AM, Cummings JH. The microbial contribution to human faecal mass. J Med Microbiol 1980 Feb;13(1):45-56.

(25) Hinton JM, Lennard-Jones JE, Young AC. A ne method for studying gut transit times using radioopaque markers. Gut 1969 Oct;10(10):842-847.

(26) Wyman JB, Heaton KW, Manning AP, Wicks AC. Variability of colonic function in healthy subjects. Gut 1978 Feb;19(2):146-150.

(27) Cummings JH, Jenkins DJ, Wiggins HS. Measurement of the mean transit time of dietary residue through the human gut. Gut 1976 Mar;17(3):210-218.

(28) Marlett JA, Slavin JL, Brauer PM. Comparison of dye and pellet gastrointestinal transit time during controlled diets differing in protein and fiber levels. Dig Dis Sci 1981 Mar;26(3):208-213.

(29) Stevens J, VanSoest PJ, Robertson JB, Levitsky DA. Comparison of the effects of psyllium and wheat bran on gastrointestinal transit time and stool characteristics. J Am Diet Assoc 1988 Mar;88(3):323-326.

(30) Parkman HP. Assessment of gastric emptying and small-bowel motility: scintigraphy, breath tests, manometry, and SmartPill. Gastrointest Endosc Clin N Am 2009 Jan;19(1):49-55, vi.

(31) van der Sijp JR, Kamm MA, Nightingale JM, Britton KE, Mather SJ, Morris GP, et al. Radioisotope determination of regional colonic transit in severe constipation: comparison with radio opaque markers. Gut 1993 Mar;34(3):402-408.

(32) Tougas G, Chen Y, Coates G, Paterson W, Dallaire C, Pare P, et al. Standardization of a simplified scintigraphic methodology for the assessment of gastric emptying in a multicenter setting. Am J Gastroenterol 2000 Jan;95(1):78-86.

(33) Lundin E, Graf W, Garske U, Nilsson S, Maripuu E, Karlbom U. Segmental colonic transit studies: comparison of a radiological and a scintigraphic method. Colorectal Dis 2007 May;9(4):344-351.

(34) Horowitz M, Maddern GJ, Chatterton BE, Collins PJ, Petrucco OM, Seamark R, et al. The normal menstrual cycle has no effect on gastric emptying. Br J Obstet Gynaecol 1985 Jul;92(7):743-746.

(35) Brennan IM, Feltrin KL, Nair NS, Hausken T, Little TJ, Gentilcore D, et al. Effects of the phases of the menstrual cycle on gastric emptying, glycemia, plasma GLP-1 and insulin, and energy intake in healthy lean women. Am J Physiol Gastrointest Liver Physiol 2009 Sep;297(3):G602-10.

(36) Degen LP, Phillips SF. Variability of gastrointestinal transit in healthy women and men. Gut 1996 Aug;39(2):299-305.

(37) Kamm MA, Farthing MJ, Lennard-Jones JE. Bowel function and transit rate during the menstrual cycle. Gut 1989 May;30(5):605-608.

(38) Jung HK, Kim DY, Moon IH. Effects of gender and menstrual cycle on colonic transit time in healthy subjects. Korean J Intern Med 2003 Sep;18(3):181-186.

(39) Davies GJ, Crowder M, Reid B, Dickerson JW. Bowel function measurements of individuals with different eating patterns. Gut 1986 Feb;27(2):164-169.

(40) Madsen JL. Effects of gender, age, and body mass index on gastrointestinal transit times. Dig Dis Sci 1992 Oct;37(10):1548-1553.

(41) Degen LP, Phillips SF. Variability of gastrointestinal transit in healthy women and men. Gut 1996 Aug;39(2):299-305.

(42) Graff J, Brinch K, Madsen JL. Gastrointestinal mean transit times in young and middle-aged healthy subjects. Clin Physiol 2001 Mar;21(2):253-259.

(43) Sadik R, Abrahamsson H, Stotzer PO. Gender differences in gut transit shown with a newly developed radiological procedure. Scand J Gastroenterol 2003 Jan;38(1):36-42.

(44) Abrahamsson H, Antov S, Bosaeus I. Gastrointestinal and colonic segmental transit time evaluated by a single abdominal x-ray in healthy subjects and constipated patients. Scand J Gastroenterol Suppl 1988;152:72-80.

(45) Lampe JW, Fredstrom SB, Slavin JL, Potter JD. Sex differences in colonic function: a randomised trial. Gut 1993 Apr;34(4):531-536.

(46) Stephen AM, Wiggins HS, Englyst HN, Cole TJ, Wayman BJ, Cummings JH. The effect of age, sex and level of intake of dietary fibre from wheat on large-bowel function in thirty healthy subjects. Br J Nutr 1986 Sep;56(2):349-361.

(47) Oettle GJ. Effect of moderate exercise on bowel habit. Gut 1991 Aug;32(8):941-944.

(48) Robertson G, Meshkinpour H, Vandenberg K, James N, Cohen A, Wilson A. Effects of exercise on total and segmental colon transit. J Clin Gastroenterol 1993 Jun;16(4):300-303.

(49) Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997 Sep;32(9):920-924.

(50) Wenzl HH, Fine KD, Schiller LR, Fordtran JS. Determinants of decreased fecal consistency in patients with diarrhea. Gastroenterology 1995 Jun;108(6):1729-1738.

(51) Degen LP, Phillips SF. How well does stool form reflect colonic transit? Gut 1996 Jul;39(1):109-113.

(52) Whelan K, Judd PA, Taylor MA. Assessment of fecal output in patients receiving enteral tube feeding: validation of a novel chart. Eur J Clin Nutr 2004 Jul;58(7):1030-1037.

(53) Eastwood MA, Kirkpatrick JR, Mitchell WD, Bone A, Hamilton T. Effects of dietary supplements of wheat bran and cellulose on faeces and bowel function. Br Med J 1973 Nov 17;4(5889):392-394.

(54) Payler DK, Pomare EW, Heaton KW, Harvey RF. The effect of wheat bran on intestinal transit. Gut 1975 Mar;16(3):209-213.

(55) Cummings JH, Hill MJ, Jenkins DJ, Pearson JR, Wiggins HS. Changes in fecal composition and colonic function due to cereal fiber. Am J Clin Nutr 1976 Dec;29(12):1468-1473.

(56) Cummings JH, Branch W, Jenkins DJ, Southgate DA, Houston H, James WP. Colonic response to dietary fibre from carrot, cabbage, apple, bran. Lancet 1978 Jan 7;1(8054):5-9.

(57) Van Dokkum W, Pikaar NA, Thissen JT. Physiological effects of fibre-rich types of bread. 2. Dietary fibre from bread: digestibility by the intestinal microflora and water-holding capacity in the colon of human subjects. Br J Nutr 1983 Jul;50(1):61-74.

(58) Vuksan V, Jenkins DJ, Vidgen E, Ransom TP, Ng MK, Culhane CT, et al. A novel source of wheat fiber and protein: effects on fecal bulk and serum lipids. Am J Clin Nutr 1999 Feb;69(2):226-230.

(59) Stasse-Wolthuis M, Hautvast JG, Hermus RJ, Katan MB, Bausch JE, Rietberg-Brussaard JH, et al. The effect of a natural high-fiber diet on serum lipids, fecal lipids, and colonic function. Am J Clin Nutr 1979 Sep;32(9):1881-1888.

(60) Stasse-Wolthuis M, Albers HF, van Jeveren JG, Wil de Jong J, Hautvast JG, Hermus RJ, et al. Influence of dietary fiber from vegetables and fruits, bran or citrus pectin on serum lipids, fecal lipids, and colonic function. Am J Clin Nutr 1980 Aug;33(8):1745-1756.

(61) Jenkins DJ, Kendall CW, Vuksan V, Augustin LS, Li YM, Lee B, et al. The effect of wheat bran particle size on laxation and colonic fermentation. J Am Coll Nutr 1999 Aug;18(4):339-345.

(62) Ventura M, Turroni F, Canchaya C, Vaughan EE, O'Toole PW, van Sinderen D. Microbial diversity in the human intestine and novel insights from metagenomics. Front Biosci 2009 Jan 1;14:3214-3221.

(63) Furrie E. A molecular revolution in the study of intestinal microflora. Gut 2006 Feb;55(2):141-143.

(64) Gill SR, Pop M, Deboy RT, Eckburg PB, Turnbaugh PJ, Samuel BS, et al. Metagenomic analysis of the human distal gut microbiome. Science 2006 Jun 2;312(5778):1355-1359.

(65) Ley RE, Backhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. Proc Natl Acad Sci U S A 2005 Aug 2;102(31):11070-11075.

(66) Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. PLoS Biol 2007 Jul;5(7):e177.

(67) Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, et al. Diversity of the human intestinal microbial flora. Science 2005 Jun 10;308(5728):1635-1638.

(68) DiBaise JK, Zhang H, Crowell MD, Krajmalnik-Brown R, Decker GA, Rittmann BE. Gut microbiota and its possible relationship with obesity. Mayo Clin Proc 2008 Apr;83(4):460-469.

(69) Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr 1995 Jun;125(6):1401-1412.

(70) Guarner F, Schaafsma GJ. Probiotics. Int J Food Microbiol 1998 Feb 17;39(3):237-238.

(71) Fotiadis CI, Stoidis CN, Spyropoulos BG, Zografos ED. Role of probiotics, prebiotics and synbiotics in chemoprevention for colorectal cancer. World J Gastroenterol 2008 Nov 14;14(42):6453-6457.

(72) Swennen K, Courtin CM, Delcour JA. Non-digestible oligosaccharides with prebiotic properties. Crit Rev Food Sci Nutr 2006;46(6):459-471.

(73) Cummings JH, Pomare EW, Branch WJ, Naylor CP, Macfarlane GT. Short chain fatty acids in human large intestine, portal, hepatic and venous blood. Gut 1987 Oct;28(10):1221-1227.

(74) Zhao G, Liu JF, Nyman M, Jonsson JA. Determination of short-chain fatty acids in serum by hollow fiber supported liquid membrane extraction coupled with gas chromatography. J Chromatogr B Analyt Technol Biomed Life Sci 2007 Feb 1;846(1-2):202-208.

(75) Livesey G. Energy values of unavailable carbohydrate and diets: an inquiry and analysis. Am J Clin Nutr 1990 Apr;51(4):617-637.

(76) Argenzio RA, Southworth M. Sites of organic acid production and absorption in gastrointestinal tract of the pig. Am J Physiol 1975 Feb;228(2):454-460.

(77) Wong JM, de Souza R, Kendall CW, Emam A, Jenkins DJ. Colonic health: fermentation and short chain fatty acids. J Clin Gastroenterol 2006 Mar;40(3):235-243.

(78) Macfarlane GT, Gibson GR. Carbohydrate fermentation, energy transduction and gas metabolism in the human large intestine. In: Mackie RI, White BA, editors. Ecology and physiology of gastrointestinal microbes New York, N.Y: Chapman & Hall; 1996. p. 269-318.

(79) Binder HJ, Mehta P. Short-chain fatty acids stimulate active sodium and chloride absorption in vitro in the rat distal colon. Gastroenterology 1989 Apr;96(4):989-996.

(80) Charney AN, Micic L, Egnor RW. Nonionic diffusion of short-chain fatty acids across rat colon. Am J Physiol 1998 Mar;274(3 Pt 1):G518-24.

(81) Ruppin H, Bar-Meir S, Soergel KH, Wood CM, Schmitt MG,Jr. Absorption of short-chain fatty acids by the colon. Gastroenterology 1980 Jun;78(6):1500-1507.

(82) Thangaraju M, Cresci G, Itagaki S, Mellinger J, Browning DD, Berger FG, et al. Sodium-coupled transport of the short chain fatty acid butyrate by SLC5A8 and its relevance to colon cancer. J Gastrointest Surg 2008 Oct;12(10):1773-81; discussion 1781-2.

(83) Vidyasagar S, Barmeyer C, Geibel J, Binder HJ, Rajendran VM. Role of short-chain fatty acids in colonic HCO(3) secretion. Am J Physiol Gastrointest Liver Physiol 2005 Jun;288(6):G1217-26.

(84) Hara H, Haga S, Aoyama Y, Kiriyama S. Short-chain fatty acids suppress cholesterol synthesis in rat liver and intestine. J Nutr 1999 May;129(5):942-948.

(85) Chen WJ, Anderson JW, Jennings D. Propionate may mediate the hypocholesterolemic effects of certain soluble plant fibers in cholesterol-fed rats. Proc Soc Exp Biol Med 1984 Feb;175(2):215-218.

(86) Venter CS, Vorster HH, Cummings JH. Effects of dietary propionate on carbohydrate and lipid metabolism in healthy volunteers. Am J Gastroenterol 1990 May;85(5):549-553.

(87) Nishina PM, Freedland RA. Effects of propionate on lipid biosynthesis in isolated rat hepatocytes. J Nutr 1990 Jul;120(7):668-673.

(88) Nishina PM, Freedland RA. The effects of dietary fiber feeding on cholesterol metabolism in rats. J Nutr 1990 Jul;120(7):800-805.

(89) Alvaro A, Sola R, Rosales R, Ribalta J, Anguera A, Masana L, et al. Gene expression analysis of a human enterocyte cell line reveals downregulation of cholesterol biosynthesis in response to short-chain fatty acids. IUBMB Life 2008 Nov;60(11):757-764.

(90) Duncan SH, Louis P, Flint HJ. Lactate-utilizing bacteria, isolated from human feces, that produce butyrate as a major fermentation product. Appl Environ Microbiol 2004 Oct;70(10):5810-5817.

(91) Roediger WE. Utilization of nutrients by isolated epithelial cells of the rat colon. Gastroenterology 1982 Aug;83(2):424-429.

(92) Topping DL, Clifton PM. Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. Physiol Rev 2001 Jul;81(3):1031-1064.

(93) Hague A, Elder DJ, Hicks DJ, Paraskeva C. Apoptosis in colorectal tumour cells: induction by the short chain fatty acids butyrate, propionate and acetate and by the bile salt deoxycholate. Int J Cancer 1995 Jan 27;60(3):400-406.

(94) Jacobsen H, Poulsen M, Dragsted LO, Ravn-Haren G, Meyer O, Lindecrona RH. Carbohydrate digestibility predicts colon carcinogenesis in azoxymethane-treated rats. Nutr Cancer 2006;55(2):163-170.

(95) Moore J, Babidge W, Millard S, Roediger W. Colonic luminal hydrogen sulfide is not elevated in ulcerative colitis. Dig Dis Sci 1998 Jan;43(1):162-165.

(96) Mortensen FV, Langkilde NC, Joergensen JC, Hessov I. Short-chain fatty acids stimulate mucosal cell proliferation in the closed human rectum after Hartmann's procedure. Int J Colorectal Dis 1999 Aug;14(3):150-154.

(97) Heerdt BG, Houston MA, Augenlicht LH. Potentiation by specific short-chain fatty acids of differentiation and apoptosis in human colonic carcinoma cell lines. Cancer Res 1994 Jun 15;54(12):3288-3293.

(98) Lupton JR, Kurtz PP. Relationship of colonic luminal short-chain fatty acids and pH to in vivo cell proliferation in rats. J Nutr 1993 Sep;123(9):1522-1530.

(99) McOrist AL, Abell GC, Cooke C, Nyland K. Bacterial population dynamics and faecal short-chain fatty acid (SCFA) concentrations in healthy humans. Br J Nutr 2008 Jul;100(1):138-146.

(100) Thornton JR. High colonic pH promotes colorectal cancer. Lancet 1981 May 16;1(8229):1081-1083.

(101) Chinda D, Nakaji S, Fukuda S, Sakamoto J, Shimoyama T, Nakamura T, et al. The fermentation of different dietary fibers is associated with fecal clostridia levels in men. J Nutr 2004 Aug;134(8):1881-1886.

(102) Cloarec D, Bornet F, Gouilloud S, Barry JL, Salim B, Galmiche JP. Breath hydrogen response to lactulose in healthy subjects: relationship to methane producing status. Gut 1990 Mar;31(3):300-304.

(103) Schneider AR, Jepp K, Murczynski L, Biniek U, Stein J. The inulin hydrogen breath test accurately reflects orocaecal transit time. Eur J Clin Invest 2007 Oct;37(10):802-807.

(104) Gibson GR, Macfarlane GT, Cummings JH. Sulphate reducing bacteria and hydrogen metabolism in the human large intestine. Gut 1993 Apr;34(4):437-439.

(105) Lajoie SF, Bank S, Miller TL, Wolin MJ. Acetate production from hydrogen and [13C]carbon dioxide by the microflora of human feces. Appl Environ Microbiol 1988 Nov;54(11):2723-2727.

(106) Weaver GA, Krause JA, Miller TL, Wolin MJ. Incidence of methanogenic bacteria in a sigmoidoscopy population: an association of methanogenic bacteria and diverticulosis. Gut 1986 Jun;27(6):698-704.

(107) Miller TL, Wolin MJ. Methanosphaera stadtmaniae gen. nov., sp. nov.: a species that forms methane by reducing methanol with hydrogen. Arch Microbiol 1985 Mar;141(2):116-122.

(108) Segal I, Walker AR, Lord S, Cummings JH. Breath methane and large bowel cancer risk in contrasting African populations. Gut 1988 May;29(5):608-613.

(109) Strocchi A, Furne JK, Ellis CJ, Levitt MD. Competition for hydrogen by human faecal bacteria: evidence for the predominance of methane producing bacteria. Gut 1991 Dec;32(12):1498-1501.

(110) Strocchi A, Furne J, Ellis C, Levitt MD. Methanogens outcompete sulphate reducing bacteria for H2 in the human colon. Gut 1994 Aug;35(8):1098-1101.

(111) Attene-Ramos MS, Wagner ED, Plewa MJ, Gaskins HR. Evidence that hydrogen sulfide is a genotoxic agent. Mol Cancer Res 2006 Jan;4(1):9-14.

(112) Attene-Ramos MS, Wagner ED, Gaskins HR, Plewa MJ. Hydrogen sulfide induces direct radical-associated DNA damage. Mol Cancer Res 2007 May;5(5):455-459.

(113) Gibson GR, Cummings JH, Macfarlane GT, Allison C, Segal I, Vorster HH, et al. Alternative pathways for hydrogen disposal during fermentation in the human colon. Gut 1990 Jun;31(6):679-683.

(114) Levitt MD. Volume and composition of human intestinal gas determined by means of an intestinal washout technic. N Engl J Med 1971 Jun 24;284(25):1394-1398.

(115) Serra J, Azpiroz F, Malagelada JR. Intestinal gas dynamics and tolerance in humans. Gastroenterology 1998 Sep;115(3):542-550.

(116) Serra J, Azpiroz F, Malagelada JR. Impaired transit and tolerance of intestinal gas in the irritable bowel syndrome. Gut 2001 Jan;48(1):14-19.

(117) Passos MC, Serra J, Azpiroz F, Tremolaterra F, Malagelada JR. Impaired reflex control of intestinal gas transit in patients with abdominal bloating. Gut 2005 Mar;54(3):344-348.

(118) Harder H, Serra J, Azpiroz F, Passos MC, Aguade S, Malagelada JR. Intestinal gas distribution determines abdominal symptoms. Gut 2003 Dec;52(12):1708-1713.

(119) Stewart ML, Nikhanj SD, Timm DA, Thomas W, Slavin JL. Evaluation of the effect of four fibers on laxation, gastrointestinal tolerance and serum markers in healthy humans. Ann Nutr Metab 2010;56(2):91-98.

(120) Vester Boler BM, Rossoni Serao MC, Bauer LL, Staeger MA, Boileau TW, Swanson KS, et al. Digestive physiological outcomes related to polydextrose and soluble maize fibre consumption by healthy adult men. Br J Nutr 2011 May 31:1-8.

(121) Blundell J, de Graaf C, Hulshof T, Jebb S, Livingstone B, Lluch A, et al. Appetite control: methodological aspects of the evaluation of foods. Obes Rev 2010 Mar;11(3):251-270.

(122) Merrill EP, Kramer FM, Cardello A, Schutz H. A comparison of satiety measures. Appetite 2002 Oct;39(2):181-183.

(123) Flint A, Raben A, Blundell JE, Astrup A. Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. Int J Obes Relat Metab Disord 2000 Jan;24(1):38-48.

(124) De Graaf C, De Jong LS, Lambers AC. Palatability affects satiation but not satiety. Physiol Behav 1999 Jun;66(4):681-688.

(125) Stubbs RJ, Hughes DA, Johnstone AM, Rowley E, Ferris S, Elia M, et al. Description and evaluation of a Newton-based electronic appetite rating system for temporal tracking of appetite in human subjects. Physiol Behav 2001 Mar;72(4):615-619.

(126) Stratton RJ, Stubbs RJ, Hughes D, King N, Blundell JE, Elia M. Comparison of the traditional paper visual analogue scale questionnaire with an Apple Newton electronic appetite rating system (EARS) in free living subjects feeding ad libitum. Eur J Clin Nutr 1998 Oct;52(10):737-741.

(127) Whybrow S, Stephen JR, Stubbs RJ. The evaluation of an electronic visual analogue scale system for appetite and mood. Eur J Clin Nutr 2006 Apr;60(4):558-560.

(128) Zabel R, Ash S, Bauer J, King N. Assessment of subjective appetite sensations in hemodialysis patients. Agreement and feasibility between traditional paper and pen and a novel electronic appetite rating system. Appetite 2009 Apr;52(2):525-527.

(129) Pereira MA, Ludwig DS. Dietary fiber and body-weight regulation. Observations and mechanisms. Pediatr Clin North Am 2001 Aug;48(4):969-980.

(130) Mathern JR, Raatz SK, Thomas W, Slavin JL. Effect of Fenugreek Fiber on Satiety, Blood Glucose and Insulin Response and Energy Intake in Obese Subjects. Phytother Res 2009 Apr 7.

(131) Chow J, Choe YS, Noss MJ, Robinson KJ, Dugle JE, Acosta SH, et al. Effect of a viscous fiber-containing nutrition bar on satiety of patients with type 2 diabetes. Diabetes Res Clin Pract 2007 Jun;76(3):335-340.

(132) Cani PD, Joly E, Horsmans Y, Delzenne NM. Oligofructose promotes satiety in healthy human: a pilot study. Eur J Clin Nutr 2006 May;60(5):567-572.

(133) Willis HJ, Eldridge AL, Beiseigel J, Thomas W, Slavin JL. Greater satiety response with resistant starch and corn bran in human subjects. Nutr Res 2009 Feb;29(2):100-105.

(134) Samra RA, Anderson GH. Insoluble cereal fiber reduces appetite and short-term food intake and glycemic response to food consumed 75 min later by healthy men. Am J Clin Nutr 2007 Oct;86(4):972-979.

(135) Willis HJ, Thomas W, Willis DJ, Slavin JL. Feasibility of measuring gastric emptying time, with a wireless motility device, after subjects consume fiber-matched liquid and solid breakfasts. Appetite 2011 Aug;57(1):38-44.

(136) Willis HJ, Thomas W, Eldridge AL, Harkness L, Green H, Slavin JL. Increasing doses of fiber do not influence short-term satiety or food intake and are inconsistently linked to gut hormone levels. Food Nutr Res 2010 Jun 29;54:10.3402/fnr.v54i0.5135.

(137) Peters HP, Boers HM, Haddeman E, Melnikov SM, Qvyjt F. No effect of added beta-glucan or of fructooligosaccharide on appetite or energy intake. Am J Clin Nutr 2009 Jan;89(1):58-63.

(138) Mattes RD. Effects of a combination fiber system on appetite and energy intake in overweight humans. Physiol Behav 2007 Apr 23;90(5):705-711.

(139) Keogh JB, Lau CW, Noakes M, Bowen J, Clifton PM. Effects of meals with high soluble fibre, high amylose barley variant on glucose, insulin, satiety and thermic effect of food in healthy lean women. Eur J Clin Nutr 2007 May;61(5):597-604.

(140) Pasman WJ, Saris WH, Wauters MA, Westerterp-Plantenga MS. Effect of one week of fibre supplementation on hunger and satiety ratings and energy intake. Appetite 1997 Aug;29(1):77-87.

(141) Hamedani A, Akhavan T, Samra RA, Anderson GH. Reduced energy intake at breakfast is not compensated for at lunch if a high-insoluble-fiber cereal replaces a low-fiber cereal. Am J Clin Nutr 2009 May;89(5):1343-1349.

(142) Freeland KR, Anderson GH, Wolever TM. Acute effects of dietary fibre and glycaemic carbohydrate on appetite and food intake in healthy males. Appetite 2009 Feb;52(1):58-64.

(143) Auerbach MH, Craig SA, Howlett JF, Hayes KC. Caloric availability of polydextrose. Nutr Rev 2007 Dec;65(12 Pt 1):544-549.

(144) King NA, Craig SA, Pepper T, Blundell JE. Evaluation of the independent and combined effects of xylitol and polydextrose consumed as a snack on hunger and energy intake over 10 d. Br J Nutr 2005 Jun;93(6):911-915.

(145) Achour L, Flourie B, Briet F, Pellier P, Marteau P, Rambaud JC. Gastrointestinal effects and energy value of polydextrose in healthy nonobese men. Am J Clin Nutr 1994 Jun;59(6):1362-1368.

(146) Figdor SK, Bianchine JR. Caloric utilization and disposition of [14C]polydextrose in man. J Agric Food Chem 1983 Mar-Apr;31(2):389-393.

(147) Hernot DC, Boileau TW, Bauer LL, Middelbos IS, Murphy MR, Swanson KS, et al. In vitro fermentation profiles, gas production rates, and microbiota modulation as affected by certain fructans, galactooligosaccharides, and polydextrose. J Agric Food Chem 2009 Feb 25;57(4):1354-1361.

(148) Probert HM, Apajalahti JH, Rautonen N, Stowell J, Gibson GR. Polydextrose, lactitol, and fructo-oligosaccharide fermentation by colonic bacteria in a three-stage continuous culture system. Appl Environ Microbiol 2004 Aug;70(8):4505-4511.

(149) Livesey G, Johnson IT, Gee JM, Smith T, Lee WE, Hillan KA, et al. 'Determination' of sugar alcohol and Polydextrose absorption in humans by the breath hydrogen (H2) technique: the stoichiometry of hydrogen production and the interaction between carbohydrates assessed in vivo and in vitro. Eur J Clin Nutr 1993 Jun;47(6):419-430.

(150) Tomlin J, Read NW. A comparative study of the effects on colon function caused by feeding ispaghula husk and polydextrose. Aliment Pharmacol Ther 1988 Dec;2(6):513-519.

(151) Saku K, Yoshinaga K, Okura Y, Ying H, Harada R, Arakawa K. Effects of polydextrose on serum lipids, lipoproteins, and apolipoproteins in healthy subjects. Clin Ther 1991 Mar-Apr;13(2):254-258.

(152) Monsivais P, Carter BE, Christiansen M, Perrigue MM, Drewnowski A. Soluble fiber dextrin enhances the satiating power of beverages. Appetite 2011 Feb;56(1):9-14.

(153) Ranawana V, Muller A, Henry CJ. Polydextrose: its impact on short-term food intake and subjective feelings of satiety in males-a randomized controlled cross-over study. Eur J Nutr 2012 Jun 21.

(154) Bassaganya-Riera J, DiGuardo M, Viladomiu M, de Horna A, Sanchez S, Einerhand AW, et al. Soluble fibers and resistant starch ameliorate disease activity in interleukin-10-deficient mice with inflammatory bowel disease. J Nutr 2011 Jul;141(7):1318-1325.

(155) Weaver CM, Martin BR, Story JA, Hutchinson I, Sanders L. Novel Fibers Increase Bone Calcium Content and Strength beyond Efficiency of Large Intestine Fermentation. J Agric Food Chem 2010 Aug 2.

(156) Maathuis A, Hoffman A, Evans A, Sanders L, Venema K. The effect of the undigested fraction of maize products on the activity and composition of the microbiota determined in a dynamic in vitro model of the human proximal large intestine. J Am Coll Nutr 2009 Dec;28(6):657-666.

(157) Karalus M, Clark M, Greaves KA, Thomas W, Vickers Z, Kuyama M, et al. Fermentable Fibers do not Affect Satiety or Food Intake by Women Who do not Practice Restrained Eating. J Acad Nutr Diet 2012 Jul 5.

(158) Kendall CW, Esfahani A, Hoffman AJ, Evans A, Sanders LM, Josse AR, et al. Effect of novel maize-based dietary fibers on postprandial glycemia and insulinemia. J Am Coll Nutr 2008 Dec;27(6):711-718.

(159) Hengst C, Ptok S, Roessler A, Fechner A, Jahreis G. Effects of polydextrose supplementation on different faecal parameters in healthy volunteers. Int J Food Sci Nutr 2008 Dec 23:1-10.

(160) Temple LK, Bacik J, Savatta SG, Gottesman L, Paty PB, Weiser MR, et al. The development of a validated instrument to evaluate bowel function after sphincter-preserving surgery for rectal cancer. Dis Colon Rectum 2005 Jul;48(7):1353-1365.

(161) Jie Z, Bang-Yao L, Ming-Jie X, Hai-Wei L, Zu-Kang Z, Ting-Song W, et al. Studies on the effects of polydextrose intake on physiologic functions in Chinese people. Am J Clin Nutr 2000 Dec;72(6):1503-1509.

(162) Birkett AM, Jones GP, de Silva AM, Young GP, Muir JG. Dietary intake and faecal excretion of carbohydrate by Australians: importance of achieving stool weights greater than 150 g to improve faecal markers relevant to colon cancer risk. Eur J Clin Nutr 1997 Sep;51(9):625-632.

(163) Spiller GA. Suggestions for a basis on which to determine a desirable intake of dietary fibre. CRC Handbook of Dietary Fiber in Human Nutrition Boca Raton, FL: CRC Press; 1993. p. 351-354.

(164) Fastinger ND, Karr-Lilienthal LK, Spears JK, Swanson KS, Zinn KE, Nava GM, et al. A novel resistant maltodextrin alters gastrointestinal tolerance factors, fecal characteristics, and fecal microbiota in healthy adult humans. J Am Coll Nutr 2008 Apr;27(2):356-366.

(165) Vester Boler BM, Hernot DC, Boileau TW, Bauer LL, Middelbos IS, Murphy MR, et al. Carbohydrates blended with polydextrose lower gas production and short-chain fatty acid production in an in vitro system. Nutr Res 2009 Sep;29(9):631-639.

(166) Heaton KW. Food fibre as an obstacle to energy intake. Lancet 1973 Dec 22;2(7843):1418-1421.

(167) Alfieri MA, Pomerleau J, Grace DM, Anderson L. Fiber intake of normal weight, moderately obese and severely obese subjects. Obes Res 1995 Nov;3(6):541-547.

(168) Appleby PN, Thorogood M, Mann JI, Key TJ. Low body mass index in non-meat eaters: the possible roles of animal fat, dietary fibre and alcohol. Int J Obes Relat Metab Disord 1998 May;22(5):454-460.

(169) Nelson LH, Tucker LA. Diet composition related to body fat in a multivariate study of 203 men. J Am Diet Assoc 1996 Aug;96(8):771-777.

(170) Slavin JL. Dietary fiber and body weight. Nutrition 2005 Mar;21(3):411-418.

(171) Howarth NC, Saltzman E, Roberts SB. Dietary fiber and weight regulation. Nutr Rev 2001 May;59(5):129-139.

(172) Parnell JA, Reimer RA. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. Am J Clin Nutr 2009 Jun;89(6):1751-1759.

(173) Johnson J, Vickers Z. Factors influencing sensory-specific satiety. Appetite 1992 Aug;19(1):15-31.

(174) Rogers PJ, Blundell JE. Umami and appetite: effects of monosodium glutamate on hunger and food intake in human subjects. Physiol Behav 1990 Dec;48(6):801-804.

(175) Brighenti F, Benini L, Del Rio D, Casiraghi C, Pellegrini N, Scazzina F, et al. Colonic fermentation of indigestible carbohydrates contributes to the second-meal effect. Am J Clin Nutr 2006 Apr;83(4):817-822.

(176) Maljaars PW, Peters HP, Mela DJ, Masclee AA. Ileal brake: a sensible food target for appetite control. A review. Physiol Behav 2008 Oct 20;95(3):271-281.

(177) Tazoe H, Otomo Y, Karaki S, Kato I, Fukami Y, Terasaki M, et al. Expression of short-chain fatty acid receptor GPR41 in the human colon. Biomed Res 2009 Jun;30(3):149-156.

(178) Karaki S, Tazoe H, Hayashi H, Kashiwabara H, Tooyama K, Suzuki Y, et al. Expression of the short-chain fatty acid receptor, GPR43, in the human colon. J Mol Histol 2008 Apr;39(2):135-142.

(179) Karaki S, Mitsui R, Hayashi H, Kato I, Sugiya H, Iwanaga T, et al. Short-chain fatty acid receptor, GPR43, is expressed by enteroendocrine cells and mucosal mast cells in rat intestine. Cell Tissue Res 2006 Jun;324(3):353-360.

(180) Longo WE, Ballantyne GH, Savoca PE, Adrian TE, Bilchik AJ, Modlin IM. Short-chain fatty acid release of peptide YY in the isolated rabbit distal colon. Scand J Gastroenterol 1991 Apr;26(4):442-448.

(181) Cherbut C, Ferrier L, Roze C, Anini Y, Blottiere H, Lecannu G, et al. Short-chain fatty acids modify colonic motility through nerves and polypeptide YY release in the rat. Am J Physiol 1998 Dec;275(6 Pt 1):G1415-22.

(182) Cuche G, Cuber JC, Malbert CH. Ileal short-chain fatty acids inhibit gastric motility by a humoral pathway. Am J Physiol Gastrointest Liver Physiol 2000 Nov;279(5):G925-30.

(183) Ostman E, Granfeldt Y, Persson L, Bjorck I. Vinegar supplementation lowers glucose and insulin responses and increases satiety after a bread meal in healthy subjects. Eur J Clin Nutr 2005 Sep;59(9):983-988.

(184) Mettler S, Schwarz I, Colombani PC. Additive postprandial blood glucose-attenuating and satiety-enhancing effect of cinnamon and acetic acid. Nutr Res 2009 Oct;29(10):723-727.

(185) Liljeberg HG, Lonner CH, Bjorck IM. Sourdough fermentation or addition of organic acids or corresponding salts to bread improves nutritional properties of starch in healthy humans. J Nutr 1995 Jun;125(6):1503-1511.

(186) Liljeberg HG, Bjorck IM. Delayed gastric emptying rate as a potential mechanism for lowered glycemia after eating sourdough bread: studies in humans and rats using test products with added organic acids or an organic salt. Am J Clin Nutr 1996 Dec;64(6):886-893.

(187) Frost GS, Brynes AE, Dhillo WS, Bloom SR, McBurney MI. The effects of fiber enrichment of pasta and fat content on gastric emptying, GLP-1, glucose, and insulin responses to a meal. Eur J Clin Nutr 2003 Feb;57(2):293-298.

(188) Darzi J, Frost GS, Robertson MD. Do SCFA have a role in appetite regulation? Proc Nutr Soc 2011 Feb;70(1):119-128.

(189) Lin HC, Prather C, Fisher RS, Meyer JH, Summers RW, Pimentel M, et al. Measurement of gastrointestinal transit. Dig Dis Sci 2005 Jun;50(6):989-1004.

(190) Bonapace ES, Maurer AH, Davidoff S, Krevsky B, Fisher RS, Parkman HP. Whole gut transit scintigraphy in the clinical evaluation of patients with upper and lower gastrointestinal symptoms. Am J Gastroenterol 2000 Oct;95(10):2838-2847.

(191) Cassilly D, Kantor S, Knight LC, Maurer AH, Fisher RS, Semler J, et al. Gastric emptying of a non-digestible solid: assessment with simultaneous SmartPill pH and pressure capsule, antroduodenal manometry, gastric emptying scintigraphy. Neurogastroenterol Motil 2008 Apr;20(4):311-319.

(192) Rao SS, Kuo B, McCallum RW, Chey WD, DiBaise JK, Hasler WL, et al. Investigation of colonic and whole-gut transit with wireless motility capsule and radiopaque markers in constipation. Clin Gastroenterol Hepatol 2009 May;7(5):537-544.

(193) Sarosiek I, Selover KH, Katz LA, Semler JR, Wilding GE, Lackner JM, et al. The assessment of regional gut transit times in healthy controls and patients with gastroparesis using wireless motility technology. Aliment Pharmacol Ther 2010 Jan 15;31(2):313-322.

(194) Maqbool S, Parkman HP, Friedenberg FK. Wireless capsule motility: comparison of the SmartPill GI monitoring system with scintigraphy for measuring whole gut transit. Dig Dis Sci 2009 Oct;54(10):2167-2174.

(195) Kuo B, McCallum RW, Koch KL, Sitrin MD, Wo JM, Chey WD, et al. Comparison of gastric emptying of a nondigestible capsule to a radio-labelled meal in healthy and gastroparetic subjects. Aliment Pharmacol Ther 2008 Jan 15;27(2):186-196.

(196) Muller-Lissner SA. Effect of wheat bran on weight of stool and gastrointestinal transit time: a meta analysis. Br Med J (Clin Res Ed) 1988 Feb 27;296(6622):615-617.

(197) Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut 1988 Aug;29(8):1035-1041.

(198) Fallingborg J, Christensen LA, Ingeman-Nielsen M, Jacobsen BA, Abildgaard K, Rasmussen HH. pH-profile and regional transit times of the normal gut measured by a radiotelemetry device. Aliment Pharmacol Ther 1989 Dec;3(6):605-613.

(199) Hasler WL, Coleski R, Chey WD, Koch KL, McCallum RW, Wo JM, et al. Differences in intragastric pH in diabetic vs. idiopathic gastroparesis: relation to degree of gastric retention. Am J Physiol Gastrointest Liver Physiol 2008 Jun;294(6):G1384-91.

(200) Kloetzer L, Chey WD, McCallum RW, Koch KL, Wo JM, Sitrin M, et al. Motility of the antroduodenum in healthy and gastroparetics characterized by wireless motility capsule. Neurogastroenterol Motil 2010 May;22(5):527-e117.

(201) McIntyre A, Vincent RM, Perkins AC, Spiller RC. Effect of bran, ispaghula, and inert plastic particles on gastric emptying and small bowel transit in humans: the role of physical factors. Gut 1997 Feb;40(2):223-227.

(202) Evans RC, Kamm MA, Hinton JM, Lennard-Jones JE. The normal range and a simple diagram for recording whole gut transit time. Int J Colorectal Dis 1992 Feb;7(1):15-17.