EFFECTS OF FIBER AND FOOD FORM ON SATIETY AND ENERGY
INTAKE IN HEALTHY HUMAN SUBJECTS

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Dedication

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Abstract

   Satiety is a complex process influenced by a number of properties in food such as physical form, macronutrient content, visual appeal, taste, pleasantness, smell and aftertaste.   From past research, we already know that the liquid form of food produces a weaker satiety response compared to the solid form of food. On the other hand, little is known about the effects of different types of solid food (i.e. solid food in the form of an energy bar vs. solid food as part of a meal) on satiety and subsequent energy intake. The following work describes two intervention studies designed to help explain the influence of various properties of food on satiety.

   In the first study, we hypothesized that a 10g dose of oat bran fiber or a 10g dose of barley bran fiber in a breakfast bar would enhance satiety more than a control bar with 3g of wheat fiber. We also hypothesized that consumption of the oat bran bar or barley bran bar for breakfast would reduce energy intake at an *ad libitum* lunch more than the wheat fiber breakfast bar. Secondary outcomes were to determine if the oat and barley bran fiber bars had any effect on gastrointestinal tolerance and colonic fermentation. Finally, we sought to determine if any of the fiber bars differed in their palatability ratings. Healthy women (n=42) participated in this randomized double-blind, crossover study comparing satiety after they consumed three different breakfast bars: one with barley bran fiber, one with oat bran fiber and a bar with low amounts of wheat fiber (control). Women used 100 mm visual analog scales (VAS) to rate satiety for 4 hours after breakfast bar consumption. Satiety did not significantly differ among treatments nor did energy intake, colonic fermentation, and gastrointestinal tolerance.

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In the second study, we hypothesized that a high protein pasta would increase satiety and decrease mid-afternoon snacking more than a high fiber pasta or a control. We also investigated whether or not the added ingredients to the pasta would have any effect on gastrointestinal tolerance, food intake and palatability. Healthy men (n=18) and healthy women (n=18) participated in this randomized double-blind crossover study. Subjects consumed three different pastas (high protein, high fiber, or control) for lunch at noon and proceeded to rate satiety with VAS over a three-hour period. *Ad libitum* snacking was assessed at 3:00pm and subjects rated any gastrointestinal symptoms and their food intake for the remainder of the evening. Once again, satiety did not significantly differ among the treatments, nor did gastrointestinal tolerance. A gender-treatment interaction was observed for food intake and men consumed significantly more calories after the high protein pasta compared to the high fiber and control pasta. We also found differences in palatability among the pastas, which suggests that hedonic properties of food may influence satiety ratings and subsequent food intake.

The results from these two studies do not support a connection between the consumption of whole foods and satiety. Changing the satiating properties of whole foods by adding more protein or fiber was a limitation in both studies because it affected our palatability ratings. Other limitations that may have contributed to these null results are a short intervention time and too small a dose of fiber and protein.

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CHAPTER ONE: Literature Review

<u>Introduction</u>

Meals are everyday eating occasions characterized by the frequency of food consumption, by the types of food in a meal, and finally by the form of food which makes a meal (i.e. solid vs. liquid) (1). In addition to this, eating events are usually categorized as either a main meal or snack. Eating events vary across cultures but traditionally, in the United States, Americans consume three main meals a day which include breakfast, lunch and dinner. Although meals are substantial contributors to daily energy intake, recent data shows that Americans are eating more and more snack foods (2). Data from the National Health and Nutrition Examination Survey (NHANES 2009-2010) shows that 96% of men and women report having at least one snack daily (3). It is unknown why snacking is so prevalent in the United States, but factors such as convenience, cost and palatability of energy-dense snack foods such as cookies, chips, and candy are contributing factors.

Understanding the relationship between eating and energy intake is important to help control the obesity epidemic and given the severe health and economic costs associated with obesity, it becomes crucial to identify factors that may help in prevention and treatment. Researchers generally agree that obesity results from energy imbalance and past studies on energy intake have focused on factors that affect two principles of appetite: satiation (the sensations of fullness and satisfaction that occur during a meal leading to its cessation) and satiety (the sensations of fullness and satisfaction that continue after the meal and during the inter-meal period (4).

It has been established that a number of dietary factors affect satiety, such as macronutrient composition and fiber content, but finding ways to enhance satiety and reduce food intake at subsequent meals still remains a challenge (5). One approach that may positively affect satiety and energy intake is changing the form in which food is consumed (ex: from a liquid to a solid). A couple of studies on this topic have been published with interesting results (5-6). For example, Flood-Obbagy et al investigated whether or not fruit served in different forms would affect satiety and energy intake at a subsequent meal. In a randomized crossover design, fifty-eight healthy and normal weight men and women completed five test visits separated by a one week period. On each test day, subjects consumed a standard breakfast followed by a lunch meal served 3 hours later. At the beginning of each lunch meal, subjects were served one of four preloads or nothing (control). The preloads were an apple, applesauce, apple juice with fiber or apple juice without fiber. Fifteen minutes following the preload, a macaroni test meal was served and ratings of hunger, fullness and thirst were measured by a 100 mm visual analog scale (VAS).

The results from this study demonstrated that subjects consumed significantly less energy from the test meal after eating whole apples compared to the applesauce (709 ± 50 vs. 800 ± 49, $p<0.0001$) and both apple juice preloads (709 ± 50 vs. 866 ± 52 for juice with fiber vs. 890 ± 51 for juice without fiber, $p<0.0001$) (5). Subjects also rated their fullness higher after consumption of the apple compared to the apple juice with and without fiber (44 ± 3 for apple vs. 36 ± 3 for juice with fiber vs. 34 ± 3 for juice without

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fiber, p<0.02). Altogether, the results suggest that solid fruit elicited a stronger satiety response than pureed fruit or fruit juice and that it reduced energy intake at a later meal.

In another randomized crossover study, Cassady et al contrasted appetitive, dietary, gastric emptying, and orocecal transit time responses of energy-matched liquids (in beverage form) and solid food forms in lean and healthy individuals. A total of fifty-two adults completed four study visits separated by a one week washout period between sessions. Subjects were asked to consume their standard breakfast at home and report to the lab at lunchtime in a fasted state (minimum 3 hours). One of four preloads were consumed and breath, blood, and appetite ratings were collected at time 0, 15, 30, 45, 60, 90, 120, 180 and 240 minutes. Energy intake was also recorded on test and non-test days. The preloads were either a cherry-flavored thickened beverage (identified as the L-L treatment), a cherry-flavored thickened beverage with 1% alginate solution to form a solid (L-S treatment), cherry flavored gelatin cubes (S-L treatment), or the same cherry gelatin cubes where subjects were informed that the cubes would remain solid in the stomach after consumption (S-S treatment).

The results showed that energy intake was significantly greater on days when the (L-L and S-L) treatments were consumed than when (L-S and S-S) treatments were consumed (2311 ± 95 vs. 1897 ± 72, p=0.007) (6). In addition to this, subjects had increased hunger and a lower fullness area under the curve (AUC) after the (L-L and S-L) treatments compared to the (L-S and S-S) treatments, p<0.01. These findings suggest that liquids stimulate weak appetitive and dietary responses compared with energy-matched semisolid or solid food forms. Since beverages require less oral processing and have

more rapid gastric emptying transit times, consumption of them evokes a lower satiety

response than solids (7).

Both of these studies were successful in showing that liquid carbohydrates evoked a

lower satiety response than solid food and that subsequent energy intake was reduced

after eating solid food. These results are important to consider especially since the global

intake of liquid carbohydrates by adults and adolescents has dramatically increased and is

contributing to positive energy balance and obesity (8). It is without question that

carbohydrates are a major source of energy in our daily diets, but some components of

carbohydrates, such as fiber, are considered more beneficial for health.

The next section will define fiber and discuss specific types that were used in my

research.

Fiber: Definitions and types

Around the world, scientific and regulatory agencies define fiber differently (9). The

reason for this is because a universally accepted definition for fiber does not exist and

many individuals are still not clear about what can be referred to as fiber (10). Part of the

challenge in defining fiber is the variation in fiber types and differences in biological,

chemical, and physiological characteristics. Historically, the term fiber was loosely

defined as any non-digestible portion of a plant cell wall (11). Through the years, the

definitions of fiber have evolved and now three main organizations have classified the

term dietary fiber. These include the Institute of Medicine (IOM), American Association

of Cereal Chemists (AACC), and Codex Alimentarius Commission. The IOM definition

is important because it is a respected source for science-based dietary recommendation in

the United States and distinguishes between naturally occurring fiber and functional fibers (12). It further describes dietary fiber as consisting of nondigestible carbohydrates and lignin that are intrinsic and intact in plants. Functional fiber consists of isolated, nondigestible carbohydrates that have beneficial physiologic effects in humans. Furthermore, total fiber is the sum of dietary and functional fiber.

The AACC defines dietary fiber as the edible parts of a plant or carbohydrates that are resistant to digestion and absorption in the human small intestine, with complete or partial fermentation in the large intestine (13). Dietary fiber includes polysaccharides, oligosaccharides, lignin and associated plant substances. Dietary fibers also promote beneficial physiologic effects such as laxation and a reduction in blood glucose and cholesterol levels (13). Finally, the Codex Alimentarius Commission describes dietary fiber as a carbohydrate polymer with ten or more monomeric units which are not hydrolyzed by the enzymes in the small intestine of humans and belongs to the following categories (14):

- Edible carbohydrate polymers that are naturally occurring in food
- Carbohydrate polymers that have been obtained from food raw material by physical, enzymatic, or chemical means and which have been shown to have a physiologic effect of benefit to health as demonstrated by accepted scientific evidence to proficient authorities
- Synthetic carbohydrate polymers that have been shown to have a physiologic effect of benefit to health as demonstrated by accepted scientific evidence to competent authorities

Besides the definitions, fiber is further classified as soluble or insoluble. This

classification is commonly seen in the United States on food labels and is based upon the

analytical methods agreed upon by the Association of Official Analytical Chemists

(AOAC) (15). To be classified as soluble, fibers should dissolve in water; whereas

insoluble fibers will not. Both soluble and insoluble fibers have beneficial health effects

such as slowing intestinal transit time, delaying gastric emptying, postponing glucose and

sterol absorption and increasing fecal bulk.

In addition to solubility, fibers can also be classified by the properties of viscosity and

fermentability. Altogether, soluble fibers are thought to be more fermentable and viscous

and insoluble fibers contribute more to fecal bulk, but are resistant to fermentation. Two

bran fibers with different physiochemical properties were used in my research and these

are described below.

Oat Bran

Similar to other grains, oat belongs to the Poaceae family and Avena sativa L. or

common oat is recognized as the most important among the grown oats (16). It is a crop

used for both animal and human nutrition and was identified as "healthy" in the 1980's

when its ability to lower serum cholesterol and reduce the risk of cardiovascular disease

was discovered. Oat bran is defined as the edible, outermost layer of the kernel that

contains a variety of B complex vitamins, fat, minerals, protein and fiber (16). The

dietary fiber content of oat bran is between 15-22%, with 10.4% consisting of a soluble

fiber called beta-glucan (16). The beta-glucan in oat bran is a linear, unbranched

polysaccharide comprised of both 1-4 and 1-3 glycosidic linkages (16). The potential

health benefits of oat beta-glucan were recently described by Cloetens et al; these benefits include a reduction of energy intake by controlling appetite, lowering blood glucose and insulin levels, and the potential to serve as a prebiotic (17). The potential to serve as a prebiotic was demonstrated in a human study where individuals significantly increased their total amount of bifidobacteria after administration of a diet containing 3.5g of oat based product consumed for five weeks (18). Altogether, the mechanisms by which beta-glucan exerts prebiotic effects is still unknown, but it has been hypothesized that it is due to its high viscosity and content of 1-3 and 1-4 glycosidic links (19).

Barley Bran

Barley (Hordeum vulgare L.) is another important cereal grain and is one of the most genetically diverse (20). Barley can be classified by type (spring or winter) and by grain composition (normal, waxy, or high amylose) (20). It is a hearty tasting, high-energy grain that has been a significant source of food in many parts of the world like the Middle East, Asia, Africa, and northern and eastern parts of Europe (20). Besides its importance as a food source, barley also has an interesting chemical composition. Whole barley grain consists of about 65-68% starch, 10-17% protein, 4-9% beta-glucan, 2-3% lipid, and 1.5-2.5% minerals. The total amount of dietary fiber ranges from 11-34% with soluble fiber ranging from 3-20% (20).

Similar to oats, barley contains a viscous and soluble beta-glucan. The glycosidic linkages are mixed with some 1-3 and some 1-4. These constitute about 75% of the barley endosperm cell wall together with 20% arabinoxylans and protein (20). The health benefits of barley beta-glucans are comparable to those of oat beta-glucans and include

reduction of blood cholesterol, and increased satiety by controlling appetite. As a result of these positive health benefits, in 1997, the US Food and Drug Administration (FDA) approved the use of a health claim for diets high in soluble fiber from whole oats and the reduction of heart disease. This claim was expanded in 2005 when whole-grain barley and dry-milled barley grain products were included as sources of soluble fiber (21). The next section will discuss how consumption of fiber can cause unwanted gastrointestinal side effects and how these symptoms are measured in research.

Fiber and Gastrointestinal Tolerance

On average, Americans consume about 15 grams of fiber per day which is well below the recommended levels of 25 grams for women and 38 grams for men (22). As a result of these suboptimal levels, food companies are adding fiber to a wide range of products. This may help Americans meet recommended levels, but often higher fiber intake is associated with adverse gastrointestinal symptoms. The symptoms may vary from person to person but often include bloating, flatulence and increased stool frequency. As a result of this, consumers need to carefully consider what fiber will help them meet recommended levels without producing unwanted side effects.

In the framework of dietary fibers, tolerance is a condition in which the unwanted side effects of fiber consumption do not exist (23). In acute satiety studies, no clear method for assessing gastrointestinal tolerance has been standardized. Subjective measurements vary from study to study and include symptom forms, questionnaires and diaries where subjects are asked to record the occurrence of a gastrointestinal symptom. For example, Rippoll et al assessed gastrointestinal tolerance by asking subjects to fill out a

questionnaire everyday before bed. Characteristics such as flatulence, bloating, and abdominal pain were rated as 0 (none), 1 (weak), 2 (moderate), 3 (high), 4 (very high). Stool consistency was rated as 0 (liquid), 1 (soft), 2 (regular), 3 (hard) and 4 (very hard) (24).

In addition to this, Hess et al evaluated tolerance by using visual analog scales. The assessment included stool consistency (0=diarrhea, 100=hard stool), stool frequency, degree of intestinal bloating and flatulence (0=minimal, 100=excessive). A symptom score was also calculated as the summary of responses (25). Overall, the methods for measuring gastrointestinal tolerance are variable and it is still uncertain what is best for fiber research. A better approach is to adopt a questionnaire that has been validated. Revicki et al validated a gastrointestinal symptom rating scale (GSRS) in a population of patients with gastroesophageal reflux disease (GERD) (26). The rating scales contain fifteen questions that cover the areas of abdominal pain, diarrhea, indigestion, constipation and reflux syndrome. The responses are based on a seven point Likert scale with lower values indicating no discomfort and higher values indicating very severe discomfort.

The benefits of the GSRS are that it can be administered in an interview format or by self-report questionnaire and can be a useful tool for evaluating gastrointestinal tolerance. This questionnaire was found helpful for the purposes of my research and fits into the framework of measuring gastrointestinal tolerance in acute satiety studies. The next section will focus on another nutrient, besides fiber, that has also shown to promote satiety.

Protein

   Dietary protein is another nutrient that has received considerable interest in the context

of weight management and satiety. This is because one of the strategies followed by

those who successfully lose weight includes the intake of a higher-protein diet (27).

Currently, the Recommended Daily Allowance (RDA) for protein is 0.8g/kg, however the

typical American consumes 1.2g/kg or near 15% of energy as protein (28). Advocates of

high protein diets often suggest that protein intakes meet or exceed 25% of total energy.

This recommendation exists because some have theories that high protein diets are

related to a greater thermic effect of food and increased satiety (29-30). The thermic

effect of food is the energy required for the digestion, absorption and removal of ingested

nutrients. The general thermic effect of protein is between 20-35% of energy consumed

compared to carbohydrates which are 5-15%; the thermic effect of fat seems to be of

much debate (28). Protein seems to have the highest thermic effect because the body

does not have enough storage capacity to deal with increased intakes and so it needs to be

metabolized right away (31).

   Protein is thought to increase satiety by stimulating postprandial ghrelin secretion and

promoting gluconeogenesis, thereby preventing a decrease in glycemia (31). These

attributes of protein make it appealing to those who are focused on weight loss and body

weight maintenance. Food manufacturers recognize how whole foods with increased

protein and fiber can promote satiety, but are challenged since it is difficult to formulate

with an additional amount without compromising appearance and taste. In spite of these

challenges, a recent review found that protein studies that were designed to match real

life situations (i.e. consumption of solid foods versus liquid) found an increase in satiety and a significant decrease in subsequent energy intake (28). Unfortunately, the other studies included in this review were not consistent. Altogether, more research is needed in this area with better agreement on methodology so further insight can be gained on the topic of protein and satiety.

CHAPTER TWO: Effects of oat and beta-glucan on gut health

Summary

   Grains are typically the largest contributor to dietary fiber intake and it is well accepted that grains affect gut health. In addition to their contribution to dietary fiber consumption, grains are high in resistant starch and oligosaccharides. Oats are concentrated in soluble fiber and are linked to lipid lowering and glucose modulation. But, oats increase stool weight, speed intestinal transit, get fermented to short chain fatty acids in the gut, and modify the gut microflora. In vitro fermentation studies also support that oats alter gut health. Carbohydrates of oat bran (rich in beta-glucan) were consumed by the bacteria faster than those of rye and wheat brans (rich in arabinoxylan). Oat fibers were fermented more slowly than inulin causing less gas production. Some in vivo studies show the prebiotic potential of whole grains, including oats. Whole grain breakfast cereal was more effective than wheat bran breakfast cereal as a prebiotic, increasing fecal bifidobacteria and lactobacilli in human subjects. Thus, the gut enhancing effects of cereal fibers, including oats, are well known.

Oats and Beta-glucan

   Avena Sativa L. (common oat) is the most important among the cultivated oats (16). Oat was recognized as a healthy crop in the 1980's when its ability to lower serum cholesterol and reduce risk of cardiovascular disease was discovered. Bran is the outermost layer of the oat kernel and can be isolated from the kernel and consumed as an isolated supplement. Oat bran contains vitamins, minerals, carbohydrate (68%), protein (17%), and fat (9%) (16).   Dietary fiber content of oat bran ranges from 15 – 22%, with 10.4% beta glucan. Beta-glucan is a linear, unbranched polysaccharide. In addition to

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this, beta-glucan is also viscous, with viscosities determined by the chain length of the beta-glucan molecule.

Digestive health

The term laxation describes a wide range of gastrointestinal effects, including stool weight, transit time, bloating and distention, flatus, constipation and diarrhea. Fiber increases stool weight and promotes normal laxation (32). Unfortunately, there are no standardized, accepted definitions for either of these conditions. Constipation is a prevalent, chronic condition in Western society, a common clinical complaint, but a poorly studied condition. It has been defined as less than 3 bowel movements per week, although most people define constipation as less than one bowel movement per day. Frequency of defecation is only one aspect of constipation. Ease of passage of stools or lack of straining are other components of normal laxation.

Bowel habit is affected by medications, stress, physical activity, and volume of food, type of food, fluid intake, hormones, and other environmental factors. Although subjective measures of bowel function are important variables to collect, objective measures such as wet and dry stool weight and gastrointestinal transit time are useful biomarkers to study. Increased bulk, softness or pliability of colonic contents and increased intestinal motility may protect against constipation. Stool weight increases as fiber intake increases, but the additional fiber tends to normalize defecation frequency to once daily and gastrointestinal transit time to between 2 and 4 days. The increase in stool weight is caused by the presence of the fiber, by the water that the fiber holds and by partial fermentation of the fiber, which increases the amount of bacteria in stool. Bacteria

also bind water, so bacterial mass increases stool weight, but generally not as much as undigested fiber.

Diarrhea is an unpleasant digestive disorder that can occur at any time. Normally when food is consumed, it remains in a liquid form during most of the digestive process; when the unabsorbed food residue passes through the large intestine, most of the remaining fluids are absorbed and what remains is a semisolid stool. However, in diarrhea the food and fluid ingested pass too quickly or in too large an amount (or both) through the intestine. The fluids are not sufficiently absorbed and the result is a watery bowel movement.

Commonly accepted criteria for clinical diarrhea are: elevated stool output (> 200 g/day); watery, difficult to control bowel movements; and frequency of bowel movements exceeding 3 per day (33). The colonic fermentation of dietary fiber may help to improve gastrointestinal tolerance and decrease diarrhea. Dietary fiber seems to reduce diarrhea by protecting from bacterial overgrowth in intestine. A meta-analysis of randomized, controlled trials found no evidence that dietary fiber is effective in treating diarrhea (34), yet in clinical practice the addition of fiber to enteral diets is well accepted (35).

Irritable bowel syndrome (IBS) is defined as "a group of functional bowel disorders" and is characterized by chronic or recurrent abdominal pain or discomfort, usually in the lower abdomen, which is associated with disturbed bowel function (i.e., diarrhea or constipation alone or alternating) and feeling of abdominal distention and bloating (36). Due to its persisting symptoms, IBS has a significant negative impact on health-related

quality of life. The prevalence of IBS is estimated to range between 10% and 20% among adults in the United States and Europe (37); however, this is an underestimate of prevalence indicated by the fact that 70% of symptomatic adults do not seek medical evaluation. Women with IBS report more symptoms of constipation and abdominal discomfort while men with IBS report more diarrhea. Psychological disturbances, such as anxiety and depression, are more common in individuals with IBS who seek medical consultation for their symptoms than in those who do not seek care for them, which suggests that psychological disturbance may amplify IBS symptoms and affect health care-seeking behavior.

Austin et al (2009) found that a very-low-carbohydrate diet improved symptoms and quality of life in patients with diarrhea-predominant IBS (38). A systematic review of dietary interventions for children with IBS concluded that there is a lack of high quality evidence on the effectiveness of dietary interventions and there is no evidence that fiber supplements, lactose free diets or lactobacillus supplements are effective in children with recurrent abdominal pain (39). Bijkerk et al (2004) conducted a systematic review of fiber in the management of IBS (40). They determined the following outcome measures: the proportion of patients reporting clinical relief (global irritable bowel syndrome symptom improvements); the proportion of patients reporting improved irritable bowel syndrome-related abdominal pain; and the proportion of patients reporting an improvement in irritable bowel syndrome-related constipation.

A meta-analysis showed that general fiber supplementation alleviates IBS symptoms globally, but there is no benefit in the relief of abdominal pain, which is the most

important feature capable of distinguishing IBS from functional constipation or

functional diarrhea (41). Bijkerk et al (2004) reported improvement in global symptoms

in only two of the six insoluble wheat fiber trials, while miller bran treatment did not

improve symptoms. Overall, bran was no better than placebo in regards to improvement

of global symptoms, but improvement was shown in IBS patients with constipation.

Neither probiotics nor prebiotics are effective in the treatment of IBS (42). Thus, it is

accepted grain fibers play a role in digestive health (22), but few studies have been

conducted on selected grains and their effects on gut health. Most studies are in diseased

populations and even in these studies the role of dietary fiber on gut health remains

inconsistent.

Short chain fatty acids (SCFA)

Fiber is fermented by anaerobic intestinal bacteria that generate SCFA, which serve as

energy sources for colonic mucosal cells (22). Fermentable dietary fibers are thought to

alter the gut environment, not only by inducing the production of SCFA, but also by

altering the gut microflora. Indeed, fermentable dietary fibers have a significant prebiotic

effect by altering the intestinal microflora composition towards a more beneficial

distribution by leading to selective stimulation of microbial growth, which eventually

helps to increase the water-holding capacity of the colonic content and fecal moisture.

Acetate, propionate, and butyrate are the SCFA produced in the highest concentrations

(43). Acetate is a fuel for skeletal and cardiac muscle, kidney, and the brain. Butyrate is

the preferred fuel of the colonic epithelium, in particular, the distal colon and rectum.

Propionate is metabolized by the liver and may play a role in cholesterol lowering.

Fibers produce varying proportions of individual SCFA and thus differing concentrations of total SCFA. Physiological status may be improved by consuming fermentable fiber, so it is important to understand the fermentability of each type of fiber.

Fiber fermentability is difficult to study in vivo due to the invasiveness of colon studies and the dynamic nature of the colon. Fiber fermentation can be estimated by measuring fiber consumed in the diet and then collecting fecal samples and measuring fiber left in feces. This is tedious and difficult since feces contain bacterial cell walls that are also isolated in fiber methods. No easy biomarkers exist to measure fiber fermentation in vivo, so generally in vitro models are used. Particle size, solubility, surface area, and other factors affect the extent of fermentation and the nature of the SCFA's.

In living systems, SCFA are absorbed from the colonic lumen shortly after they are produced. No method has been developed to accurately measure SCFA absorption in vivo and measuring SCFAs excreted in the feces is the best estimate of SCFAs being produced in the colon. However, 95-99% of SCFA are absorbed from the lumen so excreted SCFA concentration represent a very small portion of SCFA produced. Therefore, studying the amount of SCFA in the feces of human volunteers would provide only a partial picture.

In vitro models that study fiber fermentability are currently the best models to assess SCFA production in humans. A closed laboratory system can provide an estimate of fiber fermentability without losing SCFA to colonic absorption and, therefore, in vitro fermentation with representative human colonic microflora is a proven, noninvasive, time-efficient means to estimate fiber fermentability. Indeed, batch fermentation has been

shown to degrade non-starch polysaccharides (NSP) to a similar extent as the human

colon, based on residual NSP in fecal samples and fermentation flasks (44).

Large bowel effects of whole grains

Whole grains are rich sources of fermentable carbohydrates including dietary fiber,

resistant starch and oligosaccharides (45). Undigested carbohydrate that reaches the

colon is fermented by intestinal microflora to short chain fatty acids and gases. Short

chain fatty acids include acetate, butyrate, and propionate, with butyrate being a preferred

fuel for the colonic mucosa cells. Short chain fatty acid production has been related to

lowered serum cholesterol and decreased risk of cancer. Undigested carbohydrates

increase fecal and dry weight and also speed intestinal transit time.

Comparing dietary fiber content of various whole grains, oats, rye and barley contain

about one-third soluble fiber and the rest insoluble fiber. Soluble fiber is associated with

cholesterol-lowering and improved glucose response, while insoluble fiber is associated

with improved laxation. Wheat is lower in soluble fiber than most grains while rice

contains virtually no soluble fiber. Refining of grains removes proportionally more of

the insoluble fiber than soluble fiber, although refined grains are low in total dietary fiber.

Disruption of cell walls can increase fermentability of dietary fiber. Coarse wheat bran

has a greater fecal bulking effect than finely ground wheat bran when fed at the same

dosage (46), suggesting that the particle size of the whole grain is an important factor in

determining physiological effect. Coarse bran delayed gastric emptying and accelerated

small bowel transit. The effect seen with coarse bran was similar to the effect of inert

plastic particles, suggesting that the coarse nature of whole grains as compared to refined

grains has a unique physiological effect beyond composition differences between whole and refined grains (47).

McIntosh et al fed rye and wheat foods to overweight middle-aged men and measured markers of bowel health (48).   The men were fed low-fiber cereal grains foods providing 5 grams of dietary fiber for the refined grain diet and 18 grams of dietary fiber for the whole grain diet, either high in rye or wheat. This was in addition to a baseline diet that contained 14 grams of dietary fiber.   Both the high-fiber rye and wheat foods increased fecal output by 33-36% and reduced fecal-glucuronidase activity by 29%. Postprandial plasma insulin was decreased by 46-49% and postprandial plasma glucose by 16-19%. Rye foods were associated with significantly increased plasma enterolactone and fecal butyrate, relative to wheat and low-fiber diets. The authors conclude that rye appears more effective than wheat in overall improvement of biomarkers of bowel health (48). Chen et al compared mechanisms by which wheat bran and oat bran increase stool weight in humans. Both brans increased stool weight, but bacteria and lipids were the major contributors to the increase in stool weight with oat bran, while undigested plant fiber was responsible for much of the increase in stool weight with wheat bran consumption. They suggest that oat bran increases stool weight by providing rapidly fermented soluble fiber in the proximal colon for bacterial growth, which is sustained until excretion by fermentation of the insoluble fiber (49).

Fermentation of grain fiber

To compare the fermentation of grain fibers, we use an established in vitro fermentation method (50). In this system, fecal samples are obtained from 3 healthy donors. Donors

must be disease-free and consuming a typical, low fiber American diet. Exclusion

criteria for participating in the study include use of laxatives, antibiotics, dietary

supplements, any medications, and history of gastrointestinal disease. The fecal samples

from 3 subjects are mixed together and different fibers are fermented with the fecal

slurry. Production of short chain fatty acids as an endpoint of fiber fermentation are

measured at time points ranging from 0 to 48 hours.

Fermentation of 3 fibers was assessed: wheat dextrin, inulin (degree of polymerization

~10), and partially hydrolyzed guar gum (PHGG) (51). Glucose was fermented as a

positive control to ensure active fermentation of the system and no fiber was the negative

control. Statistical analyses were completed with SAS statistical software package,

version 8.0 (SAS Institute, Cary, NC). Analysis of variance and Tukey pair-wise

comparison were used to determine statistical differences between fibers. The

concentrations of acetate, propionate and butyrate, as well as total SCFA levels were

determined.

Wheat dextrin and inulin produced significantly more total SCFA than PHGG at 24

hours (p=0.002). Wheat dextrin and inulin were not statistically different from each other

at 24 hours. Inulin peaked at 4 hours and produced significantly more total SCFA at this

time with a drop in SCFA level at 8 hours. In contrast, wheat dextrin showed a steady

increase in total SCFA production during the 24-hour period. Acetate was the main

SCFA produced by these fibers, accounting for roughly 50% of total SCFA production.

In summary, all fibers tested were fermentable. PHGG consistently showed low

fermentability for all SCFA at all-time points. Wheat dextrin exhibited high and

consistent fermentability for all SCFA, and greater than that compared to PHGG. Furthermore, fermentation of wheat dextrin was slower leading to a gradual and constant increase of SCFA's production over the measured period of 24 hours, in contrast to the fermentation of inulin that was fermented fast reaching a first peak in SCFA production already at 4 hours, suggesting that it may cause excess gas production.

Few in vitro studies have been conducted with oats. Kim & White examined fermentation of high, medium, and low molecular weight (MW) beta-glucan from oat. The low MW beta-glucan produced greater amounts of SCFA than the high MW after 24 hours of fermentation (52). Connolly et al examined fermentation of different sized oat flakes, compared to oligofructose and cellulose. The larger sized oats resulted in a propionate rich SCFA profile and a significant increase in butyrate. The smaller sized oats did not produce significantly higher levels of butyrate (53).

Prebiotics and whole grains

A prebiotic is defined as 'a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon and thus improves host health' (54). The stimulated bacteria should be beneficial, with bifidobacteria and lactobacilli generally considered beneficial. The definition was recently updated and a prebiotic is described as "A selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microbiota that confers benefits upon host well-being and health" (55). The main candidates for prebiotic status include inulin, fructo-oligosaccharides, galacto-

oligosaccharides, soly-oligosaccharides, xylo-oligosaccharides, pyrodextrins, and isomalto-oligosaccharides (56).

All non-digestible carbohydrates that reach the gut may alter the microflora, but the selective properties of prebiotics support an increase in bifidobacteria and lactobacilli at the expense of other bacteria in the gut, including Bacteroides, clostridia, eubacteria, enterobacteria, and enterococci. There are currently no standards that allow a substance to be called a prebiotic. The candidates described above have supportive clinical data that they will alter colonic microflora in the manner considered beneficial. Yet wide ranges are found in microbial growth responses in healthy human subjects and the microflora are altered by diet, drugs, antibiotics, age, etc.

Not all fermentable carbohydrates in the gut come from non-digestible carbohydrates. The mucus lay of the gut provides oligosaccharides that are also fermented and alter bacterial growth. Most studies have measured changes in fecal content of microbiota, although the bacteria that grow adjacent to the colonic mucosa may be particularly important in immune function for the host. Langlands et al found that bifidobacteria numbers could be increased more than 10-fold in the mucosa of the proximal and distal colon in patients fed 15 g of a prebiotic mixture containing 7.5 g inulin and 7.5 g FOS/day for 2 weeks prior to colonoscopy (57).

Prebiotics and immunity

The immune system guards the body against foreign substances and protects from invasion by pathogenic organisms. The gut's immune system scans and inhibits growth of harmful pathogens while promoting growth of beneficial organisms (58). The immune

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system is divided into the innate or non-specific immune system and the acquired or specific immune system. Non-digestible carbohydrates can affect immunity by altering the number and composition of the intestinal microflora, but also may affect the gut-associated lymphoid tissue (GALT). The largest immune organ is situated in the gut where continuous exposure to diverse antigens takes place. The GALT contains about 60% of all lymphocytes in the body (59).

The gut is also an important organ of hormonal communications. It communicates with the brain to tell us what to eat and drink and when we have had enough (60). The importance of the gut microflora in the prevention of obesity has only recently been considered. A review of the ability of prebiotics to improve acute disorder and chronic disorders support the importance of the gastrointestinal microflora in health and disease, but find little data from human studies of an immune effect of prebiotics distinct from the alteration in microflora caused by prebiotics (61). Bruck concludes that the success of prebiotics lies in their ability to improve resistance to pathogens by increasing bifidobacteria and lactobacilli, which lowers the gut pH to a level at which pathogens are no longer able to complete. But, adverse effects of prebiotics have been found in vitro and in experimental animals and must be considered when designing prebiotics for human use.

Prebiotic potential of grains

Cereal grains are important sources of dietary fiber in the food supply. The dietary fiber content of grains varies greatly, ranging from 15% in rye to 4% in rice (62). The majority of dietary fibers occur in decreasing amounts from the outer pericarp to the

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endosperm, except arabinoxylan, which is also a major component of endosperm cell wall materials. Processing of grains will alter the carbohydrate composition of the fractions.

Fructo-oligosaccharides (FOS) are known prebiotics. The FOS content of all grains has not been systematically n determined, but wheat is particularly high in FOS, containing 0.8 to 4.0% of FOS in fresh material (63). Biesiekierski et al measured fructans in a wide range of food stuffs and found that oat 0.11 g/portion while rye had 0.6 g/portion (64). At least two types of oligosaccharides exist in cereal grains, galactosyl derivatives of sucrose, stachyose and raffinose, and fructosyl derivatives of sucrose, fructooligosaccharides (65). The distributions of these polymers within the cereal grain have not been fully established. For wheat, oligosaccharides have been reported in the bran (66) and germ (67). Wheat germ is particularly high in raffinose oligosaccharides, 7.2% on a dry basis (62). Oligosaccharides can be isolated from cereals grains and purified, although extractions have not been fully developed due to complexities and connections with other molecules, including proteins. Cereal grains are also concentrated sources of resistant starch, which has been described as an emerging prebiotic, with supportive animal trials but limited human studies (68).

Since grains are an important source of fermentable carbohydrate in the gut, there is interest in the prebiotic properties of whole grains. In cereals, beta-glucans and arabinoxylans are the major dietary fibers fermented by bacteria in the human gastrointestinal tract (68). Bifidobacteria and lactobacilli cannot ferment cereal beta-glucans well in vitro (69), but can utilize oligosaccharides resulting from its partial

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hydrolysis. In vitro studies find that Bifidobacterium longum and Bifidobacterium adolescentis can ferment arabinoxylan from cereal sources as well as arabinoxylan oligosaccharides (69). Potentially harmful bacteria such as escherichia coli, Clostridium perfringens, or Clostridium diffcile do not directly ferment these substrates. Rye bran rich in arabinoxylan was bifidogenic when fed to mice (70).

Screening methods to compare prebiotic effect of dietary oligosaccharides have been developed (71). Prebiotic index (PI) equation is based on the changes in key bacterial groups during fermentation. The bacterial groups incorporated into this PI equation include bifidobacteria, lactobacilli, clostridia and bacteroides. The changes in these bacterial groups from previous studies were entered into the PI equation to determine a quantitative PI score. PI scores were then compared with the qualitative conclusions made in these publications. It is hope that the PI equation could be used to quantify prebiotic effect in vitro and screen potential prebiotic substances.

Costabile et al conducted a double-blind, randomized, crossover study of whole grain and wheat bran in 31 volunteers (72). Numbers of fecal bifidobacteria and lactobacilli were significantly higher with whole grain ingestion compared with wheat bran ingestion. No significant differences in fecal SCFA with ingestion of either cereal. No adverse intestinal symptoms were reported and wheat bran ingestion increased stool frequency.

In addition to this, some in vitro studies have been conducted on prebiotic potential of grains. Karppinen et al compared in vitro fermentation of polysaccharides of rye, wheat and oat brans and inulin (73). The brans were first digested enzymatically to remove starch and protein. The digested brans and inulin were then fermented with human fecal

inoculum. The progress of fermentation was measured by following the consumption of carbohydrates and the production of short-chain fatty acids and gases. Inulin, a short fructose polymer, was consumed significantly faster than the more complex carbohydrates of cereal brans. Carbohydrates of oat bran (rich in beta-glucan) were consumed faster than those of rye and wheat brans (rich in arabinoxylan). In all brans, glucose was consumed faster than the other main sugars, arabinose and xylose, and arabinose degraded only slightly.

Formation of gases was fastest and greatest with inulin. Rye, wheat and oat brans were fermented in a similar way, slower than inulin. Fermentation of rye bran was found to enhance the bioactivity and technological potential of the bran (74). The presence of indigenous lactobacillus and enzymes concentrated on the outer layers of the grains contributed to the changes seen in bran during the fermentation. The authors suggest that the extent of these changes can be modulated by changing the milling process during separation of the bran prior to fermentation.

Korakli et al measured the metabolism by bifidobacteria of exopolysaccharide (EPS) produced by Lactobacillus sanfranciscensis (sourdough) (75). In addition to polyfructan (FOS) found in wheat and rye, these flours contain kestose, hystose and other fructooligosaccharides similar to inulin (76). Arabinoxylan undergoes degradation by cereal enzymes during the dough resting time causing solubilization of arabinoxylan (75). In addition to the polysaccharides from wheat or rye, strains of Lact sanfranciscensis produce exopolysaccharides in wheat and rye sourdough. This EPS is a high molecular weight fructan of the levan type. Few data are available on the metabolism of

polysaccharides isolated from wheat and rye by bifidobacteria and lactobacilli. Korakli et al found that bifidobacteria metabolize fructan from Lact. Sanfranciscensis (75). Polyfructan and the starch fractions from wheat and rye, which possess a bifidogenic effect, were degraded by cereal enzymes during dough fermentation, while the EPS were retained.

Some clinical studies have examined changes in gut microflora with consumption of grain fractions. Metteuzzi et al conducted a double blind, placebo-controlled study in 32 healthy subjects with a prebiotic wheat germ preparation (77). After 20 days of supplementation of the product, the coliform population and pH decreased significantly. The number of lactobacilli and bifidobacteria increased significantly only in subjects with low basal levels. No significant changes were found for other bacterial groups and total bacteria did not increase. An arabinoxylan-rich germinated barley product induced proliferation of bifidobacteria in the human intestine (78). The germinated barley product was also fed as treatment in experimental colitis in comparison with probiotic or antibiotic treatment. The authors conclude that modification of the intestinal microflora by prebiotics, including the germinated barley fiber, can be a useful adjunct in the treatment of ulcerative colitis (79). Additional animal trials supporting the use of the germinated barley for nutraceutical treatment of ulcerative colitis are described by Bamba et al (80).

Other mechanisms for oats effect on gut function

The viscosity of fibers in the gut is thought to alter physiological function. Diketman et al compared a range of fiber source in an in vitro system (81). Guar gum, psyllium, and

oat bran exhibited viscous characteristics throughout small intestinal simulation. Juvonen et al compared gastrointestinal hormonal responses in healthy human subjects consuming oat bran-enriched beverages (82). The oat bran beverage with low viscosity induced a greater postprandial increase in satiety, cholecystokinin, glucagon-like peptide, and peptide YY. Gastric emptying was faster after low-viscosity oat bran beverage consumption. There results support that viscosity difference in oat beta-glucan in a liquid meal with identical chemical composition strongly influences short-term gut hormone responses, suggesting the importance of food structure in the modulation of postprandial satiety-related physiology

Conclusion

Oats provide necessary dietary fiber, resistant starch, and oligosaccharides to the diet. They can also increase stool weight, but much of the increase is due to bacterial mass rather than fecal fiber. Carbohydrates that escape digestion and absorption in the small intestine and are fermented in the large intestine may be 'prebiotics.' Resistant starch and beta-glucan also show promise as prebiotics. The viscosity of oats may also provide important physiological properties. For example, clinical trials show that viscous oat bran can alter gut hormones. Unfortunately, few clinical trials of oats or oat bran with gut health as the focus have been published, so extensive work remains to define the role of oats in digestive health.

CHAPTER THREE: Effects of fiber consumption on body weight & body mass

index, a review of epidemiological evidence and randomized controlled trials

<u>Introduction</u>

Recent data indicates that the United States has the highest mean body mass index (BMI) among other countries resulting in one in three adults having a BMI >30kg/m2 (83-84). In addition to this, the incidence of adult obesity from the 2009-2010 National Health and Nutrition Examination Survey (NHANES) shows that 35.5% of adult men and 35.8% of adult women are obese (85). Several reasons may explain what causes obesity such as sedentary behavior, genetics, and easy access to a low-cost and energy dense food supply. Methods that improve nutrition and physical activity are needed to help control obesity, yet the long-term effectiveness of any particular dietary approach has not been identified.

Dietary fibers can positively influence risk factors for obesity by promoting satiety and negative energy balance (86). Historic and epidemiologic data implies that obesity is uncommon in populations that consume a high-fiber diet and widespread in populations that consume a low-fiber diet (87). Other evidence from prospective studies such as Nurses' Health demonstrate that women with a higher increase in fiber gained less body weight over a twelve year period (88). Similar results have been replicated in other long-term studies which suggest an association between fiber consumption and the prevention of weight gain (89-91).

National recommendations for fiber are 38g/day for men and 25g/day for women; however a recent analysis from NHANES reported that the mean fiber intake in the United States is only 14.8 g/day (92). Furthermore, individuals with obesity (BMI≥30) reported lower fiber intake compared to individuals with normal weight or overweight

(14.6g/day vs. 15.6g/day) (92). The gap in American's fiber intake led the 2010 dietary guidelines committee to identify fiber as a nutrient of public health concern (93). This is because foods that are sources of fiber such as legumes, nuts, fruits and vegetables are not adequately consumed in the American diet (93). To fill the fiber gap, significant public health efforts are still needed to increase fiber consumption among Americans.

One of the potential advantages of fiber is that adequate consumption can reduce body weight and BMI. In the past ten years, there have been a number of studies published on this (88-91 & 94-110). The studies are a mix of cross sectional, prospective cohort and intervention trials; all which deserve consideration when examining recent data. Previous reviews focused on fiber and body weight intervention studies published prior to the year 2000 (87, 111), therefore the purpose of this paper is to provide an updated review of the scientific evidence regarding dietary fiber and body weight or BMI.

Methods

Selection of literature

A systematic literature search was conducted in January 2012 to find research articles on the association between dietary fiber and body weight or body mass index (BMI). For the purposes of this review, fiber was defined as all forms and sources in food and in the diet. This includes intrinsic, modified or novel fibers such as inulin, Konjacmannan, beta-glucan, oat bran, and other non-starch polysaccharides. Foods that are sources of fiber were also included such as fruits, vegetables, cereal, oats and cocoa. The PubMed database was searched using medical subject heading (MESH) terms related to dietary fiber and body weight or BMI. These terms included: (fiber OR fibre OR whole grain)

AND (body weight) OR adiposity OR (body fat) OR (body mass index). Additional

articles were identified from the reference lists of articles uncovered in the Pub Med

Search. Inclusion criteria were: adult human population, normal weight, overweight, or

obese, study design (cross-sectional study, prospective cohort or randomized controlled

trial), body weight or BMI as a primary or secondary outcome, published in the year

2000 or later and in English. Studies were excluded if they did not include body weight

or BMI as a primary or secondary outcome or did not meet the definition of fiber for the

purposes of this review.

Extracted studies

The PubMed search initially found 1,021 articles, but many of these did not meet our

search criteria. A second search was conducted with Medical Subject Heading Terms

(MESH) and a total of 547 articles were retrieved. Of these, 367 studies were eliminated

based on title and another 160 studies were eliminated based on the abstract. A total of 21

studies remained and met the inclusion criteria for this review: 4 are prospective cohort

studies, 4 are cross-sectional, and 13 are randomized controlled trials. A summary of the

results is presented in Figure 3-1.

Figure 3-1. Results from PubMed Search

Initial Search
1,021 articles

Search 2-547 articles
-367 deleted by title
- 159 deleted by
abstract

4 Prospective cohort
studies

4 Cross-sectional
studies

13 Randomized trials
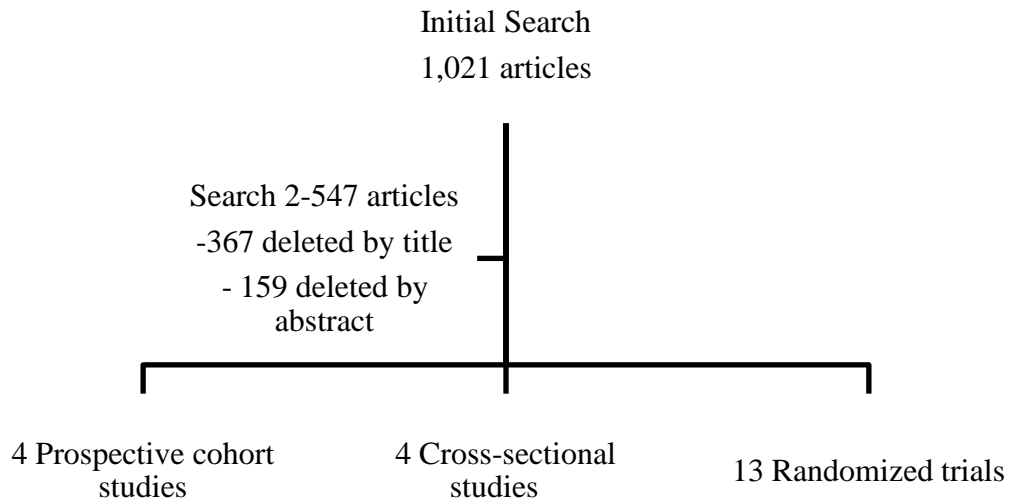
Results

Cross-sectional studies

Four cross-sectional studies met the inclusion criteria from our Pub Med search (94-97). Murkami et al investigated the associations between dietary fiber intake and BMI in 3,931healthy and normal weight Japanese women between the ages of 18 and 20 years. Fiber exposure was measured by a diet history questionnaire. The results showed that total dietary fiber intake was negatively correlated with BMI (mean difference between the lowest and highest quintiles= -0.6kg/m2; p for trend <0.0001) (94). Similarly, Howarth et al compared the associations of dietary fiber with BMI in 2,685 younger (20-59) and older (60-90) men and women who were overweight. Two twenty-four hour recalls were used to measure fiber intake. The results showed that in the younger group,

diets with a lower fiber intake was independently associated with a higher BMI (p=0.016) (95).

Furthermore, van de Vijver et al assessed the association of cereal fiber intake with BMI in 4,237 overweight and obese men and women between the ages of 55-69 years. A 150 item self-administered food frequency questionnaire was used to measure fiber intake. The results showed that cereal fiber intake was inversely associated with BMI in men only, p<0.01 (96). Finally, Newby et al examined the associations between cereal fiber intake and BMI in 1,516 overweight men and women (27-88 years) part of the Baltimore Longitudinal Study on Aging. Fiber intake was measured with a dietary record collected for seven consecutive days. The results demonstrated that BMI was inversely related to cereal fiber intake (p<0.0001) and those in the highest quintile of cereal fiber intake also had the lowest prevalence of overweight (p=0.0003) (97) (Table3-1).

<u>Prospective Cohort Studies</u>

Four long-term prospective cohort studies looked at associations between dietary fibers with long-term weight gain or weight change (88-91) (Table 3-2). Du et al prospectively followed 89,432 overweight men and women between the ages of 20-78 that were part of the DiOGenes project (Diet, Obesity, and Genes). Participants came for 5 European countries including Italy, Germany, Denmark, the Netherlands, and the United Kingdom. Using a validated food frequency questionnaire, total fiber, cereal fiber, and fiber from fruits and vegetables were estimated. After 6.5 years of follow-up, the results demonstrated that 10g/day of total dietary fiber intake was associated with an annual weight change of -39g/year, p=0.01 (89). The results for cereal fiber were similar, a

10g/day intake of cereal fiber was associated with an annual weight change of -77g/year, p=0.01. Finally, fruit and vegetable fiber intake was also positively associated with weight change. For a 10g/day intake the weight change was 2g/year, p=0.05. Altogether, larger and significant changes in weight were observed for total and cereal fiber consumption; however the fiber from fruits and vegetables did not display as large a change in weight.

Similarly, Iqbal et al examined whether associations between dietary fiber intakes predicted five year changes in body weight. In this study, 1,762 normal and overweight men and women between the ages of 30-60 years reported their dietary information by a 7-day food record. The results demonstrated that fiber intake was inversely associated with change in body weight in women but not in men (-22.8kg, p=0.03 vs. 8.7kg, p=0.14 for men) (90). Furthermore, Koh- Banerjee et al determined the associations between fiber from cereal, fruit, and vegetables with changes in weight gain over an 8 year period. The sample consisted of 27,082 healthy men (40-75 years) from the Health Professionals Follow-up Study. Dietary exposure was measured through the use of a semi-quantitative food-frequency questionnaire. The results showed that for every 20g/day increase in cereal fiber, weight gain decreased by 0.81 kg, p for trend <0.0001. Similar results were found for fruit fiber, but not for vegetable fiber. For every 20g/d increment in fruit fiber, weight gain was reduced by 2.51kg, p for trend <0.0001 (91).

Finally, Liu et al prospectively followed 74,091 females (38-63 years) part of the Nurses' Health Study for 12 years. To determine intakes of dietary fiber, exposure was measured through a food frequency questionnaire. The results showed that compared

with women in the lowest quintile of fiber intake, women who increased their intake of

dietary fiber to the highest quintile reduced their risk of major weight gain by 49%

(OR=0.51;95%CI:0.39,0.67;P<0.001 for trend) (88).

<u>Randomized Controlled Trials</u>

   Thirteen studies met our inclusion criteria (Table 3-3). The evidence from these studies

are varied; 8 studies revealed that body weight or BMI did not significantly change

during the intervention periods (98-99, 102, 105-107, 109-110), whereas 5 studies

demonstrated significant changes in body weight or BMI after the intervention period

(100-101, 103-104, 108). The studies that did show reductions in body weight or BMI

supplemented soluble sources of fiber. For example, Lyon et al conducted a double-blind

randomized controlled trial where 59 overweight and obese men and women (18-50)

years consumed a novel fiber called PolyGlycolpleX (blend of konjac, xantham gum, and

alginate) or inulin for 15 weeks. Participants in the experimental group consumed the

soluble fiber twice daily blended in yogurt. The level of the fiber started at 6g during the

first week and then gradually increased to 10g by week three until the end of the trial.

Participants in the control group followed the same pattern of consumption with inulin.

The results from this study were near statistical significance, the data demonstrated that

after the 15 week period, women in the experimental group had a lower weight when

compared to women in the control group (78.9kg vs. 85.2kg, p=0.053) (100).

   Similar to this, Wood et al conducted a 12 week double-blind randomized controlled

trial with 60 overweight and obese men between the ages of 20-69. Men consumed a

viscous and soluble fiber called Konjacmannan three times a day before each meal or a

placebo (maltodextrin). The total level of fiber consumed in the experimental and placebo group was 3g per day in capsule form. After 12 weeks, the results demonstrated a significant change in body weight in both groups. Men in the experimental group had a mean change of -7.4kg, $p<0.001$ and men in the placebo group had a mean change of -7.5kg, $p<0.001$ (108).

Other studies that found significant reductions in body weight and BMI supplemented a higher level of fiber (101, 104). Li et al conducted a 12 week double-blind randomized controlled trial with 120 overweight men between the ages of 20-35 years. Men in the experimental group consumed 17g of a soluble fiber derived from wheat and corn called Nutriose. Men consumed Nutriose twice daily (34g total fiber) mixed in with 250mL of orange juice, whereas men in the control group consumed 17g maltodextrin twice daily mixed with juice. After the 12 week period, significant reductions in body weight and BMI were found. Men in the experimental group reduced body weight and BMI more than men in the control group (72.4kg vs. 73.9kg, $p<0.001$ for body weight and 24kg/m2 vs. 24.5kg/m2, $p<0.001$ for BMI) (101).

Birketvedt et al carried out 3 separate 5- week double blind randomized controlled trials in 176 healthy and overweight men and women between the ages of 30 and 60 years. The objective was to test three different viscous fiber products (Glucosahl, Chromobalance and App-Trim) and determine their effectiveness on reducing body weight. The test products were made of a combination of fiber types such as guar gum, alginate, and glucomannan and were consumed as tablets three times a day before each meal. The total level of fiber supplemented was 18g a day for the Glucosahl product, 3g a day for the

Chromobalance product and 3 g a day for the Appe-Trim product. In terms of weight

reduction, participants in all three experimental groups experienced significant decreases

(4.4 ± 2kg, p<0.001 and 3.8 ± 0.9kg, p<0.01 and 4.1 ± 6kg; p<0.01) for Glucosahl,

Chromobalance, and Appe-Trim groups respectively (104).

  Finally, in a randomized crossover study, Lee et al tested the effects of a fiber-rich diet

on body weight in 21 non-obese and obese men and women (103). Subjects were

randomized to consume either a control diet that consisted of standard rice for 4 weeks

(6g fiber per day) or an experimental diet that consisted of Goami rice for 4 weeks,

(14.4g fiber per day). Subjects experienced a 6 week washout period between treatments

where they were allowed to consume their usual diet which mostly consisted of standard

refined rice.

  The results from this study demonstrated significant decreases in both body weight and

BMI in obese subjects after the experimental diet (67.7 ± 2.1 vs. 65.7 ± 2.0kg, p<0.001;

BMI, 26.9 ± 0.5 to 26.0 ± 0.6, p<0.001 for before vs. after) (103).

Discussion

  The purpose of this review was to evaluate human studies to determine whether or not

consumption of dietary fiber had an effect on body weight or BMI. In total, 21 studies

met the inclusion criteria from the Pub Med search and these were a mixture of cross-

sectional studies, prospective cohort studies and randomized controlled trials. To

summarize, all of the cross -sectional and prospective cohort studies demonstrated that

dietary fiber was significantly associated with a lower body weight or BMI (88-91, 94-

97). On the other hand, less than half of the randomized controlled trials reported a

significant effect of dietary fiber on body weight or BMI (100-101, 103-104, 108). Since

fibers have variable physiochemical properties, they can behave differently when

supplemented in food; altogether this may help explain why the results were so

inconsistent from study to study. For this reason, the remainder of the discussion will be

organized by type of fiber supplemented in each of these trials.

<u>Fiber types: Lupin kernel</u>

Two studies showed no differences in body weight or BMI after supplementing with

lupin kernel fiber (102, 106). Hodgson et al investigated the effects of a lupin kernel

fiber diet on body weight in 88 men and women recruited for a four month randomized

controlled trial. Subjects consumed either a control or lupin kernel fiber bread and met

with a dietitian bi-weekly to make sure the test bread was incorporated into their usual

diet. In the control group, the subjects' consumed their usual diet plus the incorporation

of 4 slices of white bread each day. The total fiber from the control bread was 9.6g fiber

per day. In the test group, the subjects' consumed their usual diet plus the incorporation

of 4 slices of lupin kernel bread each day. The total fiber from the test bread was 42.8g.

The results demonstrated no significant differences between the treatment groups in

body weight or BMI after a 16 week period, furthermore no differences were found in

separate sub-group analyses according to gender (102). The authors noted that it may

have been the fiber type in this study that did not have a significant effect. For example,

the dietary fiber present in lupin is derived from Lupinus angustifolius, a species that is

primarily insoluble. Even though lupin fiber has demonstrated that it can increase satiety,

it remains uncertain whether or not it can act to decrease body weight in the long- term.

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Furthermore, the baseline intake of fiber in the test group was not that low (28.9±12.3g/day), therefore it is possible that the men and women were already acclimated to fiber in their diet and additional consumption did not help lower their body weight or BMI.

Belski et al also reported no significant changes in body weight or BMI after subjects consumed a lupin-kernel or control diet for 8 months (106). In this study, men and women between the ages of 22-71 were randomized into either a control group (n=63) or a lupin group (n=68). Subjects in the control group incorporated the provided foods (bread, biscuits or pasta, 12.2g/fiber per day) into their usual diet. Similarly, subjects in the test group incorporated bread, biscuits, and pasta enriched with lupin fiber into their usual diets (33.3g/fiber per day). No significant differences were observed between treatment groups in body weight or BMI. It is uncertain why no differences were observed especially since these subjects' remained on the fiber enriched diet for 8 months. Information on baseline dietary fiber intake was not provided, therefore it is possible that subjects' were already high fiber consumers and did not respond to the additional fiber.

Oat bran and beta-glucan

Three intervention studies supplemented oat bran or soluble beta –glucan and did not observe any significant changes in body weight (99, 107, 110). Kristensen et al conducted a double-blind randomized crossover study in 24 healthy men and women who completed two week dietary interventions of either a low-fiber control diet (16g fiber/day) or oat bran diet (26g fiber/day). A standardized diet was provided for the

subjects' consisting of breakfast, lunch, and dinner along with snacks. The oat bran was

incorporated into bread for the experimental diet. All foods were prepared in a metabolic

kitchen and subjects were required to consume lunch at the testing center but allowed to

consume breakfast, snacks, and evening meals at home. Subjects were instructed to eat

all food, but if they couldn't they were required to bring foods back to the metabolic

kitchen. After each of the two week intervention periods, the results showed that changes

in body weight did not differ between groups (-0.3±0.5kg for oat bran versus 0.0±0.7kg

for control, p=NS) (99).

Similarly, Beck et al conducted a single-blind randomized controlled trial in 56 healthy

females between the ages of 19-45 years. Women were assigned to one of three dietary

intervention groups and consumed each diet for three months. A basal metabolic

requirement for energy was calculated to help formulate each diet. Foods with varying

amounts of beta-glucan were provided to each participant and were consumed at home.

These foods included ready to eat cereal, porridge, muesli bars, and a snack. The average

amount of beta-glucan in diets are <1g/day for control group, 5-6g/day for Group 1, and

8-9g/day for Group 2. Dietary compliance with the foods was measured by review of

food records by a registered dietitian. After the 3 month period, the results demonstrated

that weight loss was not significantly different between any of the groups (p=0.921)

(107).

Finally, Saltzman et al carried out an 8 month randomized controlled trial with 41

normal weight, overweight and obese men and women between the ages of 19-78 years.

The objective of this study was to investigate the effect of oat consumption on changes in

body composition. This was a controlled study divided into three phases. During phase 1 (2 weeks), all subjects consumed a control diet low in fiber (6.2g/day) or an oat diet (6.4g/day). During phase 2(5 weeks), subjects consumed a control diet (6.7g/day total fiber) or an oat diet (8.9g/day total fiber). Phase 3 (6 months) was a follow-up period where subjects were free to consume as much or as little food as they wished. Food was initially provided during the initial 2 weeks of phase 3, but then subjects cooked their own food at home for the remainder of the study. Over the duration of the study, none of the weight and body composition changes were significant (p=NS) (110).

<u>Cocoa bran</u>

Sarria et al carried out a 12 week single-blind randomized crossover intervention where 44 healthy men and women younger than 75 consumed two soluble cocoa products that contained different levels of fiber. After a one week run-in phase of consuming a non-cocoa product, subjects in Group A consumed a cocoa product with milk that contained 4.5g/fiber for 4 weeks and then crossed over to Group B which consisted of another cocoa product with milk that contained 13.2g/fiber for 4 weeks. The treatment periods were separated by a 3 week washout period. No significant changes in body weight were observed after either test periods, p=NS (98). Although no changes in body weight were observed, the consumption of Group B cocoa product did result in a greater dietary fiber intake compared to the non-cocoa run-in phase (23.91g/fiber per day vs. 17.29g/fiber) (98).

Nutriose (A soluble fiber derived from wheat & corn)

Pasman et al conducted a double- blind placebo controlled trial in 43 healthy men between the ages of 20-45 years (109). Subjects completed a one week run in phase where they consumed 22.5g of maltodextrin in powder form and were then randomized into one of three groups. Group one consumed 15g daily of Nutriose test fiber for the first week and then increased the amount to 30g per day for four weeks. Group two consumed 22.5g daily of Nutriose followed by 45g for the next four weeks. The control group consumed 11.25g of maltodextrin for the first week followed by 4 weeks of 22.5g of maltodextrin daily. After the five week period, body weight in group one and two did not change compared to the control group, p=NS (109). These results are contradictory to another study that demonstrated changes in both body weight and BMI after supplementing with 34g/day of Nutriose fiber (101). The difference in study populations and intervention time may help explain this discrepancy. Li et al had subjects that were overweight and consumed Nutriose for a total of 12 weeks whereas Pasman et al had normal weight men that consumed the fiber for 5 weeks (109). Even at high levels, it is possible that longer intervention times are required to see any beneficial effects of this fiber.

Other

Aller et al carried out a 3 month randomized controlled trial with 53 healthy men and women between the ages of 18-70 years. Subjects were randomized into one of two groups that received different fiber diets. Those in group one received a diet with 10.4g of total fiber, of which 1.97g was soluble fiber (mix of pectins, gums, mucilages) and

8.13g was insoluble fiber (hemicellulose, cellulose, and lignins). Those in group two received a diet with 30.5g of fiber of which 4.11g were soluble fiber and 25.08g was insoluble fiber. After a five month period, no significant changes in body weight were reported for either group (65.8± 9.4kg vs. 64.4±11.5kg for Group 1 vs. 65.8±12.5kg vs. 64.5±12.1kg for Group 2) (105). No information was provided as to how the diets were delivered, it is unknown whether or not the foods were provided in a controlled setting or if subjects were instructed to incorporate more fibrous foods into their usual diets. This lack of information makes it difficult to discern why the results were not significant.

Conclusion

The evidence from long term prospective studies demonstrates that an inverse relationship exists between the intake of high-fiber foods and weight gain (88-91). The results from cross-sectional studies reveal that total fiber or cereal fiber intake are inversely associated with BMI (94-97). On the other hand, the results from randomized trials are mixed with few studies demonstrating changes in body weight or BMI (100-101, 103-104, 108). These studies supplemented viscous and soluble fibers such as Konjacmannan, PolyGlycoplex, Nutriose, and Glucomannan for time periods that varied from 12-15 weeks. The research also shows that consumption of foods such as Goami rice, a natural source of fiber, is effective at lowering body weight in a population of normal weight and obese men and women (103).

Altogether, it is still uncertain what amount of fiber needs to be consumed to see reductions in body weight or BMI. Many of the randomized studies that did not find significant changes intervened with levels of fiber as low as 5g (98, 107) and as high as

45g (102). Similarly, the intervention times were as short as 4 weeks (99) and as long as one year (106). Altogether, the epidemiological evidence from this review confirms an association between fiber consumption and body weight/BMI, but does not establish a cause and effect relationship between the two. Results from randomized trials are inconsistent which makes it difficult to determine what amount and type of fiber needs to be consumed for a healthy body weight. Future research is warranted to help elucidate this relationship and from here on out, randomized trials should be designed with longer intervention times and higher levels of fiber.

Table 3-1. Cross-sectional studies that measured the effects of fiber consumption on body weight or body mass index

Reference	Population	Measure of fiber	Fiber Intake[1]	Results
Murakami et al (94)	n=3,931, Nrmwt F 18-20 yrs	DHQ	6.5g/day	(-) correlation w/ fiber intake & BMI , p =0.0001
Howarth et al (95)	n=2,685, Ovwt M/F, 20-90 yrs	2-24 hour recalls	M/F 20-59yrs 1.8g/day M/F 60-90yrs 2.3 g/day	↓ fiber intake was assoc. with a ↑BMI, p=0.016[2]
Van de Vijver et al (96)	n=4,237, Ovwt /Obs M/F 55-69 yrs	FFQ	Men 28.1g/day Women 25.1g/day	Total & cereal fiber intake inversely assoc. w/ BMI p<0.01
Newby et al (97)	n=1,516, Ovwt M/F, 27-88 yrs	7 diet records	14.55-25.9g/day	Cereal fiber intake was inversely assoc. w/ BMI & BW, p <0.0001 & <0.0004
[1] Mean fiber intake at baseline [2]Results are for men only 20-59 yrs				
BMI=body mass index, BW=body weight, FFQ=food frequency questionnaire, DHQ=diet history questionnaire ↑=higher,↓=lower, assoc.=associated, (-)=negative, w/=with, hlthy=healthy, nrmwt=normal weight, ovwt=overweight, obs=obese, yrs=years				

Table 3-2. Prospective cohort studies that measured the effects of fiber consumption on body weight or body mass index

Reference	Population	Measure of fiber	Fiber intake[1]	Results
Liu et al (88)	n=74,091, Hlthy F 38-63 yrs	FFQ	16±4g/day	Women w/ ↑ fiber intake had a ↓ risk of wght gain vs. women w/ lower fiber intake p<0.0001
Du et al (89)	n=89,432, Ovwt M/F 20-78 yrs	FFQ	22.8 ±5.2g/day	For every 10g/day ↑in total fiber intake, the est. for wght gain was -39g/yr p=0.01
Iqbal et al (90)	n=1,762, Nrmwt & Ovwt M/F 30-60 yrs	7 day food record	Men: 18.8 ±7.3g/day Women: 13.9±5.5g/day	Fiber intake was inversely assoc. w/ Δ in BW, p=0.03[2]
Koh-Banerjee et al (91)	n=27,082, Hlthy M 40-75 yrs	FFQ	Cereal fiber: 9.2±0.1g/day Fruit fiber: 4.6±0.04g/day	Wght gain ↓for every 20g/day ↑ in cereal fiber & fruit fiber intake p =<0.0001
[1] Mean fiber intake at baseline [2] Results are for women only				
FFQ=food frequency questionnaire, Wght=weight, BW=body weight, w/=with, ↓=decreased, ↑=increased, est=estimate, Δ=change, assoc.=associated,yrs=years, hlthy=healthy, nrmwt=normal weight, ovwt=overweight				

Table 3-3: Randomized controlled trials that measured the effects of fiber consumption on body weight or body mass index

Table 3-3. Human randomized controlled trials that measured the effects of fiber consumption on body weight or BMI				
Reference	**Design & Population**	**Fiber Type**	**Level**	**Results**
Sarria et al (98)	12 wk CO, n=44 Hlthy M/F, age ≤75	Cocoa bran	4.5 or 13.2g/day x 12 wks	No Δ in BW, p=NS
Kristensen et al (99)	4 wk CO, n=24 Hlthy M/F, age 22-30	Oat bran	19 or 26g/day x 4 wks	No Δ in BW, p=NS
Lyon et al (100)	15 wk DB RCT n=59, Ovwt/OB M/F 18-50	PolyGlycolplex or Inulin	6-10g/day x 3 wks	BW in women of HVP group were lower than inulin (p=0.053)
Li et al (101)	12 wk DB RCT n=120, Ovwt M, 20-35	Nutriose or maltodextrin	34g/day x 12 wks	BMI and BW both reduced versus maltodextrin (p<0.001)
Hodgson et al (102)	16 wk RCT, n=88 Ovwt/OB M/F 20-70	Lupin or white bread	41.6g/day or 9.6g/day x 16 wks	No Δ in BW or BMI, p=NS
Lee et al (103)	14 wk CO, n-21 Nrmwgt/OB M/F	Goami or white rice	43.2g/day or 18g/day x 14 wks	BMI and BW were reduced vs. white rice p<0.001
Birketvedt et al (104)	15 wk DB RCT n=176, Hlthy/Ovwt M/F 30-60	Glucomannan, alginate, or guar gum	3-18g/day x 15 wks	Significant ↓ in BW for all 3 fibers p<0.01 for all
Aller et al (105)	3 mo RCT n=53 Hlthy M/F 18-70	Blended fiber	10.4g/day or 30.5g/day x 3 mos	No Δ in BW
Belski et al (106)	12 mo DB RCT n=131 Hlthy M/F 20-71	Lupin or white flour	33 or 12g/day x 12 mos	No differences in BW/BMI, p=NS
Beck et al (107)	3 mo RCT n=56 Hlthy F 19-45	Oat bran	1-9g/day x 3 mos	No Δ in BW p=0.921
Wood et al (108)	12 wk DB RCT n=30, Ovwt/OB M 20-69	Konjacmannan or maltodextrin	3g/day x 12 wks	BW was reduced p<0.001
Pasman et al (109)	5 wk DB RCT n=43 Hlthy M 20-45	Nutriose or maltodextrin	15-45g/day x 4 wks for Nutriose 11-22.5g/day x 4 wks for control	No Δ in BW in Nutriose group, p=NS
Saltzman et al (110)	8 mo RCT n=41 Hlthy/Ovwt/OB M/F 19-78	Oat or low-fiber diet	8.9g/day for oat x 8mos 6.2g/day for low-fiber x 8 mos	No Δ in BW, p=NS
BW=body weight, NS=not significant, BMI=body mass index,Δ=change, wks=weeks, mos=months, ↓=decrease, hlthy=healthy, nrmwt=normal weight, ovwt=overweight, ob=obese, CO=crossover, RCT=randomized controlled trial, db=double blind, m=males, f=females				

CHAPTER 4: Bran fibers do not increase satiety in women who do not exhibit restrained eating

Summary

Background: Satiety, the feeling of fullness from a meal, is a topic that has stimulated a large amount of interest in nutrition research. Foods that are sources of dietary fiber can promote satiety, but previous studies report conflicting results since not all fibers are equally satiating. Soluble fibers such as oat and barley bran have notable health benefits such as reducing cholesterol and slowing gastric emptying, but their effects on satiety are still uncertain. Factors such as dose, variability in processing and products delivering the bran fibers may all influence satiety ratings.

Objective: The objective was to determine differences in satiety response for three breakfast bars, each with a different added fiber (10g of oat bran fiber, 10g of barley bran fiber, and 3g of wheat fiber). In addition, we compared energy intake at an *ad libitum* lunch after consumption of the breakfast bars. We hypothesized that a 10g dose of oat bran fiber or barley bran fiber provided at breakfast would increase satiety and decrease energy intake more than the breakfast bar with wheat fiber.

Design: Randomized crossover design, where each subject completed three visits in random order.

Participants and setting: Participants were 42 pre-menopausal and normal weight women (mean age 25.5±4.7, mean BMI 21.5±2.2 kg/m^2) from the University of Minnesota campus and the Minneapolis/St. Paul metropolitan area.

Intervention: On three mornings at 7:00am, fasted women consumed one of three breakfast fiber bars with their choice of coffee, tea, or water. Each visit was separated by

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at least one week and women were scheduled within the follicular phase of their menstrual cycle. An *ad libitum* pizza lunch was served 4 hours after breakfast.

Main outcome measures: Visual analogue scales (VAS) were used to assess hunger, satiety, fullness and prospective food intake at baseline, 15, 30, 45, 60, 90, 120, 180 and 240 minutes after breakfast. Breath samples were collected at baseline and 240 minutes after breakfast. Gastrointestinal tolerance was assessed by a questionnaire 24 hours after the test visit. An *ad libitum* pizza lunch was served 4 hours after breakfast and plate waste was used to determine energy intake. Twenty- four hour intake was assessed by a food diary.

Statistical Analyses: Treatments were compared using the 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. Outcomes were reported as mean ± SEM. Significant difference was determined by a two-sided test when $p < 0.05$. Statistical analysis was performed by SAS, version 9.3

Results: There were no significant differences between breakfast bars on any of the satiety scales including hunger, satisfaction, fullness, and prospective food intake. There were no significant differences between breakfast bars in energy consumed at lunch or during the 24 hours following the study visit. The fibers were well tolerated and no significant differences were found for gastrointestinal symptoms or colonic fermentation. In terms of palatability, the breakfast bar with oat bran and the bar with barley bran were not preferred by women compared to the wheat fiber bar for visual appeal, taste and pleasantness.

Conclusions: Our results do not support a strong connection between bran fibers such as oat and barley and satiety. We found that these fibers had limited satiating capabilities and behaved similar to a wheat fiber bar (control). Future studies are needed to elucidate this relationship and should focus on a longer intervention period, larger dose of fiber, and understanding if the molecular weight and solubility of the fiber influences satiety ratings.

Trial Registration: This trial was registered at clinicaltrials.gov as NCT01560000

<u>Introduction</u>

Current fiber consumption is well below recommended levels, with <3% of all

Americans meeting the Adequate Intake (AI) recommendation of 25g/day for women and

38g/day for men (22, 112). The public health implications of inadequate fiber intake are

great because fibers have several nutritional and health benefits to offer. This includes the

reduction of postprandial glucose response and promotion of satiety; the feeling of

fullness from consumption of a meal, which can prevent eating between meals (113-115).

Altogether, these benefits may contribute to the reduction of energy intake by altering

appetite; the desire to eat food.

In 2005, the Dietary Guidelines Advisory Committee identified fiber as an "under-

consumed nutrient of public health concern". This parallels what the 2010 committee

recently found, reaffirming that all Americans still need to fill the fiber gap (10). To help

Americans satisfy their fiber requirements, experts on the 2010 Dietary Guidelines

Committee agreed that a realistic solution is that all forms and sources of fiber should be

included in the diet. This includes foods that naturally contain fiber such as whole grains,

fruits, vegetables and legumes along with foods that contain isolated, modified, or

synthesized fibers such as inulin, guar gum, and bran fibers (ex: beta-glucan from oats

and barley) (10). Food manufacturers have recognized the need to increase fiber in

current and new products, but are challenged since not all fibers are equally satiating

(116).

So far, the evidence from acute satiety studies is conflicting since some report a

positive impact on satiety after fiber consumption (117-119), whereas others report no

impact on satiety (120-121). Certain characteristics of fiber such as viscosity and fermentability along with characteristics of individual consumers, such as level and duration of fiber intake may help explain why it is so difficult to find consistent results in satiety research. Soluble fiber, such as beta-glucan from oat and barley bran has notable health benefits that have been extensively studied (9, 122). For example, beta-glucan has been shown to slow gastric emptying, digestion and absorption while it increases the excretion of bile acids to produce an overall reduction in cholesterol (122). This type of fiber received considerable attention in 1997, when the US Food and Drug Administration (FDA) approved the use of a health claim for diets high in soluble fiber from whole oats and the reduction of heart disease. This claim was expanded in 2005 when whole-grain barley and dry-milled barley grain products was included as a source of soluble fiber (123).

In terms of satiety and subsequent meal intake, the efficacy of bran fibers is still unclear. Factors such as dose, variability in processing and products delivering the fiber may all influence satiety ratings; yet dose has been reported to be one of the major determinants (9). For example, in one acute study, the dose responsiveness of beta-glucan from oat bran was tested in extruded breakfast foods and the results demonstrated that subjective satiety improved at a beta-glucan dose of 2.2g and subsequent meal intake decreased by more than 400kJ with a higher beta-glucan dose (>5g) (117). Similarly, Vitaglione and colleagues reported that consumption of a beta-glucan enriched bread (3g) for breakfast resulted in a greater reduction of hunger and increase in satiety when compared to control bread with no beta-glucan. A significant reduction of energy intake

at lunch was also reported subsequent to consumption of the beta-glucan enriched bread for breakfast (118). Although it is still uncertain what the most effective dose of fiber is, results from previous acute satiety studies suggest that larger amounts of fiber are most successful at reducing subsequent energy intake (124).

Based on this rationale, the purpose of our study was to determine differences in satiety response for three different types of breakfast bars with added fiber (10 grams of oat bran fiber, 10 grams of barley bran fiber, and 3g of wheat fiber (control). In addition, we measured energy intake at an *ad libitum* lunch as well as over the 24 hour period after the test visit. Secondary objectives were to determine the effects of these fibers on gastrointestinal tolerance, colonic fermentation and palatability. Our hypothesis was that a 10g dose of oat bran fiber or 10g dose of barley bran fiber provided at breakfast would increase satiety and decrease energy intake more than 3g of wheat fiber.

Methods

In this randomized double-blind crossover study, we compared three different breakfast bars with added fiber (10g oat bran fiber, 10g barley bran fiber and 3g wheat fiber). To control for dinner, subjects were provided with a 16 ounce beverage and a dinner bar that contained the same fiber the night before their test visit. Participants were to be in a fasted state (minimum 12 hours) before they came in the morning of their test visit.

Subjects

The University of Minnesota Institutional Review Board Human Subjects Committee approved all aspects of this research and all subjects provided written informed consent. Participants were recruited by posters placed around the University campus and the surrounding community in Saint Paul and Minneapolis. Subjects were screened over the telephone and were invited into the study if they met the inclusion criteria. Eligible subjects were healthy women between the ages of 18-40 who spoke English and had a body mass index between 18 and 29.9 kg/m^2. Other inclusion criteria were to not smoke, not take any weight loss medication and be weight stable over the last 3 months.

Women were excluded if they did not regularly consume breakfast, were vegetarian or had allergies to ingredients found in any of the test products. Other exclusion criteria were: cardiovascular disease, diabetes mellitus (fasting blood sugar > 126 mg/dl); cancer in prior 5 years; renal or hepatic disease; recent bacterial infection (< 2 weeks); gastrointestinal conditions affecting digestion or absorption, antibiotic use within the past six months, weight loss > 5 kg in prior 3 months (intentional or unintentional); history of drug or alcohol abuse in prior 6 months; lipid-lowering; anti-hypertensive or anti-inflammatory steroid medication use; high fiber intake (3 or more servings of high fiber foods per day);concurrent or recent (within 30 days) participation in an intervention study; restrained eaters (score >11 on the dietary restraint factor of the Three Factor Eating Questionnaire) (Appendix 1) (125). Women who were pregnant, lactating or reported an irregular menstrual cycle were also excluded.

Test bar descriptions

All of the dinner and breakfast bars had comparable nutrient content. A total of 2 productions were required to make the dinner and breakfast bars, therefore the nutrient content is presented for the first production with the percent difference from the second production (Table 4-2). Each test bar was individually sealed and stored at room temperature in the University of Minnesota food laboratory. Breakfast bars were removed from their individual packages just prior to the morning visit and the dinner bars were removed from their package by the subject prior to consumption for dinner.

Study Visits

On 3 separate occasions, women consumed 1 of 3 fiber dinner bars along with a 16 ounce beverage. Women were instructed to consume the dinner bar and beverage by 7:00 pm and come into the laboratory for their study visit at 7:00 am in a fasted state (minimum 12 hours). Visits were held from 7:00 am to 11:00 am Monday-Sunday and were at least 1 week apart. Women participated only during the follicular phase of their menstrual cycle, so some visits were 2 to 3 weeks apart. On the morning of each visit, fasted women were weighed and completed their baseline visual analogue scale (VAS). After the initial VAS was collected, subjects were provided with 1 of 3 fiber breakfast bars along with their choice of coffee, tea or water. Beverages were kept consistent through all 3 visits and subjects were allowed to consume 6 ounces with their fiber bars.

After consumption of breakfast, the VAS for satiety was repeated at 15, 30, 45, 60, 90, 120, 180, and 240 minutes after baseline. Subjects also assessed the palatability of the test bars at 30 minutes by evaluating visual appeal, smell, taste, aftertaste, and

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pleasantness. After completion of the VAS for satiety at 240 minutes, women were presented with an *ad libitum* pizza lunch (Stouffer's, Nestle USA) and were instructed to eat as much or as little as they wished in 20 minutes. Women were then sent home with a folder that contained a food diary and gastrointestinal tolerance questionnaire to be completed over the next 24 hours. During the visits, women were seated in a quiet room and were allowed to read, use laptop computers, work quietly or listen to music. Physical conditions and location of the room were consistent for all visits.

Study Outcomes

Visual analogue scales (VAS)

Satiety was evaluated using questions from a previously validated 100mm VAS (126). Questions were taken directly from the validated literature: hunger-How hungry do you feel? Not hungry at all (0mm) vs. I have never been more hungry (100mm); satisfaction-How satisfied do you feel? I am completely empty (0mm) vs. I cannot eat another bite (100mm); fullness-How full do you feel? Not at all full (0mm) vs. totally full (100mm); prospective food intake-How much do you think you can eat? Nothing at all (0mm) vs. a lot (100mm).

The palatability of the breakfast bar was also assessed using a 100mm scale at the 30 minute time point. Five characteristics were rated including visual appeal, smell, taste, overall pleasantness and aftertaste. These were scored as good (0mm) vs. bad (100mm). Aftertaste was scored as much (0mm) vs. none (100mm) (Appendix 2).

Gastrointestinal tolerance

Gastrointestinal tolerance is a condition in which the unwanted symptoms of fiber consumption do not exist (26). Throughout the literature, assessing tolerance to dietary fibers is not consistent and not one method has been standardized. Subjective measurements vary from study to study and include questionnaires, symptom forms and diaries where subjects are asked to document the occurrence of gastrointestinal side effects (24, 109).

Tolerance to the test fibers was assessed by a ten- item questionnaire that has been previously validated (26). Subject(s) were instructed to complete the tolerance questionnaire twenty-four hours after their study visit. In total, three questionnaires were collected, one after each study visit. The topics on the questionnaire cover parameters such as stomach pain, diarrhea, reflux, discomfort and constipation. Responses are based on a seven point Likert scale with 1 meaning no discomfort at all to seven meaning severe discomfort (Appendix 3).

Fermentation

Two breath samples were collected at each visit. A sample was collected prior to breakfast (baseline) and immediately before lunch (240 minutes). Subjects took a breath and exhaled directly into a mouthpiece that was connected to a collection bag. BreathTracker TM SC (QuinTron Instruments, Milwaukee, WI) was used to analyze the samples. Samples were analyzed for hydrogen and methane content in duplicate as an indicator of colonic fermentation.

Food intake

  Women recorded their detailed food and beverage intake over the next twenty four hours after each visit. Portion guidelines and examples were provided in a study folder that was kept for the duration of all 3 visits. Women were asked to specifically record what time they ate, what they ate, how much, and how the food was prepared. The Nutrition Data System for Research was used to analyze the nutritional content of all meals, including calories, macronutrient and fiber intake (NDS-R 2012, Nutrition Coordinating Center, Minneapolis, MN).

Statistics

  The sample size of 42 women gave 80% power to find an effect size (difference from control/SD) of 0.44, which was similar to the effect size for VAS hunger reported in the literature (117) and from a previous trial (120). Subject demographic characteristics are presented as mean ± standard deviation. Repeated VAS responses at a study visit were summarized as area under the curve by the trapezoidal rule. Gastrointestinal tolerance symptoms were combined using the summary score of all ratings. Treatments were compared using the 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 interactions were checked by the mixed-effects model. Outcomes are reported as mean ± SEM. Significant difference was determined by a two-sided test when $p < 0.05$. Statistical analysis was performed by SAS (version 9.3,2013, SAS Institute Inc.).

Results: Participant Characteristics

Forty- two healthy, normal weight women who did not exhibit restrained eating (mean restraint score 8.1±2.7) participated in this study. The mean age was 25.5±4.7 and the mean body mass index was 21.5±2.2 kg/m2.   Women were also low- fiber consumers with a mean fiber intake of 5.5±3.2 g/day at baseline (Table 4-2).

Satiety: Visual Analogue Scales

There were no differences among the oat bran, barley bran or wheat fiber breakfast bars on any of the satiety scales including hunger, satisfaction, fullness, and prospective food intake (Table 4-3, Figures 4-1, 4-2, 4-3, 4-4).

Fermentation

No significant differences were found between the oat bran, barley bran, or wheat fiber breakfast bars for methane (CH_4) and hydrogen (H_2) production, p=0.17 and p=0.41 respectively (Table 4-3).

Food Intake

There were no significant differences among the breakfast bars in energy consumed at the pizza lunch or during the 24 hours following the study visit (Lunch: 702±30 vs. 679±30 vs. 693± 30; p=0.68) (24-hour: 1762±110 vs. 1743±110 vs. 1706±110; p=0.86, for barley, oat, and wheat bars respectively) (Table 4-3).

GI Tolerance

No severe symptoms or adverse side effects were reported after consumption of any of the fiber bars. No significant differences between breakfast bars were found for GI tolerance at 24 hours (Table 4-3).

Palatability Ratings

The control bar was significantly different from the barley bran bar for visual appeal and significantly different from both the barley and oat bran bars for taste and pleasantness (Table 4-3). Overall, the oat and barley bran bars were less preferred by women in terms of visual appeal, taste and pleasantness. There were no differences among the bars for smell and aftertaste.

Discussion

The findings from this study do not support the satiating effects of oat and barley bran when they are added to a breakfast bar. No significant differences in any of the appetite ratings were found suggesting that soluble bran fibers do not produce a strong satiety response. These results agree with the body of evidence on acute satiety studies that have supplemented soluble fiber in different food forms (25, 116, 120-121, 127). It is uncertain why these fibers did not alter appetite ratings, but it is likely that our short-term measures of fermentation limited our ability to determine actual impacts on satiety. Bran fibers are viscous and slowly fermented; it takes several hours for these fermentable carbohydrates to get to the colon and can take up to 24 hours to be fully digested by the colonic bacteria (127). Another study described that the effects of viscous fibers on appetite and energy intake might appear as early as 6 hours after fiber intake, therefore,

the effects of these bran fibers might not have been apparent at the time of measurement (82).

In addition to this, we found that energy intake at the *ad libitum* lunch did not differ among any of the bars. This is opposite of what we hypothesized, therefore the methodology used to measure food intake is worth mention. In satiety research, *ad libitum* meals can be served as a standardized meal or a buffet style meal (128). A buffet style meal has the advantage of allowing subjects to make their own food choices. This prevents boredom with food, but the disadvantage of this is controlling the amount of fiber a subject consumes. Consuming too much fiber at the *ad libitum* lunch can confound the relationship between the effects of the breakfast fiber and gastrointestinal tolerance. It would be difficult to distinguish if the effects on the gastrointestinal system are from the test fiber consumed at breakfast or from the fiber(s) consumed at lunch.

The advantage of a standardized meal is that it is easy to control. We offered French bread pizza (Stouffers, Nestle USA) that contained no fiber. The weakness of this approach is that women were aware of what time lunch would be served. It is possible that we did not find any differences in food intake because women took into account the future availability of food when deciding on how much pizza they would eat (128). De Graaf and colleagues explain that knowledge about the time until the next meal is a major cognitive factor that plays a role in meal termination; therefore it is possible this occurred during our study (129).

In terms of gastrointestinal effects, all fibers were well tolerated and no adverse symptoms were reported (Table 4-3). This suggests that a 10g dose of bran fiber is

appropriate for consumption and may help women meet recommended levels. We measured breath hydrogen and methane response as a measure of colonic fermentation and found that after women ate the bran fibers, the numbers were less negative than the control. This indicates they were fermented a bit more than the breakfast bar with wheat fiber (Table 4-3). This is an interesting observation, but since we did not find any differences in appetite ratings, we are unable to conclude that increased fermentation induced satiety.

Our breath hydrogen and methane measures indicate that the fibers were readily fermented in the colon, but our results do not imply that the fiber underwent complete fermentation at the time of measurement (through 240 minutes). Since we did not take breath samples at a later time point it is unknown whether or not fermentation continued over an extended period of time. Previous research supports this idea suggesting that fermentation may induce satiety, but not in a short-term study (25, 120).

Lastly, we did find significant differences in regards to the palatability of the fiber bars. The wheat fiber breakfast bar was significantly different from the oat bran and barley bran bar for visual appeal, taste, and pleasantness. This indicates that women did not prefer the breakfast bars with oat and barley bran. Since the bran fiber bars were found to be unpalatable in more than half of the ratings, it is likely that decreased palatability affected our measures of satiety. Yeomans and colleagues have examined the interaction between palatability and satiety (130). They describe an important concept called "learned satiety", in which the sensory properties of foods predict post-ingestive satiety. Furthermore, it has been described that once learned, this association comes to control the

subsequent intake of food (130). In the context of this study, the women found the bran

fiber bars unpalatable and this likely influenced the directionality of our satiety ratings.

  It is important to recognize the limitations of this study when interpreting our results.

First, even though sex differences in satiety responses have been found in previous

research (131), our design included only women, so our results cannot be generalized to

men. Second, we chose to assess *ad libitum* food intake under laboratory conditions,

however it has been suggested that the assessment of energy intake in this setting imposes

a highly artificial environment (132). It is possible that women may have been influenced

by other hedonic signals that can interfere with the regulation of food intake (132).

  In addition to this, we did not receive information regarding the molecular weight or

source of bran fibers in our test bars and some work suggests that different sources of

bran can differ in their molecular weight and viscosity (133). Furthermore, processes

such as heating and baking can decrease the molecular weight of bran fibers which would

make it less viscous and satiating. Our bars were processed; however it is unknown

whether or not this may have hindered us from finding differences in our primary

outcome. It is also reasonable to think that a 10g of soluble fiber was not a large enough

dose to see a difference in an acute study. It is possible that a larger dose would detect

more significant differences, especially if processing decreases the satiating effect of bran

fibers.

  In conclusion, our results do not support a strong connection between bran fibers such

as oat and barley and satiety. We found that these fibers had limited satiating capabilities

and behaved similar to control bar with wheat fiber. Future studies are needed to

elucidate this relationship and should focus on a longer intervention period, larger dose of fiber, and understanding if molecular weight and solubility influences appetite.

Table 4-1: Nutrition Composition of Dinner (D) and Breakfast (B) Bars[a]

	Serving Size (g)		Energy (kcal)		Protein (g)		Sugar (g)		Fat (g)		Fiber (g)	
	D	B	D	B	D	B	D	B	D	B	D	B
Barley	117 ± 0	98 ±0	530±1	459±0	7±13	10±5	43±15	21±9	19±1	17 ± 1	4± 9	3 ± 25
Oat	143 ± 0	103 ± 2	636±2	462±2	8± 8	9±4	48±7	21±15	24±9	18± 14	12 ± 0	11 ± 9
Control	117 ±39	103 ±0	715±0	456±1	10±2	11±3	62±11	22±8	26± 2	16 ± 4	12 ± 4	10 ± 5

[a]Nutrition values are for the 1st production of product, the % difference from the 2nd production is provided

Table 4-2. Participant characteristics [a]

	Age (yr)	BMI (kg/m^2)	Fiber Intake (g/day)	Restraint Score
Subjects (n=42)	25.5±4.7	21.5±2.2	5.5±3.2	8.1±2.7
Range	20-39	18-29	2-12	1-10
[a]Baseline values are presented as means ± standard deviation				

Table 4-3. Summary of results for satiety, GI tolerance, palatability, food intake, & breath hydrogen

	Barley bran	Oat bran	Control	P- value[‡]
Hunger*	15±1	16±1	15±1	0.44
Satisfaction*	20±1	21±1	21±1	0.56
Fullness*	20±1	19±1	21±1	0.44
Prospective Consumption*	18±1	19±1	18±1	0.52
GI Tolerance (24 hours)**	17±1	16.6±1	16.1±1	0.65
Visual Appeal[1]	4±0.3[a]	4±0.3[ab]	3±0.3[b]	0.03
Smell[1]	3±0.2	4±0.2	3±0.2	0.21
Taste[1]	4±0.3[a]	4±0.3[a]	3±0.3[b]	0.01
Aftertaste[1]	6±0.3	6±0.3	6±0.3	0.55
Pleasantness[1]	4±0.3[a]	4±0.3[a]	3±0.3[b]	0.02
Pizza lunch (kcal)[2]	702±0.30	679±30	693±30	0.68
24-hour (kcal)[2]	1762±110	1743±110	1706±110	0.87
Hydrogen (H$_2$) ppm[3]	-3.0±1.6	-3.0±1.6	-6.0±1.6	0.17
Methane (CH$_4$) ppm[3]	-0.4±1.4	0.7±1.4	-1.8±1.4	0.4
[†]Value is for the overall F-test				
*Data is presented as the mean AUC ±SEM, **Data is presented as the mean sum of scores ±SEM				
[1]Scale is 0-10, values are mean ±SEM, treatments with different letters are significantly different				
[2]Data is presented as the mean total calories ± SEM				
[3]Values are mean ± SEM; negative values indicate decreases from baseline				

Figure 4-1. Sensation ratings of hunger over time
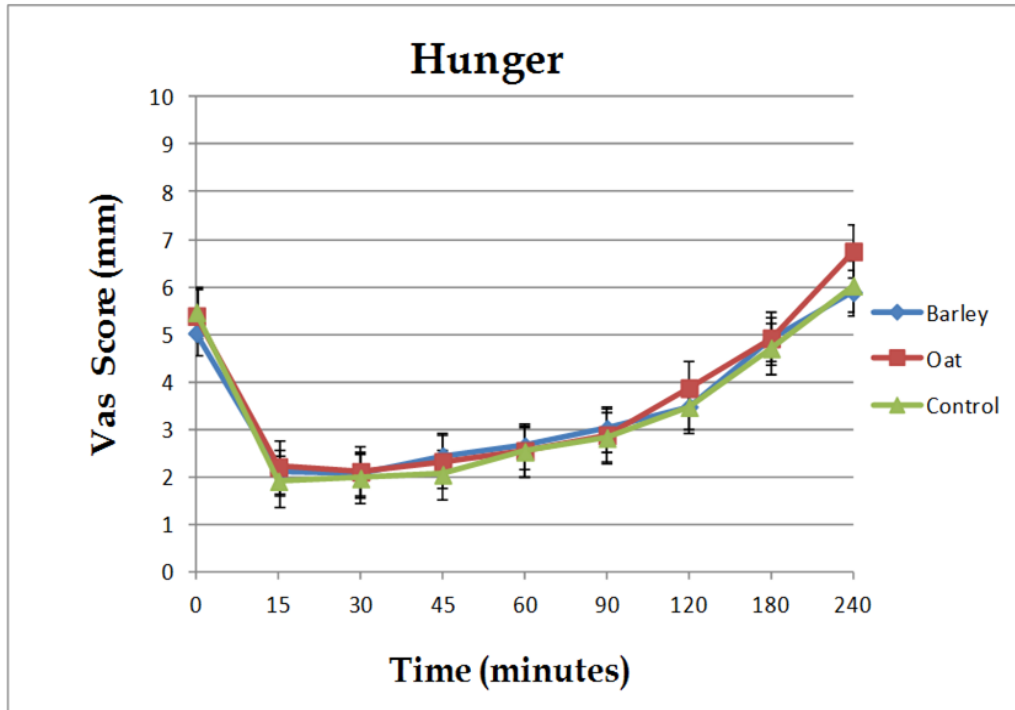

Figure 4-2. Sensation ratings of satisfaction over time
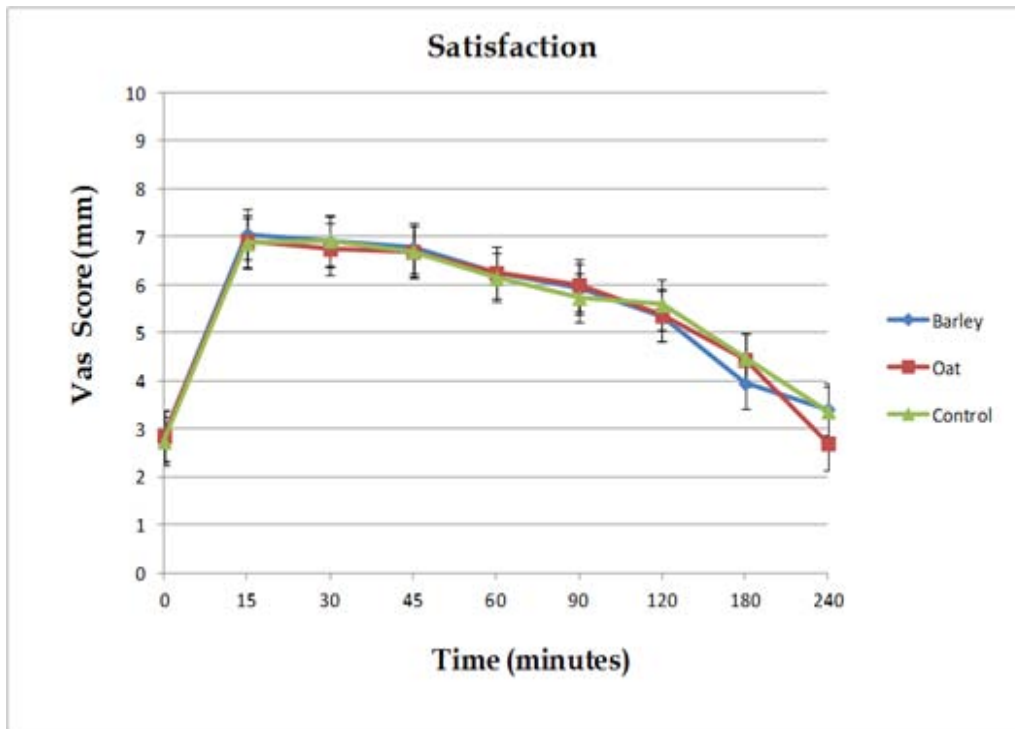
Figure 4-3. Sensation ratings of fullness over time
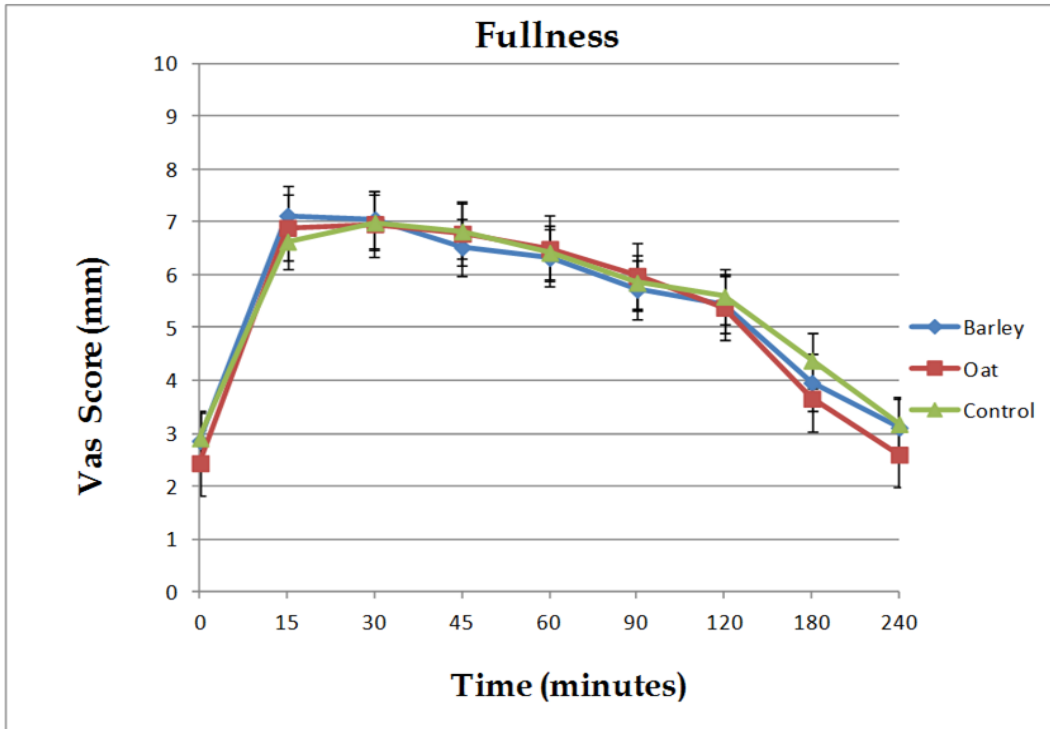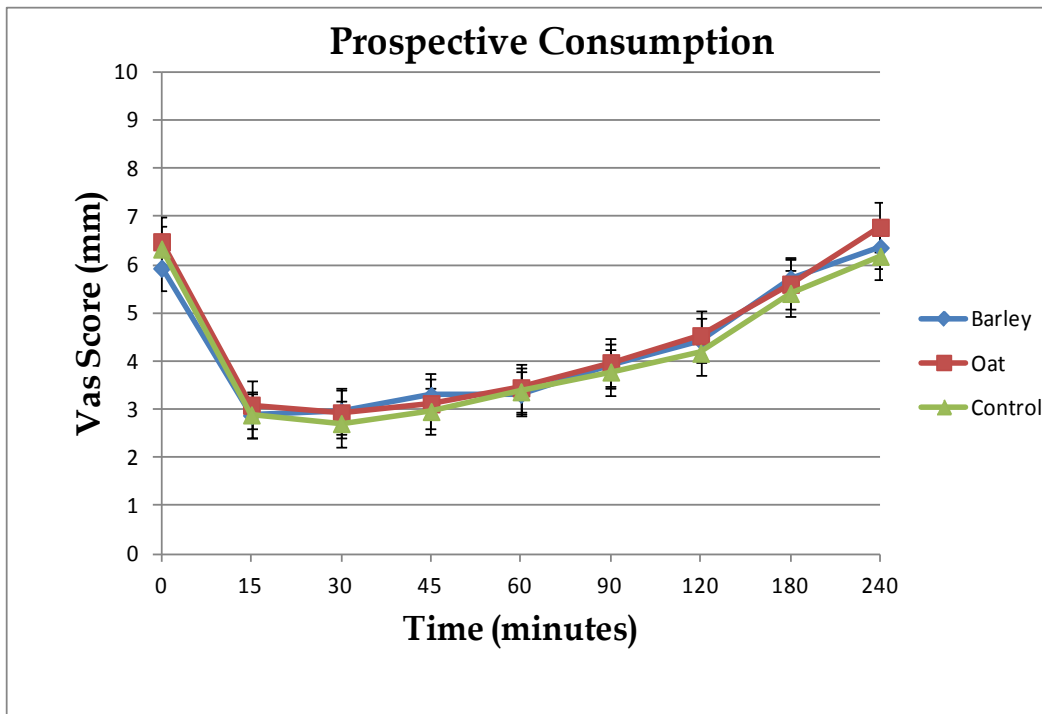

Figure 4-4. Sensation ratings of prospective consumption over time

CHAPTER 5: Effects of high protein pasta and high fiber pasta on satiety, snack intake and gastrointestinal tolerance in healthy men and women

Summary

Background: Protein and fiber have been shown to promote fullness and reduce energy intake independently, but few, if any studies have investigated whether or not the combination of nutrients could increase satiety and reduce subsequent energy intake in a population of healthy men and women.

Objective: Our primary aim was to investigate if high protein pasta (16g) would have a greater impact on satiety than high fiber pasta (8g) or control pasta (11g protein, 6g fiber). Our secondary objective was to figure out if consumption of the high protein pasta at lunch would reduce subsequent snacking in the mid-afternoon as well as food intake for the remainder of the day.

Design: Randomized crossover design, where each subject completed three separate visits with a 1 week washout period between visits.

Participants/setting: Participants were 36 healthy and normal weight men (n=18) and women (n=18) from the University of Minnesota campus and the Twin cities metro area.

Intervention: On three afternoons at 12:00pm, fasted men and women (4 hours from breakfast) consumed one of three pastas with water. Women were scheduled within the follicular phase of their menstrual cycle and an *ad libitum* sweet and savory snack tray was served 3 hours after lunch.

Main outcome measures: Satiety assessed by visual analogue scales (VAS) at baseline, 15, 30, 45, 60, 90, 120, and 180 minutes after lunch. An *ad libitum* snack tray was served 3 hours after lunch to determine subsequent energy intake. Food intake for the remainder

of the day was assessed by a food diary and gastrointestinal tolerance was assessed by a questionnaire.

Statistical Analyses: Treatments were compared using the 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. Outcomes are reported as mean ± SEM. Significant difference was determined by a two-sided test when p<0.05. Statistical analysis was performed by SAS, version 9.3.

Results: There were no significant differences among any of the pastas on appetite ratings which included hunger, satisfaction, fullness, and prospective food intake. We found a gender-treatment interaction for food intake. Food intake for men was significantly higher on the high protein pasta versus the high fiber pasta (1701 ± 154 vs. 1083 ± 154) and intermediate on the control pasta (1368 ± 154), p=0.007. No significant differences were found for gastrointestinal tolerance and for palatability, the high protein pasta was significantly different from the control and high fiber pasta in terms of taste and pleasantness, p=0.03 for taste and p=0.01 for pleasantness.

Conclusions: Our results disprove the idea that high protein pasta produces a stronger satiety response than a high fiber or a control pasta. Hedonic properties of food such as visual appeal, taste and pleasantness may influence satiety ratings which present a challenge to food manufacturers who are looking to promote foods that are both satiating and palatable.

This trial was registered at clinicaltrials.gov # NCT01792596

Introduction

   The process by which foods influence satiety and subsequent energy intake has been a topic of much interest in nutrition research (115). Satiety is defined as the sensation of fullness between eating episodes (intermeal) that tends to inhibit further eating. This is not to be confused with satiation or intrameal satiety, which is defined as the sense of fullness during an eating episode that contributes to the termination of eating (115). Foods, and more particularly macronutrient contents, can influence how full an individual feels, but this is further dependent on factors such as palatability, energy density (the caloric value of a food per unit weight or volume) and secretion of appetite regulating hormones such as ghrelin, peptide YY (PYY) and glucagon-like peptide (GLP-1).

   Certain macronutrients such as protein have been shown to promote fullness and reduce energy intake in several acute satiety studies (134-137). For example, Ratliff and colleagues conducted a randomized crossover trial with twenty one overweight men and fed them either an egg or bagel based breakfast. Subjects had frequent blood draws and completed visual analogue scales (VAS) for three hours after which they received an ad libitum lunch buffet which consisted of turkey sandwiches, apples and water. Twenty-four hour food records were kept to determine energy intake post intervention. The results showed that men consumed approximately 500 additional kilocalories during the *ad libitum* lunch after the bagel breakfast compared with the egg breakfast (137).

   In addition to this, men ate significantly fewer kilocalories during the twenty-four hours after egg compared with bagel (7641 ± 2525 versus 9328 ± 2211, $p<0.05$). In terms of hunger, men had a reduced area under the curve (AUC) after egg and were significantly

less hungry at 180 minutes compared with bagel (p<0.01) (137). Several reasons may explain why subjects felt less hungry after consuming the egg breakfast, however the authors suggested that protein may suppress ghrelin, a hormone that rises pre-prandially and initiates the onset of hunger. Previous studies also support this idea therefore; protein is thought to be the most satiating macronutrient (138-141).

Similar to this, research has demonstrated that dietary fiber can promote satiety by prolonging the secretion of appetite regulating hormones from the small intestine and delay gastric emptying by increasing the thickness of intestinal contents (142). The result of this process is a feeling of fullness and decline in hunger. Not all fibers are equally satiating and can have different physiological effects, but some studies show that viscous fibers such as beta-glucan from oats increases satiety when consumed as part of a breakfast meal (117-118). Other satiety studies are not consistent with this and found no effect of fiber on satiety and subsequent energy intake, making the current scientific evidence inconclusive (25, 116, 120-121, 127). Altogether, a gap in the literature exists as no studies have investigated whether or not the combination of two satiating nutrients such as protein and fiber can increase satiety and reduce subsequent energy intake in a population of healthy men and women.

The purpose of this study was to determine if the mixture of protein and fiber in pasta would have a greater impact on satiety than pasta with lower amounts of protein or fiber. We hypothesized that a higher amount of protein combined with fiber in pasta would increase overall satiety more than pasta with a lower amount of protein or fiber.   Since daily food intake is distributed over a certain number of meals and snacks, a secondary

objective was to figure out if consumption of the pasta meal at lunch would reduce subsequent snacking in the mid-afternoon.

Methods

In this randomized double-blind crossover study, we compared the satiating effects of high protein pasta, high fiber pasta and control pasta (Table 5-1). We hypothesized that the high protein pasta would have a greater impact on satiety than the high fiber or control pasta.

Subjects

The University of Minnesota Institutional Review Board Human Subjects Committee approved all aspects of this research and all subjects provided written informed consent. Participants were recruited by posters placed around the University campus and the surrounding community in Saint Paul and Minneapolis. Subjects were screened over the telephone and were invited into the study if they met the inclusion criteria. Eligible subjects were healthy men (n=18) and women (n=18) between the ages of 18-65 who spoke English and had a body mass index between 18 and 29.9 kg/m^2. Other inclusion criteria were to not smoke, not take any weight loss medication and be weight stable over the last 3 months.

Subjects were excluded if they were vegetarian or had allergies to ingredients found in any of the test products. Other exclusion criteria were: cardiovascular disease, diabetes mellitus (fasting blood sugar > 126 mg/dl); cancer in the past 5 years; renal or hepatic disease; recent bacterial infection (< 2 weeks); gastrointestinal conditions affecting digestion or absorption, antibiotic use within the past six months, intentional or

unintentional weight loss in the past 3 months (> 5 kg); history of drug or alcohol abuse

in the past 6 months; lipid-lowering; anti-hypertensive or anti-inflammatory steroid

medication use; high fiber intake (3 or more servings of high fiber foods per

day);concurrent or recent (within 30 days) participation in an intervention study;

exhibited restrained eating (score >11 on the dietary restraint factor of the Three Factor

Eating Questionnaire) (125). Women who were pregnant, lactating or reported an

irregular menstrual cycle were also excluded.

Study Visits

  On 3 separate occasions, subjects consumed 1 of 3 pastas for lunch along with 16.9

ounces (500mL) of water. Visits were held from noon to 3:30pm Monday-Sunday and

were at least 1 week apart. Women participated only during the follicular phase of their

menstrual cycle, so some visits were 2 to 3 weeks apart. Subjects were to avoid alcohol,

vigorous physical activity, and follow a low-fiber lead in diet 24 hours prior to coming in

for their study visit. On the morning of each visit, subjects were instructed to consume

their usual breakfast at home (no later than 8am) and come into the laboratory in a fasted

state (minimum four hours) for lunch at 12pm. Subjects were weighed and then sat in a

quiet room where they were asked to record their breakfast in a food diary. Subjects were

then provided with instructions on how to complete their baseline visual analogue scale

(VAS). After the initial VAS was completed, subjects were provided with 1 of 3 pastas

along with 16.9 ounces (500mL) of bottled water. Subjects were instructed to consume

everything on their plate within 15 minutes.

Additional VAS for satiety was completed at 15, 30, 45, 60, 90, 120, 180, and 200 minutes after baseline. Subjects also assessed the palatability of the pasta at 30 minutes by evaluating visual appeal, smell, taste, aftertaste, and pleasantness. After completion of the VAS for satiety at 180 minutes, participants were presented with 16.9 ounces (500mL) of water and a snack tray that contained assorted sweet and savory items such as cookies, Sun Chips, trail mix, Slim Jims, and granola bars. Subjects were instructed to eat until they were comfortably full and to leave all uneaten items on the tray. They were then sent home with a folder that contained a food diary and gastrointestinal tolerance questionnaire to be completed before bedtime that evening. During the visits, men and women were seated in a quiet room and were allowed to read, use laptop computers, work quietly or listen to music. Physical conditions and location of the room were consistent for all visits.

Description of the pasta and snacks

All pasta and sauce was produced by the Barilla Company and each container of pasta was individually sealed and stored at room temperature in the University of Minnesota food laboratory. A standard tomato sauce was served over the pasta for all three treatments. The pasta and sauce were removed from their individual packages just prior to the lunch and heated in the microwave for one minute or until warm enough for consumption. The executive summary from the Mintel Database (September 2012) was used to identify the most popular snacks purchased from vending machines. Trail mix, granola bars, Slim Jims, Sun Chips, and cookies were identified and purchased from a local warehouse. The nutrition information for the snack items is provided (Table 5-1).

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Study Outcomes

Visual analogue scales (VAS)

  Satiety was evaluated using questions from a previously validated 100mm VAS (126). Questions were taken directly from the validated literature: hunger-How hungry do you feel? Not hungry at all (0mm) vs. I have never been more hungry (100mm); satisfaction-How satisfied do you feel? I am completely empty (0mm) vs. I cannot eat another bite (100mm); fullness-How full do you feel? Not at all full (0mm) vs. totally full (100mm); prospective food intake-How much do you think you can eat? Nothing at all (0mm) vs. a lot (100mm) (Appendix 1).

  The palatability of the pasta was assessed at the 30 minute time point. Certain characteristics were rated including visual appeal, smell, taste, and overall pleasantness. These were scored as good (0mm) vs. bad (100mm). Aftertaste was scored as much (0mm) vs. none (100mm) (Appendix 1).

Gastrointestinal tolerance

  Tolerance to the test fibers was assessed by a ten- item questionnaire that has been previously validated (26). After subject(s) completed each of their study visits, they were provided instructions to complete the tolerance questionnaire right before they went to bed that evening. The topics on the questionnaire covered parameters such as stomach pain, diarrhea, reflux, discomfort and constipation. Responses were based on a Likert scale with responses varying from no discomfort at all to severe discomfort (Appendix 2).

Snack and food intake

   Participants were provided with a tray that consisted of 1 package of trail mix, 1 bag of

chips, 1 package of cookies, 1 granola bar, and one Slim Jim (Table 5-2). Participants

were instructed to snack until comfortably full and not to discard any uneaten items.

Snack intake was recorded after the participants left the study visit. Snacks were weighed

on a scale and the nutrition facts panel was used to calculate the amount of energy

consumed. In terms of food intake for the remainder of the day, subjects recorded all

food and beverage(s) consumed after they left the study visit. Portion guidelines and

examples were provided in a study folder to help participants estimate the quantity of

food and beverages consumed. Subjects were asked to specifically record what time they

ate, what they ate, how much, and how the food was prepared up until bedtime that

evening. The Nutrition Data System for Research was used to analyze the nutrition

content for all foods eaten (NDS-R 2012, Nutrition Coordinating Center, Minneapolis,

MN).

Statistics

   Subject demographic characteristics are presented as mean ± standard deviation.

Repeated VAS responses at a study visit were summarized as area under the curve by the

trapezoidal rule. Gastrointestinal tolerance symptoms were combined using the summary

score of all ratings. Treatments were compared using the 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 interactions were checked by the mixed-

effects model. These were not significant and were dropped from the final model. Outcomes are reported as mean ± SEM. Significant difference was determined by a two-sided test when p<0.05. Statistical analysis was performed by SAS (version 9.3, 2013, SAS Institute Inc.).

Results: Participant Characteristics

Thirty- six, healthy, normal weight men (n=18) and women (n=18) participated in the study. The mean age was 23.3 ± 4.6 for men and 23.7 ± 2.7 for women and the mean body mass index (BMI) was $23\text{kg/m}^2 \pm 2.5$ for men and $21.3\text{kg/m}^2 \pm 2.0$ for women. Men had a mean fiber intake of 3.1g/day ± 1.1 at baseline, whereas women had a mean fiber intake of 2.6g/day ± 1.0 at baseline (Table 5-3).

Satiety: Visual Analogue Scales

There were no significant differences between pastas on any of the satiety scales including hunger, satisfaction, fullness, and prospective food intake, p=NS, (Table 5-4 and Figures 5-1, 5-2, 5-3, 5-4).

Snack and food intake

A gender- treatment interaction was observed for snack and food intake and we wanted to know about differences between treatments within each gender. For women, no within treatment differences were observed for food or snack intake. For men, no within treatment differences were found for snack intake, but a within treatment difference was observed for food intake. Men consumed a significant amount more after the high protein pasta compared to the high fiber pasta, 1701 ±154 vs. 1083 ±154. An intermediate amount was consumed on the control pasta, 1368 ± 154, p=0.007, (Table 5-4).

Gastrointestinal Tolerance

No significant differences between pastas were found for overall GI tolerance (Table 4); however a number of adverse events were reported for the high protein pasta. These events included diarrhea, gas, nausea and bloating (Table 5-4 and 5-5).

Palatability ratings of the pastas

There were no significant differences between the pastas for visual appeal, smell or aftertaste, however, the high protein pasta was significantly different from the control and high fiber pasta for taste (p=0.03) and pleasantness (p=0.01). Overall, the high protein pasta was less preferred in terms of taste and pleasantness. (Table 5-4).

Discussion

The results from this study do not support the hypothesis that high protein pasta would increase satiety more than a high fiber or control pasta. We did not observe significant differences between the pastas on any of the satiety scales including hunger, satisfaction, fullness, and prospective food intake. These results build upon previous research to show that it is challenging to find differences in satiety with a population that is comprised of healthy, normal weight men and women (4, 120-121, 143). The effects of satiating foods with added protein or fiber on satiety and subsequent energy intake may be more likely observed in overweight and obese populations and previous studies support this (137, 144-145).

Also, protein and fiber are thought to be satiating nutrients, however in order to influence satiety, an increased amount may need to be consumed at all meals and snacks

and for time periods longer than one day. Our acute model was limited to a one day visit separated by a one week washout period. Furthermore, the macronutrient compositions of the test pastas were not that different from one another which may have hindered us from seeing changes in satiety. The control and high fiber pasta had similar levels of fiber and protein (6g of fiber and 11g protein for control vs. 8g of fiber and 11g protein for high fiber); whereas the high protein pasta had 6g fiber and 16g of protein. Some studies that found differences in satiety had variances of 5g for fiber between the test and control treatments and 25g for protein; therefore the lack of large differences in protein and fiber likely resulted in null results for satiety (144-145). In addition to this, we gave a standard serving to all participants instead of dosing based on estimated energy needs, which may have been too much or too little depending on the person.

Finally, some differences were observed in the palatability ratings of the pasta. The high protein pasta was significantly different from the other pastas in terms of taste and pleasantness. According to our palatability scale (Appendix 1), this would indicate that participants found the high protein pasta less pleasant and less tasty compared to the control and high fiber pasta. Although not significant, the high protein pasta was also less visually appealing than the control and high fiber pasta. It is possible that if the high protein pasta was not perceived well, it may have affected satiety ratings.

Although we have acknowledged some limitations, this study is strengthened by its crossover design which allowed each subject to serve as his or her own control. We also included an equal amount of men and women and modeled a typical meal-snack feeding pattern. Subjects were able to consume their standard breakfast at home then come in

four hours later for a pasta lunch. Snacks were presented exactly three hours after lunch in the mid-afternoon, a time when usual snacking occurs. We offered a blend of sweet and savory snacks on a tray that represented what would commonly be found in a vending machine. Subjects were instructed to eat as much or as little of the items as they wanted. It was important to incorporate this into our design to better understand the relationship of these foods to satiety and energy intake, especially since snacks contribute to one fourth of adults' total daily energy intake (146).

In conclusion, the lack of differences in satiety is not uncommon or unprecedented. A recent systematic review determined the effect of fiber treatments on satiety ratings and found that only 39% of fiber treatments had a benefit on satiety, but not all fiber types affected appetite equally (147). Fibers such as beta-glucan, lupin kernel fiber, whole grain rye, and rye bran were found to improve satiety ratings more than other fiber types. Additional work is still needed to elucidate the relationship between fiber and satiety as many research questions remain unanswered. For example, what is the long-term effect of fiber consumption on satiety and energy intake? Several studies such as this one are designed to test acute satiety and measure energy intake for a short period of time post intervention. This is likely too brief to determine if the consumption of fiber contributed to the voluntary reduction of energy intake through the modulation of appetite.

The results from this study disprove the idea that high protein pasta causes increased satiety compared to a high fiber or control pasta. We found no differences in satiety or total calories consumed during snacking time or post-intervention. On the other hand, we did find that the high protein pasta was significantly different from the control and

high fiber pasta in terms of taste and pleasantness. Subjects found this pasta to be less

tasty and pleasant and it is possible that our ability to detect differences in satiety may

have been hindered by these hedonic properties. This idea is confirmed by Sorensen et al

who described that palatable foods are related to increased satiety and that the

consumption of unpalatable foods may alter how subjects rate their satiety (148).

   Altogether, whole foods that are sources of satiating nutrients such as protein and fiber

have previously been shown to offer nutritional benefits, but did not promote satiety or

reduce energy intake in this study. This conveys a challenge as nutrition experts and

dietetic professionals continue to search for successful dietary strategies to help with

weight management.   Data from the most recent NHANES survey indicates that 68% of

the adult population is overweight including 34% who meet the criteria for obesity (4). It

is crucial to recognize factors that may aid in the prevention and treatment of obesity.

Reducing obesity will likely require the collaboration of multiple sectors within

communities and changing the satiating properties of the food supply is just one part of

the solution.

Table 5-1. Nutrient composition of pasta

	Serv Size	Calories	Protein	Fat	Carbs	Fiber
Control	255g	320	11g	4.5g	59g	6g
High fiber	255g	290	11g	5g	51g	8g
High protein	255g	320	16g	5g	54g	6g

Table 5-2. Nutrient composition of snack items

Snack	Serv Size	Calories	Protein	Fat	Carbs	Fiber
Trail Mix	57g	280	8g	18g	27g	<1g
Slim Jim	8g	40	2g	3.5g	<1g	<1g
Peanut butter granola bar	24g	100	2g	3g	17g	1g
Smores granola bar	24g	90	1g	2g	19g	1g
Chocolate granola bar	24g	100	1g	3g	17g	1g
Original SunChips	42.5g	210	3g	10g	29g	4g
French onion SunChips	42.5g	210	4g	10g	28g	4g
Garden salsa SunChips	42.5g	210	3g	9g	29g	4g
Cheddar SunChips	42.5g	210	3g	10g	29g	4g
Oatmeal raisin cookies	70.8g	310	4g	12g	46g	3g
Chocolate chip cookies	70.8g	340	4g	17g	44g	2g
Brownie cookies	70.8g	320	4g	14g	47g	3g
Peanut butter cookies	70.8g	340	7g	17g	38g	4g

Table 5-3. Participant Characteristics[b]

	Men (n=18)	Women (n=18)	All (n=36)
Age (yr)	23.3±4.6	23.7 ± 2.7	23.5±3.7
Body Mass Index (kg/m^2)	23±2.5[a]	21.3±2.0[b]	22.2±2.4
Baseline fiber intake (g/day)	3.1±1.1	2.6±1.0	2.8±1.1
Restraint Score[a]	5.8±2.4	6.3±2.0	6.0±2.2
[a] Cognitive restraint of eating (Stunkard and Messick, 1985)			
[b]Data is presented as the mean ± standard deviation			
Means with different letters are significantly different from one another, $p<0.05$			

Table 5-4. Summary of results for satiety, palatability, GI tolerance & food intake

	Control	**High Fiber**	**High Protein**	**P- value[‡]**
Hunger*	18.8±1.1	17.7±1.1	17.8±1.1	0.3
Satisfaction*	18.9±1.1	20.2±1.1	20.2±1.1	0.2
Fullness*	18.5±1.2	19.2±1.2	19.6±1.2	0.3
Prospective Consumption*	20.5±1.1	20.1±1.1	20.3±1.1	0.9
Gastrointestinal Tolerance**	3.8±0.8	3.1±0.8	3.5±0.8	0.7
Visual Appeal[1]	2.8±0.3	2.8±0.3	3.2±0.3	0.2
Smell[1]	2.5±0.2	2.3±0.2	2.4±0.2	0.4
Taste[1]	2.8±0.3[a]	2.9±0.3[a]	3.6±0.3[b]	0.03
Aftertaste[1]	7.0±0.3	7.0±0.3	6.0±0.3	0.3
Pleasantness[1]	3±0.3[a]	3±0.3[a]	3.8±0.3[b]	0.01
Food intake-Women[2]	771±154	700±154	684±154	0.93
Food intake-Men[2]	1368±154[ab]	1083±154[b]	1701±154[a]	0.007
Snack intake-Women[2]	423±85	391±85	550±85	0.25
Snack intake-Men[2]	632±85	669±85	658±85	0.91

†Value is for the overall F-test

*Data is presented as the mean AUC ±SEM, **Data is presented as the mean sum of scores ±SEM

[1]Scale is 0-10, values are mean ±SEM, treatments with different letters are significantly different

[2]Data is presented as the mean total calories ± SEM, treatments with different letters are significantly different

Table 5-5. Count of adverse GI events reported by subjects' after pasta consumption

	Control	**High Fiber**	**High Protein**
Diarrhea	0	0	3
Gas	0	2	3
Bloating	0	1	2
Nausea	0	0	1

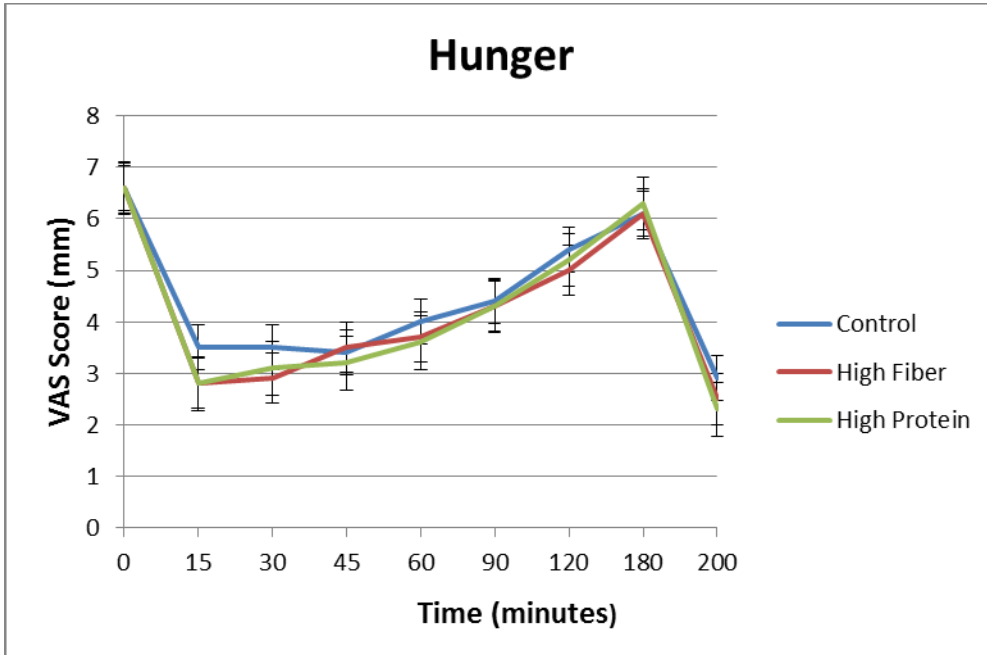**Figure 5-1**. Sensation ratings of hunger over time

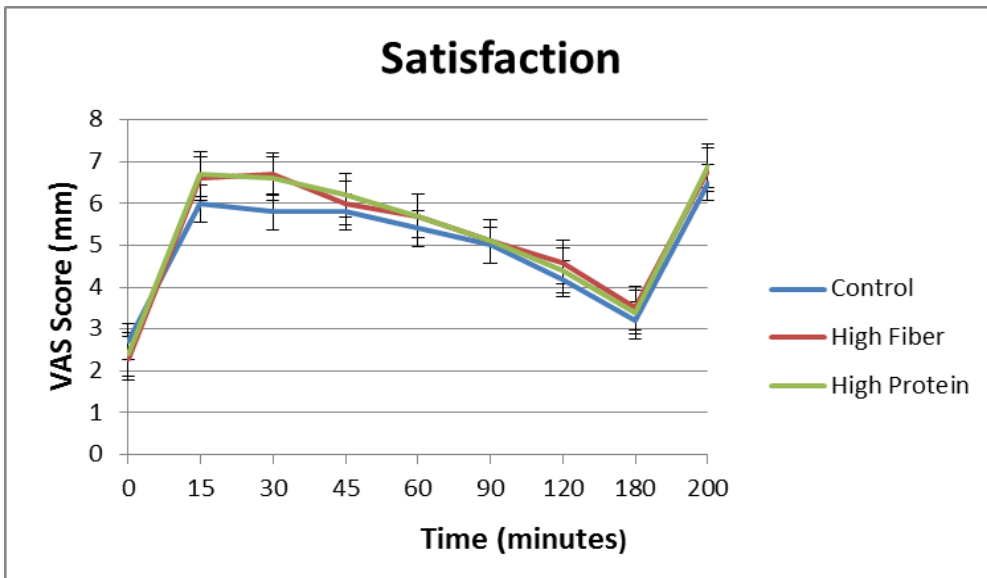**Figure 5-2**. Sensation ratings of satisfaction over time

Figure 5-3. Sensation ratings of fullness over time
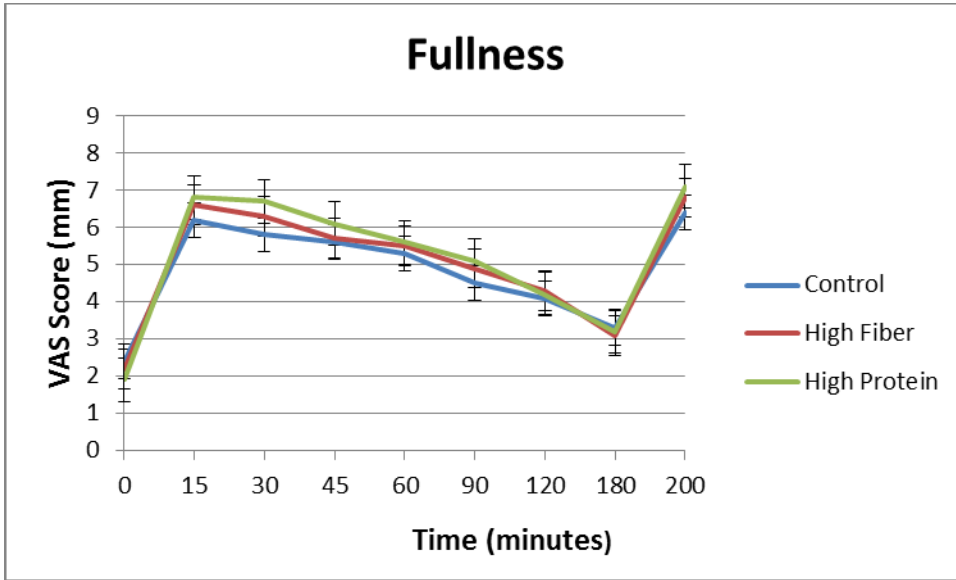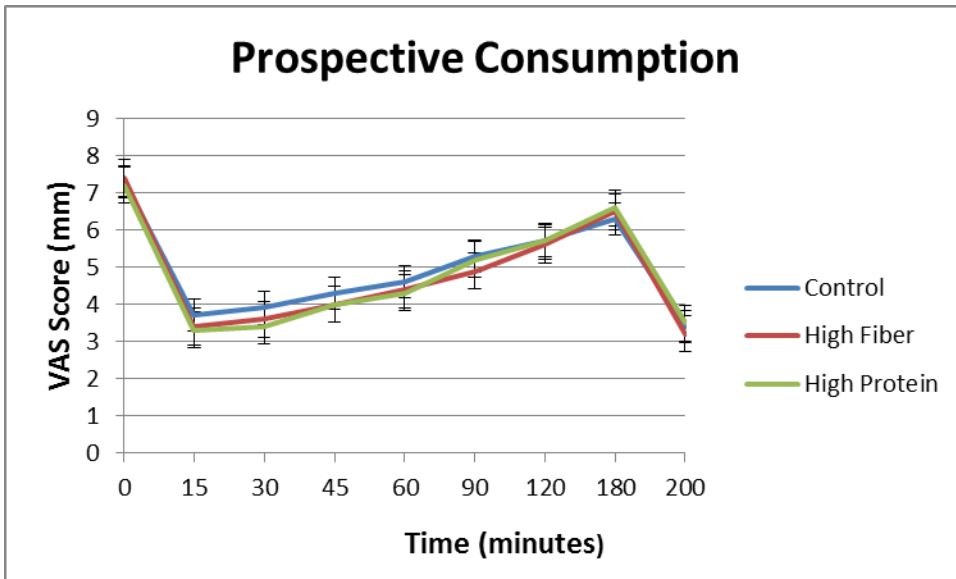

Figure 5-4. Sensation ratings of prospective consumption over time

Methodological issues in satiety research

Food intake and satiety studies have been a popular topic for the past decade as researchers continually strive to find what food(s) can promote fullness while simultaneously offering a nutritional benefit. The form of food that evokes a strong satiety response is also of interest since food intake encompasses many items such as beverages, energy bars, fruits, vegetables, meats and grains. This thesis has described the results from two intervention studies that explored what happened when fiber or protein were supplemented in different forms of food such as a bar for breakfast and pasta for lunch. No differences were found in either study even though we had sample size estimates that were calculated to find differences in satiety. It is difficult to explain these null findings, but the results emphasize the complexity of factors that drives satiety and food intake regulation.

Future studies in this area are evolving, but controversy exists as to what the best methods are to measure satiety and subsequent food intake, therefore it is useful to understand methodological limitations (8). To evaluate the effects of food on satiety, the use of self-reported visual analog scales is the most popular method. This method was used in both of my studies and subjects were generally comfortable rating their appetite at numerous time points and found it easy to use. The downfall of this method is that the same four questions are repeated at every time interval therefore, boredom may play a role in how a subject rates their level of satiety. Individuals who are bored can be careless

when rating their satiety and not pay attention to their internal signals. Altogether, their data may not be the most useful when conducting statistical analysis.

Second, for acute satiety studies, the time lapse between the test meal and the *ad libitum* meal are important factors. This can be a difficult decision to make when designing a study, especially since people have different eating habits; however the main idea is to resemble a typical feeding pattern where subjects would naturally want to eat. Offering an *ad libitum* meal or snack too early may bias the results. For example, a subject would not each as much if they were offered food just 2 or 3 hours after breakfast simply because they were not hungry yet. In addition to this, when offering food *ad libitum,* it is important to ensure subjects have access to as much food as they would like to consume. For example, in the second intervention study, it is possible that the "ceiling effect" was observed. This means that some individuals ate all of the snacks on their tray, but were not offered more to eat even if they were still hungry. Under true *ad libitum* conditions, a subject should have access to as much food as they can eat; this eliminates any chance of bias when interpreting results from statistical analysis.

Finally, it is important to conduct satiety studies in a controlled environment with minimal distractions. Both of the intervention studies were held in a quiet room near our laboratory, but several challenges arose which made it difficult to run. Our kitchen and preparation space was limited due to ongoing construction in the building. We did our best to block out noise and find alternate kitchen space, but subjects were still interrupted by noise and the smell of construction materials. In addition to this, a cooking class was

held down the hall from our study space. It is possible that the smell of other foods may have influenced our subjects' perception of the test food and *ad libitum* items.

Future Directions

Information generated from these studies will be useful when thinking about future directions for fiber, protein and satiety research. The following paragraphs explain a few lessons I learned from my own research that could be helpful to others.

Subjective Satiety and Food Intake Studies

Finding men and women who fit the criteria for satiety studies is difficult. Typically, we screen for low- fiber consumers (< than 3 servings a day) who are healthy and not restrained in their eating habits. After running both studies, I found there are no good tools to screen for fiber consumption. As of now, we use a system based on self-recall and most individuals are unsure of what a serving of fiber is. We do our best to describe serving sizes over the phone, but the uncertainty is still evident. In the future, it would be helpful if individuals had a portion size guide at home before they answered what their typical consumption pattern is. The other option would be to have a trained dietitian screen subjects in person so she could provide real examples of what a serving size is. Overall, this would provide a better representation if the subject was a high fiber consumer or not.

Second, the tool we used to measure dietary restraint was both confusing and difficult to conduct over the phone. Both male and female subjects found the questions awkward and were unsure of how to respond even when choices were provided. As a result of this, I felt that restrained eaters were part of the study even though their scores on the

questionnaire qualified them as non-restrained. Third, it would be helpful to screen for food security when determining if a person meets the inclusion or exclusion criteria for a study. Some subjects were not food secure and ate all of the ad libitum food at every visit; this can bias food intake results. Finally, it would be interesting if future studies could focus on the long-term effects of fiber and protein consumption on satiety. As of now, the majority of the evidence is from acute studies and the results have been very inconsistent. Dietary manipulations that enhance satiety are essential and this may be part of the reason why epidemiological evidence has demonstrated that people who habitually consume fiber have a lower body weight and body mass index than those who do not (88-91). These findings need to be confirmed in intervention trials that shift away from the acute model with focus on the long- term effects of fiber consumption.

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Appendix 1: How to measure dietary restraint- Adopted from the Three Factor Eating Questionnaire

1. When I have eaten my quota of calories, I am usually good about not eating any more (T +1 F)
2. I deliberately take small helpings as a means of controlling my weight (T +1 F)
3. Life is too short to worry about dieting (T F +1)
4. I have a pretty good idea of the number of calories in common food (T +1) (F)
5. While on a diet, if I eat food that is not allowed, I consciously eat less for a period of time to make up   for it (T +1) (F)
6. I enjoy eating too much to spoil it by counting calories or watching my weight (T) (F+1)
7. I often stop eating when I am not really full as a conscious means of controlling what I eat (T +1) (F)
8. I consciously hold back at meals to not gain weight (T +1) (F)
9. I eat anything I want, anytime I want (T) (F +1)
10. I count calories as a conscious means of controlling my weight (T +1) (F)
11. I do not eat some foods because they make me fat (T +1) (F)
12. I pay a great deal of attention to changes in my figure (T +1) (F)
13. How often are you dieting in a conscious effort to control your weight? Rarely Sometimes Often (+1) Usually (+1)
14. Would a weight fluctuation of 5 lbs. affect the way you live your life? Not at all Slightly Moderately (+1) Very Much (+1)
15. Do your feelings of guilt about overeating help you to control your food intake? Never Rarely Often (+1) Always (+1)
16. How conscious are you of what you are eating? Not at all Slightly Moderately (+1) Extremely (+1)

17. How frequently do you avoid stocking up on tempting foods?
Almost never Seldom Usually (+1) Almost Always (+1)

18. How likely are you to shop for low-calorie foods?
Unlikely Slightly likely Moderately likely (+1) Very likely (+1)

19. How likely are you to eat slowly in a conscious effort to cut down the amount you eat?

Unlikely Slightly likely Moderately likely (+1) Very likely (+1)

20. How likely are you to consciously eat less than you want?
Unlikely Slightly likely Moderately likely (+1) Very likely (+1)

21. On a scale of 0 to 5, where 0 means no restraint in eating and 5 means total restraint in eating, what number would you give yourself?
(0) Eat whatever you want, whenever you want?
(1) Usually eat whatever you want, whenever you want
(2) Often eat whatever you want, whenever you want
(3) Often limit food intake but never give in (+1)
(4) Usually limit food intake, rarely give in (+1)
(5) Constantly limiting food intake and never giving in (+1)

Appendix 2: Satiety and palatability questions on the Visual Analogue Scale (VAS)

1. How hungry do you feel?

   I am not hungry at all ----------------------------- I have never been hungrier

2. How satisfied do you feel?

   I am completely empty ---------------------------- I cannot eat another bite

3. How full do you feel?

   Not at all full---Totally full

4. How much do you think you can eat?

   Nothing at all--A lot

1. Visual appeal

   Good -- Bad

2. Smell

   Good -- Bad

3. Taste

   Good -- Bad

4. Aftertaste

   None -- Much

5. Overall Pleasantness

   Good --Bad

Appendix 3: 10- item Gastrointestinal Tolerance Questionnaire

Please rate your response to each question on the following scale:

    (1) No discomfort at all
    (2) Slight discomfort
    (3) Mild discomfort
    (4) Moderate discomfort
    (5) Moderately severe discomfort
    (6) Severe discomfort
    (7) Very severe discomfort

Questions (Circle the number that corresponds to your response)

1. Have you been bothered by a stomach ache or pain since dinner last night? (Stomach ache refers to all kinds of aches or pains in your stomach or belly.)
   1 2 3 4 5 6 7

2. Have you been bothered by heartburn since dinner last night? (By heartburn we mean a burning pain or discomfort behind the breastbone in your chest.)
   1 2 3 4 5 6 7

3. Have you been bothered by acid reflux since dinner last night? (By acid reflux we mean regurgitation or flow of sour or bitter fluid into your mouth.)
   1 2 3 4 5 6 7

4. Have you been bothered by hunger pains in the stomach or belly since dinner last night? (This hollow feeling in the stomach is associated with the need to eat between meals.)
   1 2 3 4 5 6 7

5. Have you been bothered by nausea since dinner last night? (By nausea we mean a feeling of wanting to be sick.)
   1 2 3 4 5 6 7

6. Have you been bothered by stomach rumblings other than hunger since dinner last night? (Rumbling refers to vibrations or noise in the stomach.)
   1 2 3 4 5 6 7

7. Has your stomach felt bloated since dinner last night? (Feeling bloated refers to swelling in the stomach or belly.)
   1 2 3 4 5 6 7

8. Have you been bothered by burping since dinner last night? (Burping refers to bringing up air or gas.)
   1 2 3 4 5 6 7

9. Have you been bothered by passing gas or flatus since dinner last night? (Passing gas or flatus refers to the release of air or gas from the bowel.)

1   2   3   4   5   6   7

10. Have you been bothered by constipation since dinner last night? (Constipation refers to a reduced ability to empty the bowels.)

1   2   3   4   5   6   7