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Comparison of the Effects of Two Oat-based Cereals on Appetite and Satiety, and the Effect of a Fat Emulsion of Appetite, Satiety, Food Intake, and Body Weight

Candida Joan Rebello
Louisiana State University and Agricultural and Mechanical College, rebellcj@pbrc.edu

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ABBREVIATIONS

Analysis of variance: ANOVA

Area under the curve: AUC

Body mass index: BMI

Gastrointestinal tract: GI

Glucagon-like peptide-1: GLP-1

Glycemic Index: Gi

Kilocalories: Kcal

Long chain fatty acids: LCT

Medium chain triglycerides: MCT

National Health and Nutrition Examination Survey: NHANES

Pennington Biomedical Research Center: PBRC

Peptide YY: PYY

Randomized double blind controlled: RDBC

Randomized double blind placebo-controlled: RDBPC

Resting energy expenditure: REE

Randomized single blind placebo-controlled: RSBPC

Ready-to-eat breakfast cereal: RTEC

United States: US

Visual analog scales: VAS

Within subject: WS

ABSTRACT

The objective of these studies was to investigate the satiety effects of foods typically consumed as part of a breakfast meal, and a novel fat emulsion designed to stimulate satiety signals. The first study compared the satiety effects of oatmeal with a popular ready-to-eat breakfast cereal (RTEC). The second study assessed the effects of the fat emulsion Olibra™, on satiety, food intake, and body weight.

Forty-eight healthy individuals, ≥18 years of age were enrolled in a randomized controlled crossover trial. Following an overnight fast, subjects consumed either oatmeal or RTEC in random order at least a week apart. Visual analogue scales (VAS) of appetite and satiety were completed at baseline, and 30, 60, 120, 180 and 240 minutes postprandial. Appetite and satiety scores were analyzed by area under the curve (AUC) assessed across the time-points. Oatmeal, resulted in greater increase in fullness (AUC: p=0.005 [120min: p=0.0408, 180min: p=0.0061, 240min: p=0.0102]) than the RTEC. Hunger (AUC: p=0.0009 [120min: p=0.0197, 180min: p=0.0003, 240min: p=0.0036]), desire to eat (AUC: p=0.0002 [120min: p=0.0168, 180min: p<0.0001, 240min: p=0.0022]), and prospective intake (AUC: p=0.0012 [120min: p=0.0058, 180min: p=0.006, 240min: p=0.0047]) decreased to a greater extent with oatmeal as compared with the RTEC.

In the study investigating Olibra™, 82 subjects (18-60 years of age, body mass index: 25-40 kg/m^2) were enrolled in a randomized, placebo-controlled, double-blind, parallel trial. During a 12-week period, the effects of Olibra™ fat emulsion (2.1g twice daily) on food intake, appetite, satiety, weight, and body composition were compared with those of a twice daily administered placebo (1.95g milk fat). Data relating to 71 subjects were analyzed using analysis of covariance.

Differential weight and waist circumference reductions were not significant. Differential group effects were not significant for body fat, waist-hip ratio, food intake, appetite, and satiety.

The studies showed that oatmeal increased satiety to a greater extent than the RTEC in the four hour period post-prandial; however, consumption of Olibra™ had no effect on satiety or food intake. Additionally, daily consumption of Olibra™ had no effect on body weight or body composition at the end of 12 weeks.

CHAPTER 1

INTRODUCTION

The results from the latest National Health and Nutrition Examination Survey (NHANES) showed that in 2009-2010, the prevalence of obesity in the United States was 35.5% among adult males, 35.8% among adult females,[1] and 16.9% among children and adolescents.[2] Despite evidence of a leveling off in the steep rises previously observed[1, 2] the number of obese individuals in the world today is higher than it has ever been.[3] Weight gain is the result of a chronic energy imbalance. The decision to eat rarely arises out of a biological deficit. More likely, it is appetite sensations interacting with environmental and social cues that trigger meal initiation.[4] In this context, appetite and satiety become important elements in the adjustment of energy intake to expenditure.

Appetite and Satiety

Appetite is controlled by a complex sequence of interactions among elements that form a psychobiological system. This system is bound by interrelationships between the external environment, psychological and behavioral profiles, physiological responses, and neural mechanisms.[5] The intra-meal processes generated by ingestion which result in termination of a meal are collectively referred to as satiation and the suppression of the desire to eat, decline in hunger, and increase in fullness after a meal is eaten is referred to as satiety.[6] Although satiation and satiety are distinct concepts, they act together along with myriad other factors to determine eating behavior.[7] Appetite and satiety are states of the moment, liable to change with the availability of food and drink, the combination of foods consumed, and changes in the physical

and social contexts.[8] Nevertheless, appetite and satiety have been shown to be good predictors of food intake.[9, 10]

Eating behavior is influenced by metabolic and sensory factors. The metabolic factors include the neural and hormonal signals arising from the gastrointestinal (GI) tract and conveyed to the brain, whereas the sensory factors include learned responses, and the reward value attached to a food. The satiating power of a food depends on its ability to mediate the right balance (one that results in satiation or satiety) between sensory, cognitive, post-ingestive (but pre-absorptive), and post-absorptive events and processes that comprise what is called the 'satiety cascade' proposed over 20 years ago.[7] The satiety cascade has subsequently been modified to include liking (orosensory stimulation of food) and desire (motivation to engage in eating).[11] Sensations of hunger, fullness, desire to eat, and prospective consumption, are indices of the drive for food and reflect the strength of satiety.

Functional foods are defined as components of the usual diet that may provide health benefits beyond basic nutrients.[12] A functional food may influence satiety by providing fewer kilocalories (kcals) while maintaining the same weight or volume of the original food, resulting in the consumption of less energy. However, the difficulty arises in ensuring that compensatory homeostatic mechanisms do not come into play to defeat the purpose of the reduction in energy intake. Alternatively, the food could be engineered to contain elements that strengthen the satiety signals thereby prolonging the interval between meals when hunger or the desire to eat return.[13]

Macronutrients can influence the satiating power of a food.[14] Thus, manipulating the specific macronutrient compositions of foods as a means of enhancing satiety and regulating food intake is a valid proposition. Evidence suggests that diets with relatively high protein content contribute to weight loss and weight maintenance. These effects on energy balance are

largely mediated by enhanced energy expenditure and protein-induced satiety.[15] The satiating effect of carbohydrates is determined by the type as well as the form of carbohydrate. Fiber influences satiety largely through its bulking and viscosity properties.[16] The role of high and low glycemic index (Gi) carbohydrate foods in satiety is not resolved fully.[17, 18] Data from human intervention studies do not appear to support a role for short chain fatty acids derived from colonic fermentation of undigested carbohydrates and protein in appetite regulation.[19-21] Fat generates satiety signals,[22] but it increases the energy density of a food. This seeming contradiction notwithstanding, the physicochemical properties of fat have been manipulated to induce satiety.[23-25]

Protein

Satiety mediated by protein is closely related to increases in energy expenditure. Protein intake influences energy expenditure primarily through its effects on diet induced thermogenesis. The thermic effect of nutrients is related to the adenosine triphosphate required for metabolism, storage, and oxidation.[15] Three phosphate bonds are used for the incorporation of each amino acid into protein.[26] The body is unable to store protein under conditions of high protein intake, and has to metabolize it, which increases thermogenesis. Additionally, elevated concentrations of blood and plasma amino acids, which cannot be channeled into protein synthesis, activate satiety mechanisms.[15] Further, it has been hypothesized that protein induced satiety is related to increased concentrations of the anorexigenic hormones glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) and a decrease in the orexigenic hormone ghrelin.[27, 28]

Dietary Fiber

The means by which dietary fiber influences satiety is related to its intrinsic physical and chemical properties.[16] Soluble fibers, by their inherent ability to absorb water, form gels that

contribute to gastric distension. Viscous fibers which include many soluble fibers such as gums, pectins, sea weeds, alginates and ß-glucans induce thickening when mixed with liquids.[29] Consumption of highly viscous soluble dietary fiber delays gastric emptying which can increase stomach distension[30] thereby stimulating afferent vagal signals of fullness.[4] Increased viscosity of intestinal contents reduces the absorption rate of nutrients. Exposure of the intestinal mucosa to nutrients stimulates the release of peptides that affect satiety.[31] The degree of viscosity however depends on the chemical composition and concentration of the specific fiber.[32] Additionally, energy density is inversely associated with satiety.[33] Dietary fiber, by lowering the energy density of a food[34] enhances satiety.

Fat

Fats have been shown to reduce hunger when present in the GI tract by eliciting satiety signals.[22] Fat in the duodenum stimulates the release of cholecystokinin and other gastrointestinal peptides that affect satiety.[31] Exposure of the ileum to fat stimulates an even larger satiety response than exposure to the duodenum.[35] Fat reaching the ileum stimulates an inhibitory feedback mechanism referred to as the ileal brake. Activation of the ileal brake is mediated through an interaction of neural and hormonal signals[31] which delays gastric emptying[36, 37] prolongs GI transit time,[37] and influences satiety.[38, 39] The ability of fat to regulate GI motor function, depends on its physicochemical properties. While long chain fatty acids (LCT) (>12 carbons) are more potent effectors of GI satiety signals than shorter chain fatty acids (≤10 carbons),[40, 41] medium chain triglycerides (MCT) (6-12 carbons) have been shown to influence satiety through increased energy expenditure.[42] Unlike LCT, MCT are directly absorbed into portal circulation and are more rapidly metabolized. Reports on the effects of the degree of saturation on satiety are conflicting.[43, 44]

Olibra™ is a fat emulsion that has been demonstrated in some studies to increase satiety and reduce food intake[23-25] however, the effects have not been replicated in other studies.[45-48] Oats contain significant amounts of the soluble fiber ß-glucan, which exhibits high flow viscosities at relatively low concentrations.[49] Among breakfast products, oatmeal was found to induce the highest level of satiety in a study to assess the satiating capacities of several foods.[50] Thus, as satiety-enhancing functional foods, Olibra™ and oatmeal appear to be targets that merit investigation.

Justification

The biological drive to eat is inextricably linked to the satiating power of a food, and thereby to the adjustment of energy intake to energy expenditure. Although weight loss is complex and difficult, enhancing satiety is a legitimate means of facilitating the process especially if the proposed food forms part of a culturally accepted eating pattern such as regular consumption of a breakfast meal. The concept of the satiety cascade implies that different nutritional components of a food will interact in different ways with the mediating processes to result in varying effects on satiety.[5] Thus, in helping people to eat less, exploring the field of satiety through the use of functional foods is worthy of consideration.

Research Questions

1. Does consumption of Olibra™ result in an increase in satiety and a reduction in food intake that causes weight loss?
2. Does consumption of oatmeal enhance satiety as compared with an isoenergetic serving of an oat-based ready-to-eat breakfast cereal (RTEC)?

Hypotheses

1. Consumption of Olibra™ will result in an increase in satiety and a reduction in food intake 4 hours and 9 hours postprandial.
2. Daily consumption of Olibra™ will result in an increase in satiety and a reduction in food intake at the end of four weeks.
3. Daily consumption of Olibra™ will result in weight loss at the end of 12 weeks.
4. Consumption of oatmeal will result in greater satiety than the RTEC, over the 4 hour period following consumption.

Objectives

1. To evaluate the effect of Olibra™ on subjective satiety and food intake, acutely and after four weeks.
2. To evaluate the effect of Olibra™ on body weight and body composition after 12 weeks.
3. To compare the subjective satiety ratings of oatmeal with a popular oat-based RTEC over the four hour period following consumption.

Limitations

1. Hormone levels were not measured; hence, it is difficult to draw any definitive conclusions on the effects of hormones on appetite and satiety.
2. Although subjects were asked to maintain a 10-12 hour overnight fast, there was no control exercised over subjects' food intake prior to each test day which may have influenced the results.
3. Relatively small convenience samples including predominantly female subjects were used; thus, the generalizability of the results is compromised.

4. The effects of oatmeal or the RTEC preload on subsequent food intake were not measured; thus, the effects on regulation of food intake are unknown. However, as part of a multi-stage proof of concept, effects of oatmeal on food intake and body weight can be assessed in future studies.
5. The study comparing the effects of oatmeal and the RTEC only measured short term satiety; thus, the possibility of recurrent activation of the satiating mechanisms was not assessed.
6. The nutrient contents of the two cereals were not matched; thus, the effects of each nutrient on satiety could not be clearly differentiated.
7. No information on subjects' usual intake was obtained, to determine if previous patterns of nutrient exposure were related to the results of the study investigating the effects of Olibra™ on satiety.

CHAPTER 2

REVIEW OF LITERATURE

Introduction

Overweight and obese individuals are at an increased risk for several medical conditions that contribute to morbidity and mortality.[51] According to the latest results of NHANES, in 2009-2010, 69.2% of adults in the United States (US) and 16.9% of children and adolescents were overweight or obese.[1, 2] The prevalence of obesity among both males (35.5%) and females (35.8%) has not significantly changed in the two most recent years, as compared with the previous six years.[1] Despite the evidence for a leveling off in the prevalence of obesity,[3] it is predicted that by 2030, 86.3% of all adults in the US will be overweight or obese.[52] The accompanying rise in health care costs is expected to account for 16-18% of total US health care costs (860.7 to 956.9 billion US dollars) by 2030.[52] Despite a high per capita expenditure on health care, life expectancy in the US ranked 34th in the world in 2009.[53] The unusually high rate of obesity in younger age groups, and higher rates of severe obesity in the US, have contributed to the reduction in life expectancy as compared with other countries.[54]

Obesity, is a multifaceted problem with complex contributing factors, including genetics, hormone levels,[55] behavioral patterns, and their environmental determinants.[56] Obesity results from a small but chronic energy imbalance. The impetus to initiate a meal is rarely based on a biological deficit. More likely, it is appetite sensations that trigger an eating episode.[57] The disease burden from excess weight[58] calls for novel strategies aimed at achieving healthier weights. Weight loss is complex and difficult, and controlling appetite may not be the solution,

but it is certainly a means of facilitating the process, especially if the proposed food is consumed regularly as part of a culturally accepted eating pattern such as breakfast.

Appetite and Satiety

Appetite is controlled by a network of interactions referred to as the psychobiological system, and reflects the synchronous operation of events occurring on three levels: 1) psychological events and behavior, 2) peripheral physiology, and 3) the central nervous system.[5] However, apart from the desire to satisfy their appetite sensations, humans are also prompted to eat by sensory hedonics, sensory stimulation, tension reduction, social pressure, and boredom.[4] Thus, a broad definition of appetite would encompass the whole field of food intake, selection, motivation, and preference.[7]

Satiety is the process that inhibits further eating, causes a decline in hunger, and an increase in fullness after a meal is eaten, whereas, the inhibitory processes that lead to termination of a meal cause satiation. Although satiation and satiety are distinct concepts, they act together along with other factors to determine eating behavior.[7] The satiety cascade provides a framework for examining the processes (sensory, cognitive, post-ingestive, and post-absorptive) that mediate the satiating effect of foods.[5] A modification to the satiety cascade includes the concepts of 'liking' which is the pleasure derived from the oro-sensory stimulation of food and 'wanting' which refers to the desire or motivation to actually engage in eating.[11]

Eating behavior is controlled by metabolic factors that drive appetite and satiety, and sensory factors that drive food choice. In the brain, the sensory signals of food are linked to the metabolic consequences leading to a conditioning of eating and nutrition patterns. Cognitive factors such as an estimation of the satiating effect of foods, and the timing of the next meal intervene and contribute to making eating a learned behavior.[7] It has been argued that food intake

is controlled by an integrated set of signals at a momentary level, liable to change with the environment in which food is available, as each combination of items is consumed, and with every change in the physical and social context.[8] By this argument, food intake tests and appetite rating scales fail in their assessment of satiety as they do not account for the changing influences over eating within, before, or after the test period, reactive responses, and the rater's mental state at the moment that the quantitative judgment is being expressed.[59]

Short term control of eating is influenced by episodic signals that arise largely from the GI and are generated periodically as food intake occurs. The peptides involved in GI signaling include cholecystokinin, GLP-1, PYY, and ghrelin. Long term control of eating, also referred to as tonic signaling, reflects the metabolic state of adipose tissue. Tonic or enduring effects influence traits (stable predispositions) whereas episodic or transient control influences states (dispositions subject to rapid fluctuations).[60] Psychometric tests such as the Eating Inventory[61] are used to identify traits that predispose individuals to opportunistic eating. States reflect the drive to eat, are expressed as appetite ratings, and are measured using VAS.[60]

In a review of 80 studies[4] that assessed satiety using subjective ratings of appetite, or by measuring actual energy intake, the vast majority of the studies showed that appetite ratings correlated with food intake in a standardized setting. Further, subjective appetite ratings and food intake were associated with changes in hormone concentrations.[4] Subjective satiety responses usually coincide with the time of occurrence and magnitude of the effect of physiological processes such as stomach filling, and the absorption of nutrients.[7] Nevertheless, satiety claims do not need to be substantiated by physiologic data.[13] It has been demonstrated that appetite scores measured through VAS can be reproduced and are therefore feasible tools to measure

appetite and satiety sensations.[7, 62, 63] Moreover, appetite and satiety have been found to be good predictors of food intake.[9, 10]

Functional foods are defined as components of the usual diet that may provide health benefits beyond basic nutrients.[12] Ingredients contained in functional foods can help consumers gain control over their eating behavior.[13] Foods that influence satiety may counteract impairments in satiety hormone production or response to ingestion, thereby modulating the behavioral response to ingestion.[6] While some functional foods may produce short term effects on appetite regulation others may have more enduring effects that translate into reductions in body weight; however, both have value in helping consumers to resist the situational and personal factors that drive overconsumption.[6]

Macronutrient composition, energy density, and physical structure influence satiety.[7] Different amino acids, fatty acids, and carbohydrates have differing effects on the markers of appetite regulation.[4] The differing effects imply that each nutrient interacts with the processes that mediate satiety in different ways.[5] Dietary protein may promote weight loss by increasing energy expenditure and by inducing satiety.[15, 27, 64, 65] Carbohydrates that are resistant to digestion, or which have a pronounced effect on glucose metabolism, have the potential to produce changes in appetite, and affect satiety. [66] Similarly, novel oils designed to reduce their absorption rate can potentially produce beneficial effects on appetite and satiety.[6] The challenge lies in understanding which components of food interact optimally with the mediating processes to influence food intake.

Protein

High protein diets with their potential to act on metabolic targets regulating body weight, have become the subject of a body of research. Results from intervention studies suggest that an

increase in the relative protein content of the diet reduces the risk of positive energy balance and the progress to weight gain.[67, 68] In short term studies (lasting for 24 hours up to five days), evaluating subjective satiety sensations, high protein diets have been shown to be more satiating than isoenergetic intakes of carbohydrate and fat.[27, 64, 65] Contrary evidence is scarce.[69]

Satiety mediated by protein is closely related to the increased energy expenditure accompanying protein intake. Protein-induced satiety is mainly due to the increase in the oxidation of amino acids ingested in excess. In respiratory chamber experiments satiety and thermogenesis increased with a high protein diet[27, 65] and satiety was positively related to 24 hour diet induced thermogenesis.[65] The modulation of glucose homeostasis and glucose signaling to the brain, precipitated by enhanced gluconeogenesis has been proposed as a mechanism for the satiating effect of protein. However, although gluconeogenesis increased with a high protein diet, there was no correlation between the appetite ratings and gluconeogenesis.[70]

It has been hypothesized that protein induced satiety is related to increased concentrations of the anorexigenic hormones GLP-1 and PYY and a decrease in the orexigenic hormone ghrelin.[27, 28] In a crossover trial,[27] GLP-1 concentrations were measured nine times throughout the day, on the fourth day of consuming a high protein (30% of energy from protein) or adequate protein (10% of energy from protein) diet. After dinner, GLP-1 concentrations were significantly higher on the high protein diet as compared with the adequate protein diet. Energy expenditure, protein balance, and fat oxidation were also significantly higher on the high protein diet as compared with the adequate protein diet. Although ghrelin concentrations decreased, it could not be clearly attributed to the protein content of the diet, since the adequate protein diet with relatively high carbohydrate content also resulted in a decrease in ghrelin concentrations. Additionally, the increase in GLP-1 was related to the increase in satiety.[27]

In a three week crossover trial, an effect of protein consumption on PYY concentrations was demonstrated with significantly higher plasma PYY and greater satiety responses to a high protein meal in normal weight and obese individuals, as compared with isoenergetic high fat and high carbohydrate meals.[28] However, in another study,[64] there were no differences in ghrelin and PYY responses between a high protein (25% of energy) and average protein (10% of energy) diets. GLP-1 response was in fact lower following the high protein meal as compared with the average protein (but higher carbohydrate) meal.

Specific amino acids may influence satiety by virtue of the fact that they are precursors for certain neurotransmitters involved in the regulation of appetite and body weight. Tryptophan is a precursor for the neurotransmitter serotonin, tyrosine can be converted into the neurotransmitters dopamine and norepinephrine and histadine can be converted into the neurotransmitter histamine. Each of these neurotransmitters has been linked with food intake regulation, although there is no direct evidence for their role in protein-induced satiety.[15]

Milk and Eggs

Milk and eggs are among the high protein foods often consumed as part of a breakfast meal. Dairy products have been shown to induce satiety and reduce food intake.[71-73] Additionally, dietary patterns that include increased consumption of milk have been associated with the prevention of body weight gain.[74] The physiologic actions of the protein and calcium components of milk have been associated with regulatory effects on food intake and body weight.[71, 75]

Casein and whey comprise 80% and 20% respectively of the protein in cow, sheep, goat, and buffalo milk.[76] Whey protein has been found to be more satiating in some studies,[77, 78] while other studies have found no difference in the satiating effects of whey and casein proteins[75, 79] or

that casein protein leads to a greater satiating effect than whey protein.[80] However, the effect of protein source is modulated by several factors including dose, form (solid or liquid), time to the next meal, and the presence or absence of other macronutrients.[76] Nevertheless, energy intake was 9% lower after intake of milk than after intake of casein or whey.[75] Thus, complete milk proteins might elicit an intermediate yet optimal satiating effect, or other bioactive components in milk influence its satiating power.

Satiety has been reported after consumption of dairy foods. Chocolate milk and a carbonated soft drink were matched for energy density and energy content, in a study to compare the satiety effects of the two beverages. Increased short term satiety was observed after consumption of chocolate milk as compared with the soft drink, but did not affect the *ad libitum* energy consumption at lunch served 30 minutes later.[72] The addition of 600 ml of skim milk to a fixed energy breakfast induced greater satiety than a fruit drink, and reduced energy intake at a buffet sandwich meal four hours later.[73]

Very few studies have assessed the impact of calcium consumption alone on the regulation of food intake. In women consuming < 800 mg/day of calcium, daily supplementation of calcium + vitamin D (1200 mg calcium + 10 µg vitamin D) for 15 weeks, reduced fat and total energy intake at an *ad libitum* food intake test.[81] Subjects participating in a six month energy restriction program were assigned to either milk (1000 mg of calcium) or placebo (0 mg calcium) supplemented groups. Milk supplementation resulted in an increase in measured fullness that was significantly different from the decrease predicted by weight loss. Additionally, weight loss was found to induce orexigenic effects that were attenuated in the group receiving the milk supplementation.[71] However, milk supplementation led to an increase in protein intake; hence, it was difficult to distinguish between the effects of protein and calcium on food intake regulation.

The protein content of eggs is 35% of their total energy content.[82] Isoenergetic egg (23% of energy from protein) and bagel (16% of energy from protein) breakfast meals were compared. The egg breakfast significantly reduced the insulin, glucose, and ghrelin concentrations. Additionally, hunger was reduced and satisfaction increased after the egg breakfast as compared with the bagel breakfast, resulting in a reduction in food intake at a subsequent meal.[83] In another study comparing isoenergetic egg (18.3 g protein) and bagel (13.5 g protein) breakfasts, matched for weight, the egg breakfast resulted in an increase in satiety and a reduction in energy intake at lunch. There was no compensation for the reduction in energy intake in the 24 hour period following breakfast, as assessed by self-reported food intake.[84] No difference in energy intake was found at dinner following consumption of three isoenergetic test lunches: omelet, jacket potato, and chicken sandwich, although the omelet meal was found to elicit a higher satiety response than the potato and chicken meals.[82]

Carbohydrates

Carbohydrates influence satiety through multiple mechanisms related to their hormonal effects, intrinsic properties, and intestinal fermentation.[85-90] The hormonal effects of carbohydrates on satiety are mediated by insulin[90] and gastrointestinal hormones.[88, 89] Intrinsic properties include the bulking and viscosity effects of dietary fiber.[85, 87] Carbohydrates that evade small intestinal digestion, enter the large bowel and are fermented by colonic bacteria into short chain fatty acids which have been shown to enhance satiety.[86]

The potential physiologic mechanisms relating the Gi to the regulation of food intake are based on the postprandial metabolic milieu precipitated by hyperglycemia and hyperinsulinemia. It has been suggested that a high glycemic load (product of Gi and available carbohydrate content) meal elicits a high insulin and low glucagon response that promotes uptake of glucose

in muscle, liver, and fat tissue, thereby restraining hepatic glucose production and inhibiting lipolysis.[90] Limited access to the two major metabolic fuels in the post-absorptive state, may lead to a quick hunger response and overeating, in the body's attempt to restore the concentration of metabolic fuels to normal.[90] Low Gi foods are characterized by a slow rate of digestion and absorption, thereby eliciting a low glycemic response.[91]

A majority of studies reviewed support an increased short term satiety with low Gi foods or meals compared with high Gi foods or meals.[17] A systematic review of the effect of low Gi diets on satiety and body weight in the long term (several days or weeks duration) found inconsistent results.[18] The clinical relevance of diets based on the Gi remains unclear. A large part of the debate appears to center around inconsistencies in the data. The Gi is influenced by the nature of the starch, the physical form, the amount of fiber, fat and protein, and the cooking times and methods.[92] Other dietary factors affecting food digestibility, gastrointestinal motility, or insulin secretion also determine the Gi of a food.[93] The Gi relates to a food and not the individual; therefore, there exists the possibility of intra- and inter- individual variances in the Gi. The random day-to-day variation in the glycemic response that occurs even in repeated experiments of the same food under standardized conditions is seemingly inexplicable.[94]

Dietary fiber may be classified into soluble and insoluble fiber on the basis of water solubility. Colonic fermentation of soluble fiber yields short-chain fatty acids. Insoluble fiber generally has low fermentability, but it has water-attracting properties that promote fecal bulk.[95]

Several mechanisms have been proposed to explain the effects of dietary fiber on the regulation of appetite, and satiety: (1) Dietary fiber traps nutrients and retards their passage through the GI tract, enhancing the interaction between the intestinal wall and nutrients. Exposure of the intestinal mucosa to nutrients stimulates the release of appetite regulating

peptides which function as hormones, or activate neural pathways involved in appetite regulation.[29] (2) Energy density is inversely associated with satiety.[33] Dietary fiber lowers the energy density of a food[34] and by implication enhances satiety. (3) Fiber increases mastication, and it requires time and effort to eat the fiber-containing food. Additionally fiber limits intake by stimulating the secretion of saliva and gastric secretions that cause stomach distension, thereby promoting satiety.[16] (4) Lastly, although colonic fermentation of undigested carbohydrate to short chain fatty acids has been hypothesized to increase satiety, data from human intervention studies do not appear to support a role for intestinal fermentation in appetite regulation.[19-21]

Consumption of highly viscous soluble dietary fiber delays gastric emptying which can increase stomach distension[30] thereby stimulating afferent vagal signals of fullness.[4] While gastric satiety is mechanical in origin, intestinal satiety is nutrient-dependent, nevertheless, there exists evidence for a synergy of the two types of stimulation.[31, 96] Satiety signals are released following interaction between the gut wall and nutrients. In the small intestine, the increased viscosity of contents prolongs transit time and reduces the absorption rate of nutrients, thereby enhancing the possibility of interaction between nutrients and the cells that release satiety hormones.[29] Although hunger and satiety sensations originate in the central nervous system, gut hormones play a key role in the regulation of food intake.[97]

Whole-grain products are good sources of dietary fiber. The 2010 Dietary Guidelines for Americans recommend that at the 2000 kcal level, grain products should comprise six servings of which at least three servings should come from whole-grains.[98] In the US, total grains servings are typically over-consumed; however, most Americans are not consuming adequate amounts of whole grains.[99] From an analysis of NHANES data from 1999 – 2004 it was determined that

mean whole grain consumption among adults aged 19-50 years, and 51 years and over was 0.63 and 0.77 servings/day respectively. Less 5% of adults in the age group 19 -50 years consumed the recommended servings of whole grains.[100] There appears to be evidence to indicate that since the 2005 Dietary Guidelines for Americans, consumers have increased purchases of whole-grains, especially cereals, breads, and pasta. Competition among manufacturers leading to more products with whole grains being made available, may have triggered the increase in consumption.[101]

Breads and Breakfast Cereals

Ready-to-eat cereals (28.7%) yeast breads (25.3%) and hot cereals (13.7%) are the major sources of whole-grain consumption in the US;[102] and they have been shown to enhance satiety.[87, 103-106] However, not all whole-grain breads increased satiety. In a comparison of whole-grain wheat bread and refined grain wheat bread, subjective satiety and food intake following consumption of the whole-grain bread providing 10.5 g of fiber per day for three weeks was not significantly different as compared with refined grain bread providing 5.8 g of fiber per day.[107] Yeast breads contribute 26% to non-whole grain consumption[102] and enriched and fortified grains provide important nutrients, especially folate.[99] The addition of fiber components to refined grain flours used in the production of breads and breakfast cereals has also been found to have beneficial effects on the regulation of appetite.[89, 108] Thus, it is important to encourage consumption of both enriched grains as well as whole grains in the recommended proportion.

Although rye is not among the grains commonly consumed in the US,[109] it is a good source of soluble and insoluble dietary fiber.[110] The main fiber components of the cell wall in rye are arabinoxylan, ß-glucan, and cellulose. Arabinoxylan is the dominant fiber, and the water

extractable component of arabinoxylan exhibits a high viscosity when dispersed in water.[111] While ß-glucan is susceptible to degradation, arabinoxylan is resistant to the bread making process and retains its average molecular weight.[110] The molecular weights of the individual fiber types affect their physiologic properties, including viscosity.

Rye flour is usually made from a blend of different rye varieties. Several whole grain rye breads made with different rye varieties, including a commercial blend of rye varieties, were compared with bread made from refined wheat flour. Subjective satiety was significantly higher following consumption of the commercial blend which had the highest insoluble fiber content (10.3 g) as compared with the wheat bread (2.4 g insoluble fiber). However, not all varieties of rye increased satiety.[103, 104]

In an assessment of a dose-response relationship it was found that while rye bread (60% rye bran flour, 40% wheat flour) with 5 g or 8 g of fiber served as part of isoenergetic breakfasts increased satiety as compared with a wheat bread breakfast, there was no significant difference in satiety between the two rye bread breakfasts.[112] Varying the structure of rye flour (whole rye kernels or milled rye kernels) used to make bread did not result in different effects on satiety.[113]

Rye porridge and rye bread made from different parts of the rye grain (endosperm, whole-grain, and bran) were compared with bread made from refined wheat. It was found that the porridge made from whole-grain and bran fractions, elicited an increase in satiety as compared with the bread made from the same parts of the grain, however all rye products increased satiety as compared with wheat bread.[114] The same investigators also compared the effects of similar rye breads on appetite and satiety, with meals made by boiling rye kernels. Consumption of rye kernel meal was not only found to be more satiating than the breads, but it also reduced food intake at a subsequent meal.[115]

Whole grain rye porridge breakfast (followed by whole grain wheat pasta lunch or refined wheat pasta lunch) and refined wheat bread breakfast (followed by refined wheat pasta lunch) were compared. The meals were matched for macronutrient content. Satiety ratings were significantly higher after the rye porridge breakfast when compared with the refined wheat bread breakfast. Following consumption of the refined wheat pasta lunch meal subjects who ate the rye porridge breakfast meal continued to have greater sensations of satiety as compared with those who ate the refined wheat bread breakfast meal.[116] In another study, whole-grain rye porridge increased satiety as compared with an isoenergetic refined wheat breakfast. Although the effect on satiety was sustained during three weeks of regular intake, it was only maintained up to four hours and energy intake at subsequent meals were not significantly different.[117]

Lupin-kernel flour, derived from the endosperm of lupin seeds, contains 40-45% protein and 25-30% fiber with negligible amounts of sugar and starch.[108] A lupin-kernel fiber-enriched sausage patty was shown to produce greater effects on satiety than both a conventional patty and an inulin fiber-enriched patty.[118] Partial substitution of lupin-kernel flour for wheat flour in bread-making increases the protein and fiber content of bread. Bread made by a substitution of 40% of wheat flour with lupin-kernel flour was compared with bread made with 100% wheat flour. Served as isoenergetic breakfasts with margarine and jam, the lupin-kernel fiber bread resulted in greater satiety and lower energy intake at lunch when compared with the wheat bread.[108]

β-glucan, found in significant amounts in oat and barley, exhibits a high viscosity at relatively low concentrations.[119] The satiating effect of ß-glucan has been demonstrated in several studies using ß-glucan in doses ranging from 2.2 g to 9 g. [85, 88, 89, 120-122] Other studies found no effect of ß-glucan on satiety.[123-125] Bread made with 100% wheat flour was compared

with bread in which 4.5% of the wheat flour was replaced with 3 g of concentrated extract of barley ß-glucan, a viscous soluble fiber. The bread containing barley ß-glucan increased satiety and reduced food intake at a subsequent meal by 19% as compared with the bread made with 100% wheat flour.[89] In contrast, inclusion of barley ß-glucan into breakfast and lunch meals (including barley cereal at breakfast and barley bread at lunch) did not increase satiety as compared with wheat-containing meals (including bran flakes at breakfast and refined wheat bread at lunch) with similar energy and nutrient contents. Barley-containing meals were in fact associated with higher energy intake during the remainder of the day, assessed through self-reported food records.[126] However, self-reported data are notorious for their susceptibility to misreporting and altered feeding behavior.[127]

Regular consumption of breakfast cereals, as assessed through food frequency questionnaires has been associated with a lower body mass index, and reduced likelihood of being overweight.[128] Crushed or rolled oats are often used in the production of breakfast cereals.[119] The content of β-glucan in commercial grade oats in North America varies from 35-50 g/kg.[129] Variations in the source, processing treatments, manufacture of a product, and the interactions with other constituents in the food matrix affect the amount, solubility, molecular weight, and structure of the β-glucan in the products.[130] Thus, the functionality of β-glucan differs from one product to another.

Viscosity is controlled by concentration in solution and molecular weight.[131] Oat β-glucan is more soluble in hot water than in water at room temperature, so processing steps that involve moisture and heat will in all likelihood increase the solubility of β-glucan.[132] Cooking of oats has been shown to increase the percentage of β-glucan solubilized by three-fold.[49] β-glucan is integral with cellulose and other noncellulosic polysaccharides in the cell wall and cooking

releases it from this matrix.[133] Thus, food structure and matrix of the product delivering the β-glucan affects its bioavailability.[130]

Breakfast cereals containing oat ß-glucan in amounts ranging from 2.2 g to 5.7 g and a corn-based breakfast cereal (0 g ß-glucan) were compared. The breakfasts were isoenergetic. Subjective satiety increased with each of the breakfast meals containing oat ß-glucan as compared with the corn-based breakfast meal. However, there was no difference in the overall satiety responses between the breakfasts containing oat ß-glucan.[85] In a separate study, the same investigators, examined the effects of varying the dose of oat ß-glucan from 2.2 g to 5.5 g delivered through breakfast cereals, and concluded that the optimal dose of β-glucan affecting satiety and other markers of appetite regulation were between 4 g and 6 g and that the hormonal effects were mediated through increased viscosity. Increasing the dose of β-glucan resulted in a greater release of PYY.[88]

Other studies have shown that ß-glucan had no effect on satiety. Muesli containing 4 g of oat ß-glucan served in yogurt, did not result in a significantly prolonged period of satiety as compared with an isoenergetic meal consisting of cornflakes served in yogurt.[123] Satiety ratings were compared following ingestion of wheat bran flakes (7.5 g fiber), whole-meal oat flakes (4 g fiber: 0.5 g ß-glucan), and cornflakes (1.5 g fiber) of equal weight served with milk. Bran flakes or oat flakes did not result in significantly higher satiety when compared with corn flakes.[124]

In a study investigating the satiating effects of barley ß-glucan, hunger was found to be lower with barley products (9 g β-glucan) as compared with whole wheat, and rice products served at breakfast as a hot cereal, and at mid-morning as a snack mix.[122] In other studies 1.2 g barley β-glucan in a meal replacement bar,[19] had no effect on satiety and 2 g of barley β-glucan served in a hot cereal did not affect short term satiety in overweight individuals.[134]

The insoluble fiber found in breakfast cereals made with whole-grain wheat has also been demonstrated to increase satiety as compared with cornflakes of equal weight,[87] or equal energy content,[105] however, the amounts of insoluble fiber ranged from 26-33 g/meal.[87, 105] In a comparison of isoenergetic breakfasts, increased fullness was observed with a meal high in insoluble fiber (whole grain wheat bran breakfast cereal: 18.1 g fiber) as compared with a breakfast of bacon and eggs,[106] which was higher in fat and comparable in protein. Additionally, the total fiber content of a food by lowering its energy density affects satiety as energy density and satiety are inversely associated.[33]

Fat

Fats have been shown to reduce hunger when present in the GI tract by eliciting satiety signals.[22] Fat in the duodenum stimulates the release of cholecystokinin and other gastrointestinal peptides that affect satiety.[31] Exposure of the ileum to fat stimulates an even larger satiety response than exposure to the duodenum.[35] Fat reaching the ileum stimulates the ileal brake, a distal to proximal feedback mechanism that controls the transit of food through the GI tract. Nutrients in the small intestine, influence satiety and food intake by activation of neural afferents or by stimulating the release of gut hormones involved in appetite regulation.[31, 135]

Bariatric surgery is arguably the most effective weight loss treatment for the morbidly obese.[136] The Roux-en-Y gastric bypass surgery results in a speedy delivery of nutrients to the distal parts of the GI tract. Meal-stimulated increases in PYY and GLP-1, gut hormones with anorectic effects, implicated in the ileal brake activation, have been observed after the Roux-en-Y gastric bypass.[136, 137] Thus, bariatric surgery provides evidence that a sustained appetite reducing effect is possible through a recurring activation of the ileal brake.[35]

Infusion of triglycerides into the ileum has been shown to alter duodenal motility and delay gastric emptying.[138] Ileal fat infusion has also been shown to cause a dose-dependent delay in gastric emptying and has been related to increased plasma concentrations of PYY.[36, 37] An ileal infusion of corn oil increased feelings of satiety and reduced *ad libitum* food intake at a meal 30 minutes after the start of the infusion. However, the rate of infusion of fat can be compared to what one may find in normal subjects after eating a heavy meal.[38, 39] Nevertheless, a low physiologic dose of fat (6 g) into the ileum elicited a significant reduction in hunger and food intake when compared with an oral ingestion of the same amount of fat.[139] A pooled analysis of studies investigating the effects of fat on gastric emptying and GI hormone release determined that the magnitude of stimulation of pyloric pressures and release of cholecystokinin, a hormone with anorexigenic effects, are independent predictors of subsequent energy intake.[140]

The physicochemical properties of fat affect its ability to regulate GI motor function, gut hormone release, and satiety. These effects are more pronounced with LCT (>12 carbons) than shorter chain fatty acids.[22, 40, 41] A 180 kcal duodenal infusion of long chain fat emulsions reduced food intake by over 200 kcal as compared with a saline infusion.[40] Duodenal infusion of 12 carbon fatty acids reduced appetite and energy intake at a subsequent meal as compared with 10 carbon fatty acids. The effects on gastroduodenal motility that were observed are typically associated with delayed gastric emptying.[41] Hunger and gastric emptying are closely related. It has been suggested that accelerated gastric emptying decreases gastric distension, thereby promoting hunger.[141] The effects of fat on gastric emptying are however, dependent on digestion of fats and consequent release of free fatty acids.[141]

Medium chain triglycerides (MCT) (6-12 carbons) have been shown to influence satiety through increased energy expenditure.[42] Unlike LCT, MCT are directly absorbed into portal

circulation and are more rapidly metabolized. The role played by the degree of saturation in modulating the effects of fat on the GI tract has not been resolved fully.[43, 44]

Novel Oils

Pinnothin™ is a natural oil pressed from Korean pine nuts and contains linoleic acid (C18:2), pinolenic acid (C18:3), and oleic acid (C18:1). Consumption of Pinnothin™ triglycerides and free fatty acids has been shown to produce an increase in cholecystokinin and GLP-1 in post-menopausal overweight women. However, appetite ratings did not significantly differ in comparison with olive oil.[142] In overweight women, appetite ratings were not significantly different after consumption of Pinnothin™ triglycerides or free fatty acids as compared with olive oil, although Pinnothin™ free fatty acids reduced food intake by 7% at a subsequent meal.[143] In both the studies[142, 143] participants consumed Pinnothin™ in capsule form. When Pinnothin™ triglycerides were added to a yogurt, appetite sensations and energy intake were not significantly different as compared with milk fat.[144]

Delaying lipid digestion is an important factor in stimulating the ileal brake. The digestion of fat can be slowed down by manipulating the oil emulsion interfacial composition using galactolipids. It has been shown that galactolipids reduce the rate and extent of lipolysis by sterically hindering the penetration of pancreatic colipase and lipase at the oil-water interface in the duodenum.[145] Olibra™ is a fat emulsion comprised of fractionated palm, and oat oil in the proportion of 95:5. The palm oil is emulsified by hydrophilic galactolipids derived from oat oil.[146]

Early studies[23-25] all using crossover designs, reported a reduction in energy, macronutrient and total weight of food intake, following consumption of yogurt containing the Olibra™ emulsion. The suppressive effects on appetite ratings (hunger, desire to eat, and

preoccupation with thoughts of food or perceived fullness) were only demonstrated in one study[24] and one part of another study.[23] The effects were evident four hours[23] after consumption of the test product, were maintained at least until eight hours, and were evident in non-overweight, overweight and obese subjects.[24] Using self-reported food intake data, it was concluded that the treatment effects of Olibra™ were maintained up to 36 hours.[25] Additionally, the effects of Olibra™ were shown to be dose dependent but results were not consistent across gender or proportional across dose levels. Lower mean energy (21%, 25%, and 30% with 2g, 4g, and 6 g of Olibra™, respectively) macronutrient, and total weight of food, intake were observed after consumption of the test product, as compared with a placebo.[25]

Subsequent studies investigating Olibra™ failed to confirm the reduction in energy intake.[45-47] In one study with a crossover design wherein each subject was studied for a period of nine weeks (two, three-week intervention phases that were separated by a three-week period) no treatment effect for energy, macronutrient, or total weight of food, intake was observed four hours after consuming the test product as assessed by a food intake test, or during the remainder of day and on the post-test day based on self-reported food records.[45] Ratings of hunger, fullness, desire to eat, prospective consumption or preoccupation with thoughts of food did not reflect any treatment effects of Olibra™.[45] However, in another study a suppressive effect over appetite ratings at three hours, and a lower return to baseline hunger in normal weight women aged between 18 and 30 years was observed which did not translate into a reduction in food intake.[46]

A meta-analysis[147] of the short term effects of Olibra™ on food intake, indicated that Olibra™ may suppress appetite more effectively at doses that are less than 5 g. No relationships were found between the appetite suppressant effects of Olibra™ and sex, age, or BMI. The divergent results from various studies were attributed in part to the manufacture, processing, or

preparation of Olibra™. It has been speculated that the functional integrity of the Olibra™ emulsion structure is affected when it is subjected to processing such as homogenization and pasteurization, along with the yogurt used in most studies as the vehicle for delivering Olibra™. The emulsion is susceptible to breakdown when exposed to thermal and shear processing and to an acidic environment.[147] Although the unprocessed emulsion, and not the processed form produced a modest decrease in food intake measured eight hours following consumption, there was no effect on appetite and satiety ratings.[148] More recently, Fabuless™ (also known as Olibra™) added to yogurt beverages exposed to minimal processing had no effect on satiety or food intake.[48]

The beneficial effects of Olibra™ on body composition and weight maintenance after weight loss have been demonstrated.[149] In the weight maintenance phase following weight loss as a result of a very low calorie diet, there was no significant increase in body weight, BMI, and waist circumference in the group consuming Olibra™ for 18 weeks, whereas the control group showed a significant increase. Additionally, there was a significant decrease in fat mass and an increase in lean body mass in the test group as compared with the control group.[149] However, in another study the addition of Olibra™ to a meal replacement diet plan following weight loss, resulted in a 0.9% decrease in body fat mass but caused no change in body weight at the end of 12 weeks.[150]

In these studies, the energy restriction imposed during the weight loss period may have had a role to play in the beneficial effects. In humans, it has been shown that exposure to a high fat or high energy diet decreases sensitivity to the GI mechanisms involved in appetite regulation.[22, 141, 151] It has been suggested that dietary restriction may reverse these effects resulting in enhanced nutrient sensing and exacerbation of appetite suppression.[22] A high fat diet

(58% of energy intake) for two weeks has been shown to modify appetite perceptions, increasing hunger and decreasing fullness. A significant increase in energy intake of approximately 160kcal/day was observed for the following two week period.[152] Placing subjects on a high fat diet derived from sunflower oil for only three days resulted in an acceleration of gastric emptying.[151] However, a delay in GI transit and a reduction in satiety following a high fat diet shown to occur over a one week period was found to return to pre-diet levels by the end of four weeks.[151]

A 45 minute delay in intestinal transit time following consumption of Fabuless™ has been reported.[30] However, the methodology for computation of orocecal transit time by measuring sulfapyridine, a colonic metabolite of salazopyrine has been questioned.[41] Following an intragastric administration of Fabuless™ a significantly higher amount of total lipids and the occurrence of crystals was observed in the jejunal samples as compared with an intragastric administration of milk fat. The authors suggested that the formation of palmitic acid crystals led to the gradual release of free palmitic acid as the crystals are transported further down the intestine into the ileum. Exposure of the ileum to unabsorbed lipids stimulated the activation of the ileal brake mechanism.[146]

While it is important to demonstrate that Olibra™ produces conditions conducive to stimulation of the ileal brake mechanism, such manipulation must also produce the directional changes in feeding behavior consistent with the activation of this mechanism. Eating behavior comprises a large learned and anticipatory component.[127] Behavioral and environmental factors can overcome physiological drives and influence feeding behavior.[153] Therefore, a physiologic impetus would have to be sufficiently large to consistently correlate with altered energy and nutrient intakes.

Journal Articles

Two articles are presented in this thesis. The article reporting the effects of a novel fat emulsion, Olibra™, on satiety, food intake, and body weight has been published in the Journal of Diabetes Science and Technology (2012;6(3):695-708). This article also reviewed the published human studies that investigated the effects of Olibra™. The article reporting the short term effects of oatmeal on appetite and satiety as compared with a RTEC will be submitted to The American Journal of Clinical Nutrition.

CHAPTER 3

EFFECT OF OATMEAL ON APPETITE AND SATIETY WHEN COMPARED TO A READY-TO-EAT BREAKFAST CEREAL

Introduction

Obesity, caused by a chronic energy imbalance is a multifaceted problem with complex contributing factors, including genetics, hormone levels,[55] behavioral patterns, and their environmental determinants.[56] The decision to eat often arises as a consequence of appetite as opposed to the need for energy, and meal initiation is therefore non-homeostatic.[57] Thus, appetite and satiety become important elements in the adjustment of energy intake to expenditure. Appetite sensations influence the search, choice, and ingestion of food.[4] Satiety refers to a subjective feeling of the absence of the motivation to eat, decline in hunger, and increase in fullness after a meal is eaten.[7] Appetite sensations and satiety have been shown to be good predictors of energy intake.[9, 10] Although weight loss is complex and difficult, enhancing satiety is a legitimate means of facilitating the process especially if the proposed food is consumed regularly as part of a culturally accepted eating pattern such as breakfast.

Macronutrient content can influence the satiating power of a food.[7] Relatively more protein in a particular meal results in relatively elevated amino acids, anorexigenic hormones, or the activation of energy expenditure feedback mechanisms on the central nervous system.[15] The satiating effect of carbohydrates is determined by the type and form of carbohydrate. It has been hypothesized that foods with a high glycemic index (Gi) elicit a higher immediate insulinemic response. The ensuing hypoglycemic period increases hunger and lowers satiety as compared with a lower Gi food.[90] Dietary fiber through its bulking and viscosity effects poses a physiological obstacle to energy intake. Consumption of highly viscous soluble dietary fiber

delays gastric emptying which can increase stomach distension,[30] and thereby stimulates afferent vagal signals of fullness.[4]

Gastric satiation is volume-dependent and intestinal satiety is nutrient-dependent, yet, there is evidence for a synergy of the two types of stimulation.[31, 96] Satiety signals are released following interaction between the gut wall and nutrients. In the small intestine, the increased viscosity of contents prolongs transit time and reduces the absorption rate of nutrients.[35] Although hunger and satiety sensations originate in the central nervous system, gut hormones play a key role in the regulation of food intake.[97]

Crushed or rolled oats are often used in the production of breakfast cereals. β-glucan, a soluble fiber found in significant amounts in oat kernels exhibits a high viscosity at relatively low concentrations.[119] The content of β-glucan in commercial grade oats in North America varies from 35-50 g/kg.[129] Variations in the source, processing treatments, manufacture of a product, and the interactions with other constituents in the food matrix affect the amount, solubility, molecular weight, and structure of the β-glucan in the products.[130] Thus, the functionality of β-glucan differs from one product to another.

The satiety effect of an oatmeal breakfast was compared with the most widely sold ready-to-eat breakfast cereal (RTEC) in the United States (based on IRI Liquid Data, 52 Weeks Ending March 11, 2012). It was hypothesized that the oatmeal breakfast with a higher content of fiber would result in greater satiety than the oat-based RTEC, over the four hour period following consumption.

Subjects and Methods

Subjects

Forty-eight healthy subjects 18 years of age or older, were enrolled in a randomized, crossover trial. All subjects participated in an initial screening that involved measurement of body weight, height, waist and hip circumferences, vital signs (blood pressure, pulse rate), chemistry-15 panel, complete blood count with differential, and β-HCG pregnancy test-urine (in females of child-bearing potential). Questionnaires related to dietary restraint (Eating Inventory)[154] which have been used extensively to measure individual variability in eating behavior,[155] were completed to exclude restrained eaters. Female subjects also completed a menstrual cycle questionnaire so that breakfast test days would fall within the luteal phase of the menstrual cycle.[156] In addition to the laboratory tests and measurements of vital signs, a medical screening questionnaire was used to confirm health. Exclusion criteria were: (i) women who were pregnant or nursing, (ii) self-reported weight gain or loss of 4kg or more in the last 3 months, (iii) fasting glucose >126mg/dL, (iv) dietary restraint score ≥ 14, and (v) allergy or intolerance to oats or milk.

The study was approved by the Institutional Review Board of the Pennington Biomedical Research Center and participants provided written informed consent. The trial was registered on ClinicaTrials.gov with registration number NCT01372683.

Study Design

Each participant was tested on two days. On one occasion the breakfast meal consisted of Quaker Old Fashioned Oatmeal™ and on the other occasion the breakfast meal served was the RTEC, Honey Nut Cheerios™. Order of the two breakfasts was randomly assigned. The breakfasts contained 355 kcals, consisting of 250 kcals of cereal, and 105 kcals of lactose-free,

fat-free milk. A nutrient analysis of both breakfasts is presented in Table 3.1. The oatmeal (66.8 g dry weight), was cooked in a microwave at high power for three minutes with 355.5 g of water, allowed to stand for a minute, and served with 307 g of milk. The RTEC (63.6 g dry weight), was prepared by adding 307 g of milk, and served with 355.5 g of water. The participants had the option of adding 1 g of Splenda™ and one-half teaspoon of cinnamon to the oatmeal. If the participant added Splenda™ and cinnamon to the oatmeal, they were required to add both, in the same amounts to the RTEC.

At the first test breakfast visit, participants arrived at the center after a 10 hour overnight fast, and having avoided strenuous exercise for 24 hours prior to the test meal. They completed a questionnaire about colds or allergies that might affect taste, and were asked to return on another day if such a condition was present. Electronic visual analog scales (VAS),[7, 62] were administered prior to serving the test meal. Participants rated each subjective state by placing the cursor over a line on a computer screen and clicking at a point, which was anchored using the descriptors "Not at all" to "Extremely." Visual analog scales were scored by the computer on a 0 to 100 millimeter (mm) scale and the score was sent directly to the database. Hunger, fullness, desire to eat, and prospective intake, were assessed. Satisfaction with the meal which introduces a hedonic component into the measurement of satiety,[63] was included to determine if satiety measures were judged from a comparable baseline during the repeated testing.

The subjects were presented with their first breakfast test, and given 20 minutes to eat it. Test meals were supervised to ensure that the entire breakfast was eaten. Visual analog scales were then administered at 30, 60, 120, 180, and 240 minutes following the start of the breakfast meal. Subjects were asked an open ended question, "How do you feel?" at each of the time

points that the VAS were completed to elicit any adverse events. Subjects returned on another day separated by at least a week to repeat the breakfast test.

Table 3.1 Energy and nutrient content of breakfast meals which included the breakfast cereal and lactose-free, fat-free milk

	Quaker Oatmeal[1]	Honey Nut Cheerios[2]	Lactose-Free, Fat-Free Milk
Kilocalories (kcal)	250	250	105
Fat (g)	5.01	3.41	0.25
Protein (g)	8.35	4.54	10.33
Carbohydrates (g)	45.09	49.97	15.6
Fiber (g)	6.68	4.54	0
Soluble Fiber (g)	3.34	1.70	0
β-Glucan (g)	2.28	1.67	0
Sugar (g)	1.67	20.44	0
Serving Size (g)	66.8	63.6	306.3

[1]Quaker Oats; (Pepsico Inc. Barrington IL);
[2]Honey Nut Cheerios; (General Mills Inc. Minneapolis MN)

Statistical Analysis

A mixed model ANOVA for a 2 x 2 crossover trial was performed to analyze the primary outcomes. Visual analog scale scores for hunger, fullness, desire to eat, prospective food intake, and satisfaction with the meal were analyzed in terms of the area under the curve (AUC). The model included fixed effects (residual treatment carryover effects from test day 1 to test day 2 [treatment sequence effects], test day main effects, and treatment main effects), and random effects (subjects within treatment sequence groups). The secondary outcomes, were changes in VAS for hunger, fullness, desire to eat, prospective intake, and satisfaction from time 0 to 30, 60, 120, 180, and 240 minutes following the start of the breakfast meal. Secondary outcomes were analyzed using a mixed model ANOVA for a doubly repeated measures crossover trial where the first repeated measures variable was test day, and the second variable was time since start of breakfast. The changes from time zero were summarized as least squares means plotted for each

cereal type across the assessment times. Thus, differential treatment effects were compared with respect to AUC, and per time point using SAS (version 9.2, 2002-2008, PROC MIXED; SAS Institute, Cary, NC). Area under the curve was estimated using the linear trapezoidal rule and calculated as the area between the zero change line and the measured change curve which could be either above or below the zero change line.

During the planning phase of the study, sample size was estimated using G*Power, Version 3.1.2 (F. Faul, Universitat Kiel, Germany) with the following assumptions: (i) power ≥ 0.78 was considered acceptable, (ii) the significance level under the null hypothesis was set at α=0.05, (iii) the primary outcome was VAS AUC with *a priori* standard deviation assumed to be 3047mm×min based on previous research[142] and (iv) the null hypothesis was to be tested against a two-directional alternative. The study was sufficiently powered with 46 participants for detecting a minimum difference of 1258 mm×min between cereal types, which is similar to observed differences in AUC (1213 mm×min) for desire to eat from a similar food intake study.[142]

Results

Forty eight subjects were enrolled in the study. Two subjects who were unable to complete the study withdrew. Data related to 46 subjects were analyzed. There were no adverse events. Descriptive characteristics of the subjects at baseline are summarized in Table 3.2.

Table 3.2 Subject Characteristics at baseline including age, body mass index, waist circumference, gender, and race

	n = 46 Mean ± SD
Age	34.1 ± 14.3
BMI (kg/m^2)	26.1 ± 7.2
Waist Circumference (cm)	82.2 ± 15.5
	n (%)
Gender	
Female	29 (63)
Male	17 (37)
Race	
American Indian	1 (2.2)
Asian	2 (4.3)
Black	16 (34.8)
White	27 (58.7)

Hunger

The reduction in hunger was significantly greater after consuming oatmeal as compared with the RTEC (p=0.0009) based on the AUC (oatmeal: 12,372±817.96 mm×min versus RTEC: 9,656±817.96 mm×min), and the least squares means (Figure 3.1) at 120min (p=0.0197), 180min (p=0.0003), and 240min (p= 0.0036) following consumption of the breakfast meals.

Fullness and Satisfaction

Increase in the sensation of fullness was significantly greater after consuming oatmeal as compared with the RTEC (p=0.005) based on the AUC (Oatmeal: 13,392±740.57 mm×min versus RTEC: 11,233±740.57 mm×min) and the least squares means (Figure 3.2) at 120min (p=0.0408), 180min (p=0.0061), and 240 min (p=0.0102). The response to how satisfied subjects felt, was not significantly different between the two breakfast meals, except for greater satisfaction after consuming oatmeal at 180min (p=0.0392) as depicted in Figure 3.3.

Desire To Eat and Prospective Intake

Reduction in the desire to eat was significantly greater after consuming oatmeal as compared with the RTEC p=0.0002), based on the AUC (oatmeal: 13,188±804.53 mm×min versus RTEC: 10,425±804.53 mm×min) and the least squares means (Figure 3.4) at 120min (p=0.0168), 180min (p<0.0001), and 240min (p=0.0022). Reduction in subjects' perceptions of prospective food intake, was significantly greater after consuming oatmeal as compared with the RTEC (p=0.0012), based on the AUC (oatmeal: 10,360±823.67 mm×min versus RTEC: 7,780±823.67) and the least squares means (Figure 3.5) at 120min (p=0.0058), 180min (p=0.006), and 240min (p=0.0047).

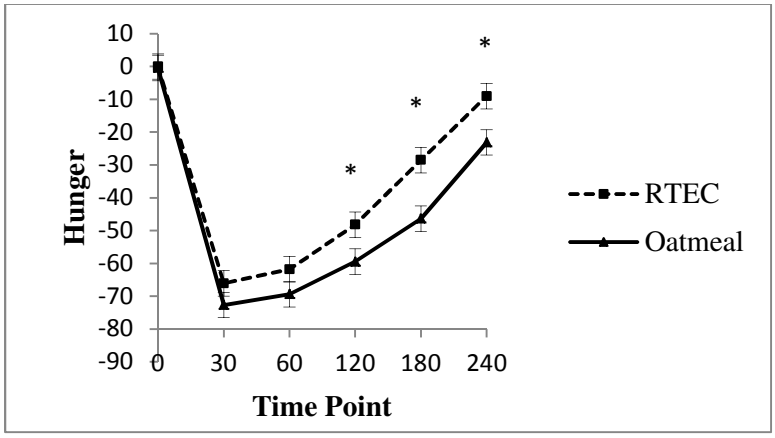

Figure 3.1 Visual analog scale ratings for hunger (n = 46) before and after consumption of oatmeal and a ready-to-eat breakfast cereal (RTEC): Hunger was reduced to a greater extent with oatmeal as compared with the RTEC.*Least squares means: {120 minutes (p=0.0197), 180 minutes (p=0.0003) and 240 minutes (p= 0.0036)}

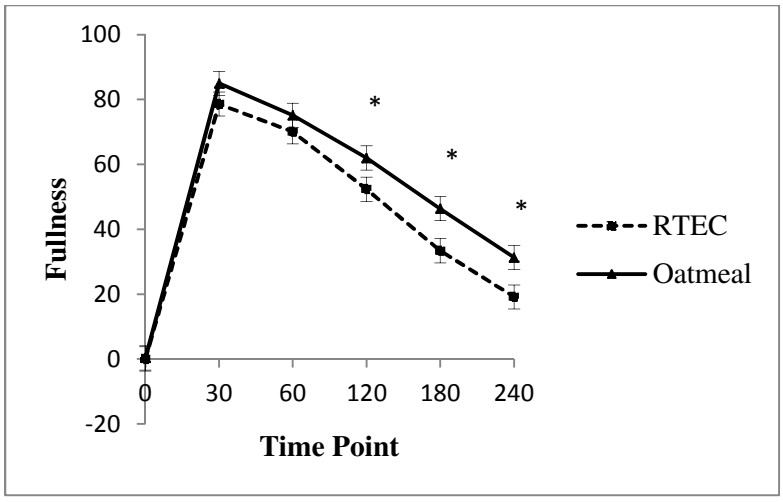

Figure 3.2 Visual analog scale ratings for fullness (n = 46) before and after consumption of the oatmeal and a ready-to-eat breakfast cereal (RTEC): Fullness increased to a greater extent with oatmeal as compared with the RTEC. *Least squares means: 120 minutes (p=0.0408), 180 minutes (p=0.0061) and 240 minutes (p= 0.0102).

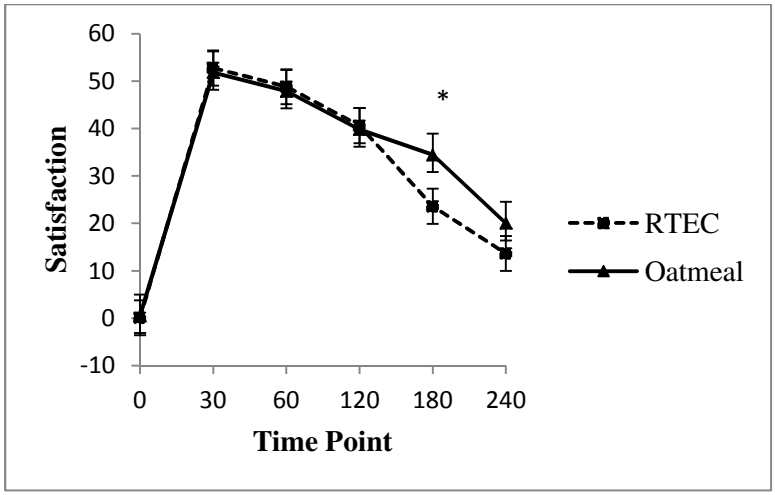

Figure 3.3 Visual analog scale ratings for satisfaction (n = 46) before and after consumption of the oatmeal and a ready-to-eat breakfast cereal (RTEC): Satisfaction was not significantly different between the breakfast meals.*Least squares means: p=0.0392 at 180 minutes.

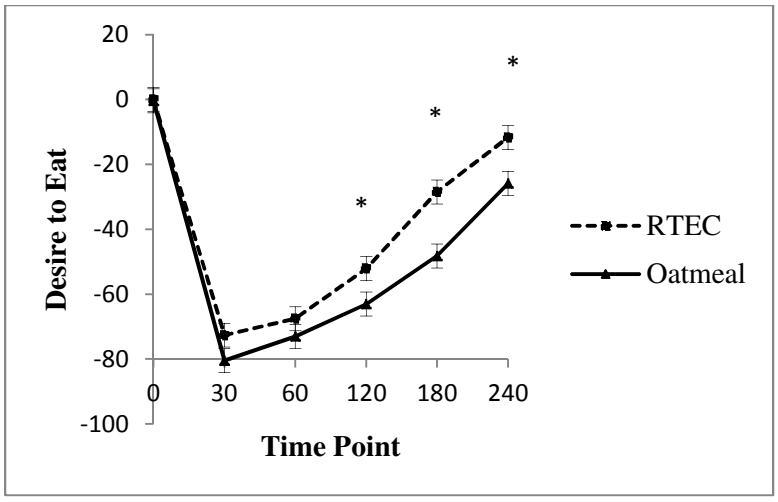

Figure 3.4 Visual analog scale ratings for desire to eat (n = 46) before and after consumption of the oatmeal and a ready-to-eat breakfast cereal (RTEC): Desire to eat was reduced to a greater extent with oatmeal as compared with the RTEC. *Least squares means: 120 minutes (p=0.0168, 180 minutes (p<0.0001) and 240 minutes (p= 0.0022).

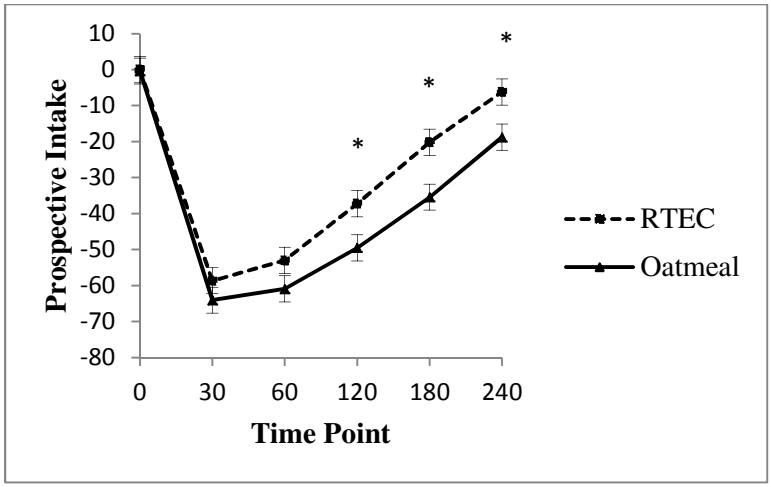

Figure 3.5 Visual analog scale ratings for prospective intake (n = 46) before and after consumption of the oatmeal and a ready-to-eat breakfast cereal (RTEC): Prospective food intake was reduced to a greater extent with oatmeal as compared with the RTEC. *Least squares means: (120 minutes (p=0.0058, 180 minutes (p=0.0006) and 240 minutes (p= 0.0047).

Discussion

The oatmeal breakfast resulted in a greater increase in perceptions of fullness, and a lower decrease in hunger, desire to eat, and prospective intake as compared with the RTEC. Satisfaction with the meal did not significantly differ between the two breakfast meals.

In agreement with the hypothesis, oatmeal with a higher content of fiber increased satiety to a greater extent in the four hour period following consumption when compared with the RTEC. ß-glucan is the main component of oat soluble fiber and is primarily responsible for its physiologic effects.[129] Humans lack the enzymes to hydrolyze ß-glucan which remains intact increasing the viscosity throughout the small intestine.[129] The satiating effect of ß-glucan has been demonstrated in several studies however, the ß-glucan content ranged from 2.2 g to 9 g,[85, 88, 89, 120-122] making it difficult to determine the concentration at which an increase in satiety is likely to occur.

Using breakfast cereals containing oat ß-glucan and served with milk, Beck *et al,*[88] concluded that the optimal dose of β-glucan affecting satiety and other markers of appetite regulation were between 4g and 6g and that the hormonal effects were mediated through increased viscosity. However, the same investigators concluded in an earlier study that subjective satiety increased even at a relatively low dose of 2.2 g of oat β-glucan in a breakfast cereal that was served with milk.[85] In other studies 1.2 g barley β-glucan in a meal replacement bar,[19] had no effect on appetite ratings or food intake, but, a bread containing 3 g of a concentrated extract of barley β-glucan was demonstrated to control appetite in the short term (3 hours).[89] However, breakfast cereals containing 4 g of oat ß-glucan did not result in a significantly prolonged period of satiety as compared with meals consisting of cornflakes[123, 124] In the present study, it was

demonstrated that satiety increased to a greater extent with consumption of oatmeal containing 2.3 g of β-glucan as compared with an oat-based RTEC.

The physicochemical properties of β-glucan affect viscosity-dependent mechanisms. Viscosity is controlled by concentration in solution and molecular weight.[131] β-glucan in foods not solubilized at 37ºC under physiologic conditions would not produce viscosity in the aqueous environment of the gut. Oat β-glucan is more soluble in hot water than in water at room temperature, so processing steps that involve moisture and heat will in all likelihood increase the solubility of β-glucan.[132] The cooking of oats has been shown to increase the percentage of β-glucan solubilized by three-fold.[49] β-glucan is integral with cellulose and other noncellulosic polysaccharides in the cell wall and cooking releases it from this matrix.[133] Thus, differences in the properties of β-glucan in each food may profoundly affect the physiologic response.

The divergent results from various studies suggest that, although there may be a dose response relationship, the magnitude of the effect may also be controlled by the molecular weight and solubility of β-glucan under physiologic conditions. The increase in viscosity is considered to be the primary factor influencing the physiologic effects of β-glucan, but very few measurements of intestinal viscosity have been conducted, since such measurements are not readily obtained in people[49, 157] It is therefore difficult to demonstrate a correlation of effect with viscosity. Food structure and matrix under physiological conditions may have a role to play in appetite regulation.

Breakfast cereals high in insoluble fiber have been demonstrated to increase satiety, however, the amounts tested ranged from 18-33 g/meal.[87, 105, 106] In the present study the insoluble fiber content of the two breakfasts may have been too small (RTEC: 2.84 g and oatmeal: 3.34 g) to have an appreciable effect on satiety.

The protein content of the oatmeal breakfast was higher than the RTEC, and protein-induced satiety has been demonstrated in several studies.[27, 64, 65, 72] In a study comparing a high protein meal (25% of energy) with a low protein meal (10% of energy) it was found that satiety significantly increased after the high protein meal.[64] A low fat chocolate milk drink (23% of energy from protein) increased satiety as compared with a cola drink (0% energy from protein).[72] In respiratory chamber experiments, energy expenditure and satiety have been shown to be greater with high protein diets (30% of energy) as compared with low protein diets (10% of energy).[27, 65] These studies,[27, 64, 65, 72] compared meals or diets that differed by 15% to 23% in their energy content from protein.

In contrast, a high protein breakfast (58.1% of energy from protein) did not significantly increase satiety three hours after consumption as compared with a high carbohydrate breakfast (19.3% of energy from protein) matched for weight, volume, fat and energy content, viscosity, and palatability (VAS ratings for taste and texture were not significantly different).[69] In the present study, protein comprised 19.5% (RTEC) and 24.5% (oatmeal) of the energy contents of the meals, which is less than the proportion that has been shown to facilitate satiety. Thus, it is unlikely that the increase in satiety was mediated by protein. However, the higher protein content of the oatmeal breakfast cannot be completely ruled out as a mediating factor in the increase in satiety.

There was no significant difference in the Gi of the two breakfast products tested, despite the lower sugar and higher fiber content of oatmeal (Predicted Gi based on Elquist method: oatmeal 84.5, RTEC 82.3). A lower glycemic response to food has been associated with a higher perception of satiety.[18] The clinical relevance of the concept of Gi, however, remains unclear. The Gi is influenced by the nature of the starch, the physical form, the amount of fiber, fat and

protein, and the cooking times and methods.[92] The random day-to-day variation in the glycemic response that occurs even in repeated experiments of the same food under standardized conditions is seemingly inexplicable.[94] Thus, while protein may have contributed to satiety, the fiber content, especially β-glucan may have played the major role in enhancing satiety.

This study had some limitations. The effects of oatmeal on appetite may have been mediated by hormone release, resulting from delayed intestinal transit of nutrients. Since hormone levels were not measured in this study it is difficult to draw any definitive conclusions as to the effects of hormones on appetite and satiety. The breakfasts were not matched for nutrient content, thus, it is difficult to clearly distinguish between the satiating effects of the nutrient components. Additionally, molecular weight and solubility of ß-glucan in the products used in the study were unavailable, precluding a comparison on that basis. Further, food intake at a subsequent meal was not assessed to determine a correlation between satiety and food intake.

Conclusions

In a comparison of two oat based cereals, oatmeal resulted in greater satiety than the RTEC over the four hour period following consumption. The increase in satiety sensations may be attributed to the satiating effects of the fiber and protein contents of oatmeal. The product delivering the nutrients may have a role to play in the bioavailability, functionality, and thereby the satiating effect of the various nutrient components.

CHAPTER 4

EFFICACY OF OLIBRA: A 12 WEEK RANDOMIZED CONTROLLED TRIAL AND A REVIEW OF EARLIER STUDIES*

Introduction

The overweight and obese population both in the United States and globally, has increased over several decades. For example in the US, 68% of adults are overweight or obese.[158] The consequent rise in the associated diseases such as type 2 diabetes, cardiovascular diseases, and some cancers[51, 58] is a major public health concern. It is estimated that health care costs attributable to overweight and obesity will double every decade, reaching 860.7 to 956.9 billion US dollars and accounting for 16-18% of total US health care costs by 2030.[52]

Body weight is influenced by the interaction of biological, environmental, and physiologic factors. A number of hormonal, neuronal, and metabolic responses that orchestrate this process are located in the gut.[57, 136, 137] Thus, the gastrointestinal (GI) tract plays a pivotal role in regulating food intake. The ileal brake is a negative feedback mechanism that is activated by the entry of nutrients into the ileum.[135] The inhibitory effects of the activation of the ileal brake are a result of the interaction of neural and humoral signals[31] exerting their influence on the proximal parts of the intestine. Exposure of the ileum to fats and fatty acids delays gastric emptying,[36, 138]prolongs GI transit time [37] and influences satiety.[38, 39, 139] The physicochemical properties of fat affect its ability to regulate GI motor function, gut hormone release, and satiety. These effects are more pronounced with long chain fatty acids (≥12 carbons) than shorter chain fatty acids (≤10 carbons).[40, 41] There is also growing evidence that free fatty acids are stronger

*Originally appeared as Rebello CJ, Martin CK, Johnson WD, O'Neil CE, Greenway FL. Efficacy of Olibra: A 12-Week Randomized Controlled Trial and a Review of Earlier Studies. J Diabetes Sci Technol 2012;6:95-708. Reprinted with permission from the Journal of Diabetes Science and Technology

mediators of the GI effects of fat than triacylglycerides.[141] The role played by the degree of saturation in modulating the effects of fat on the GI tract has not been resolved fully.[43, 44]

Delaying lipid digestion is an important factor in stimulating the ileal brake. By manipulating oil emulsions using galactolipids, lipolysis can be delayed through the inhibition of lipase activity.[145] Olibra™ (Lipid Technologies Provider AB (Karlshamn, Sweden) is a fat emulsion comprised of fractionated palm, and oat oil in the proportion of 95:5. The palm oil is emulsified by hydrophilic galactolipids derived from oat oil.[146] Olibra™ has been demonstrated in some studies to increase satiety and reduce food intake.[23-25] Other studies, however, have not replicated these effects on food intake[45, 46] although a positive effect on maintenance of weight loss[149] and fat loss[149, 150] have been demonstrated. Randomized, clinical weight loss trials have not been reported. Studies that employed methods of delivering the emulsion directly into the GI tract demonstrated a delay in GI transit.[146, 159] However, when ingested orally, this fat emulsion may not elicit the GI responses manifested by an intragastric or intraduodenal administration. In the dynamic environment of the GI tract, resistance of the emulsion to digestion is crucial for stimulating an increase in satiety and a reduction in food intake.

The purpose of this study was to determine whether Olibra™ in conjunction with a healthy diet and exercise plan, would result in weight loss that was associated with a reduction in food intake. The incidence of adverse effects of Olibra™ administration was also evaluated.

Methods

Subjects

Subjects of both sexes 18-60 years of age, with a body mass index (BMI) between 25 and 40kg/m^2, inclusive, were recruited from the communities surrounding the Pennington Biomedical Research Center (PBRC) in Baton Rouge, Louisiana. Subjects were eligible for the

trial if they were determined to be healthy at a physical exam and had clinically normal findings in laboratory measurements. Questionnaires related to dietary restraint,[61] sandwich rating to ensure that food used in the study was not disliked, and food selection,[160] were completed. All subjects completed a 6-n-propylthiouracil[161] test to determine if they were non-tasters, medium-tasters, or super-tasters. Exclusion criteria included: (1) a dietary restraint score of > 13, (2) weight loss ≥ 4.5kg in the preceding three months, (3) a medical condition or taking regular medication (4) history of alcohol or other drug abuse in the preceding one year, and (5) pregnancy, lactation, or post-partum less than six months.

The study was approved by the Institutional Review Board of the PBRC and participants provided written informed consent. The trial was registered on ClinicalTrials.gov under NCT01416051.

Study Design

The study followed a two-phased, randomized, placebo-controlled, double-blind, parallel design.

Phase I

At Visit 1 (Day -7±2) qualified subjects arrived at the PBRC in the morning after a 12-hour overnight fast. Vital signs and weight were measured. Subjects were asked to consume an entire 382 kilocalorie (kcal) breakfast consisting of a serving of yogurt containing placebo (milk fat), followed by a cereal bar. Subjects returned four hours later for a lunch meal consisting of a serving of yogurt containing placebo, followed by more sandwiches, chips, and cookies than could reasonably be consumed. They returned five hours later for a buffet dinner meal. The food intake at lunch and dinner was determined by subtracting the weight of the uneaten food from its original weight. The kcal and macronutrient intakes were calculated using product information,

and the USDA nutrient database.[162] Subjective ratings (appetite and satiety) were recorded through visual analog scales (VAS). Concomitant medications and any adverse events were assessed throughout the entire study to determine the feasibility of subjects' continuance with the study. One week later, at Visit 2 (Day 0±2), the subjects arrived at the PBRC in the morning after a 12-hour overnight fast and were randomized to the Olibra or placebo group. Vital signs, weight, waist and hip circumferences, and body fat measurements were taken. The food intake test conducted at Visit 1 was repeated, except that subjects were given the yogurt with Olibra™ or the placebo added to it, at breakfast and lunch.

Phase II

After the food intake test at visit 2, subjects were instructed by a registered dietitian to follow a 1500-kcal diet, and encouraged to increase their current activity level. Olibra™ or the placebo was dispensed in a double blind manner in ready to use portion packs. The subjects were instructed to consume the product twice daily, preferably with breakfast and lunch, for 12 weeks. Vital signs and weight measurements followed at Visits 3-6 (Days 14, 28, 56, 84, [±2]). Subjects were considered compliant if they consumed the recommended dose at least 70% of the time. At Visit 4, subjects repeated the food intake testing protocol followed at Visit 2. At Visit 6 (Day 84±2), subjects arrived at the PBRC after a 12-hour overnight fast. Body fat, and waist and hip circumferences were measured. Blood tests, and the physical exam performed at screening were repeated at visit 6. A schedule of assessments is presented in Table 4.1.

Table 4.1 Schedule of study procedures, from screening visit to the end of study

	PHASE I			PHASE II			
Procedure	Screening Visit	Visit 1 Baseline Day -7±2	Visit 2 Day 0±2	Visit 3 Day 14±2	Visit 4 Day 28±2	Visit 5 Day 56±2	Visit 6 Day 84±2
Medical History	X						
Physical Exam	X						X
Height	X						
Weight	X	X	X	X	X	X	X
Vital Signs (BP, Pulse rate)	X	X	X	X	X	X	X
Body Composition	X		X				X
Waist and Hip Circumference	X		X				X
Chemistry panel	X						X
Lipid profile	X						X
Complete blood count, with differential	X						X
Concomitant Medications	X	X	X	X	X	X	X
β-HCG Pregnancy Test-Urine	X						
PROP taste-sensitivity test	X						
Visual Analogue Scales		X	X		X		
Eating Inventory	X				X		
Food Selection Questionnaire	X						
Sandwich Rating Questionnaire	X						
Cold/Allergy Questionnaire		X	X		X		
Dietitian consultation			X				
Adverse Events		X	X	X	X	X	X
Food Intake Tests (w/placebo)		X					
Food Intake Tests (w/test product or placebo)			X		X		

Test Products

One serving of the test product was 7.5 g (19kcal) providing 2.1 g of the fat emulsion, Olibra™. One serving of the placebo was also approximately 7.5 g (18.5 kcals), providing 1.95 g of 100% milk fat, and small amounts of carbohydrate (0.2 g) and protein (0.3 g). At the food intake tests, Olibra or the placebo was added to a 200 g carton of fruit flavored yogurt-194 kcals, 1.8 g fat, 38.6 g carbohydrate and 5.8 g protein.

Measurements

Anthropometry

Body weight was measured[163] at all visits. Fasting measurements were taken, at screening, and at visits 1, 2, 4 and 6. Height was measured[163] at screening to determine BMI (weight [kg]/height squared [m^2]). Waist and hip circumferences were measured[163] and the waist/hip ratio was calculated.[164] Body composition was measured using bioelectrical impedance (RJL Systems, BIA101A, Clinton Township, Michigan).

Questionnaires

Each food intake test was preceded by a questionnaire about colds or allergies that might affect taste. Eating Inventory (EI)[31] was administered at screening, and prior to the food intake test on day 28. The food intake tests were accompanied by visual analog scales administered before and after, breakfast, lunch, and dinner. Participants rated their degree of each subjective state by placing a hash mark on a 100 mm line. The 100 mm line was anchored using the descriptors "Not at all" to "Extremely". Hunger, fullness, desire to eat, food craving, desire for sweet, desire for salty, and desire for fatty foods were assessed. Visual analog scales were also used to assess hedonic (sensory) responses to the yogurt served at breakfast and lunch, on all food intake test days. The Food Selection Questionnaire[32] was used to rate the participants' food preferences, from a wide variety of foods that were offered at the buffet dinner meals.

Adverse Events

An adverse event was defined as any adverse change from baseline (pre-treatment) condition, which occurred during the course of the study after treatment had started, whether considered related to treatment or not. All adverse events, including intercurrent illnesses and an

increase in severity or frequency of a concomitant sign/symptom of a concomitant illness, were documented.

Statistical Analysis

The food intake testing reported in the literature suggests that Olibra™ will reduce food intake by 20-30%.[23-25] From past experience, one can detect a 12% decrease in food intake in the eating laboratory with 30 subjects as their own controls.[165] The difference in food intake decreases with time on a diet.[165] Therefore, 82 subjects were randomized in this study. This allowed for 30 subjects per group to complete week 4 of the study assuming a 30% dropout. Assuming a standard deviation of 2.3 kg and an alpha of 0.05 the study was powered at 89% to detect a difference of 2 kg in weight loss between the groups at 12 weeks, if 28 subjects finish per group.

Observations made during Visit 1 of the study were considered as baseline measurements. A repeated measures analysis of covariance (ANCOVA), with baseline covariates, was used to test if change in energy intake from baseline to week four differed significantly between the test and control groups. Body weight, percent body fat, waist circumference, waist/hip ratio, and EI scores were analyzed similarly. The changes from baseline, for the scores for appetite and satiety assessed through VAS, were analyzed by doubly repeated measures ANCOVA. Visual analog scales used to assess hedonic responses to the test and control yogurt were analyzed directly, rather than as change scores in a repeated measures analysis of variance. Chi-square test was used to analyze the distribution of tasters. Food intake and body weight were analyzed by stratifying taster status. Post hoc tests when conducted followed the Tukey-Kramer adjustment. All analyses were carried out using SAS (v. 9.2; SAS

Institute, Inc., Cary, NC). Subject characteristics are presented as mean ± SD and efficacy endpoints are presented as mean ± standard error of the mean (SEM).

Results

Data related to 71 subjects were analyzed, and 57 subjects completed the study (Figure 4.1). Descriptive characteristics of the subjects at baseline are summarized in Table 4.2.

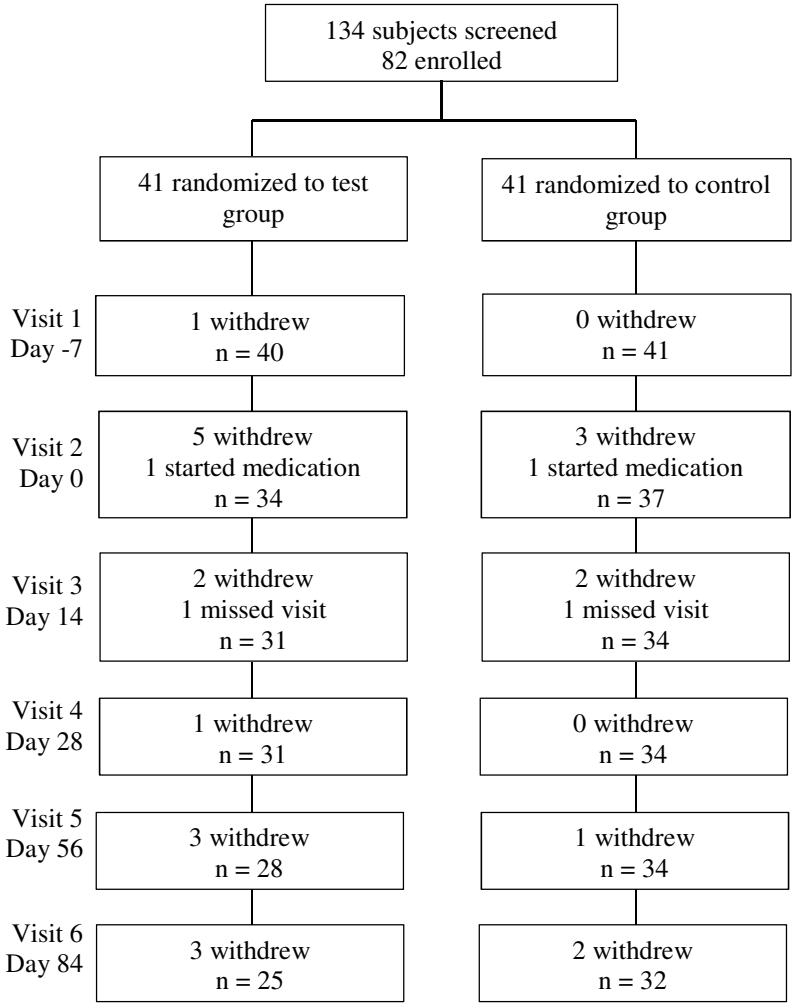

Figure 4.1 Subject recruitment, randomization, and continuance with the study

Table 4.2 Subject characteristics at baseline, including demographics

	Total (n = 71)	Test (n = 34)	Control (n = 37)	
	Mean ± SD	Mean ± SD	Mean ± SD	P value
Age (years)	40.5 ± 12.1	38.4 ± 12.8	42.4 ± 11.2	0.2
Height (cm)	166.4 ± 8.41	166.0 ± 8.2	166.7 ± 8.7	0.7
Weight (kg)	89.3 ± 13.0	88.5 ± 14.6	90.0 ± 11.5	0.6
BMI (kg/m^2)	32.3 ± 3.92	32.1 ± 4.5	32.4 ± 3.4	0.7
Waist (cm)	97.6 ± 9.3	98.1 ± 10.5	97.2 ± 8.3	0.7
Hip (cm)	112.6 ± 7.9	111.9 ± 8.7	113.3 ± 7.1	0.5
Body Fat %	40.7 ± 6.0	40.3 ± 6.9	41.1 ± 5.0	0.6
Waist/Hip Ratio	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.7
	n (%)	n (%)	n (%)	
Sex				
Female	60 (84.5)	28 (82.3)	32 (86.5)	
Male	11 (15.5)	6 (17.7)	5 (13.5)	
Race				
White	47 (66.2)	22 (64.7)	25 (67.6)	
Black	24 (33.8)	12 (35.3)	12 (32.4)	

Anthropometry

At the end of 12 weeks body weight was significantly reduced in both groups (test group: 2.17±0.46 kg, P<0.0001) (control group: 1.68±0.42 kg, (P<0.0001) with no significant difference between groups (Table 4.3). The waist circumference decreased by 2.93±0.85 cm in the test group (P=0.001), and by 1.78±0.74 cm in the control group (P=0.02), with no significant difference between the two treatment regimens. The waist/hip ratio decrease by 0.014±0.007 in the test group and by 0.012±0.006 in the control group was not significant, with no statistical difference between the groups. Neither group experienced a significant change in per cent body fat or lean tissue as assessed by bioelectrical impedance.

Table 4.3 Body weight and body composition measurements, from Day -7 to Day 84, including change from Day 0 to Day 84 (Between group P value = non-significant)

	Day -7	Day 0	Day 14	Day 28	Day 56	Day 84	Δ Day 0 - Day 84	P-value
Test	n = 34	n = 34	n = 31	n = 31	n = 28	n = 25	n = 25	
Control	n = 37	n = 37	n = 34	n = 35	n = 34	n = 32	n = 32	
Weight (kg)								
Test	88.4 ± 2.2	88.5 ± 2.2	87.1 ± 2.2	87.1 ± 2.2	86.6 ± 2.2	86.4 ± 2.2	-2.17 ± 0.5	< 0.0001
Control	90.0 ± 2.1	90.0 ± 2.1	90.0 ± 2.1	89.2 ± 2.1	88.9 ± 2.1	88.3 ± 2.1	-1.68 ± 0.4	< 0.0001
% Change in Weight								
Test	.	0.2 ± 0.4	-1.4 ± 0.42	-1.4 ± 0.4	-1.9 ± 0.4	-2.1 ± 0.5	-2.2 ± 0.5	< 0.0001
Control	.	0.1 ± 0.4	-1.0 ± 0.4	-0.8 ± 0.4	-1.2 ± 0.4	-1.8 ± 0.4	-1.9 ± 0.4	< 0.0001
Waist (cm)								
Test	-	98 ± 1.6	-	-	-	95.0 ± 1.7	-2.9 ± 0.9	0.001
Control	-	97.2 ± 1.5	-	-	-	95.5 ± 1.6	-1.8 ± 0.7	0.02
Waist/hip Ratio			-	-	-			
Test	-	0.87 ± 0.01	-	-	-	0.86 ± 0.01	-0.01 ± 0	0.06
Control	-	0.86 ± 0.01	-	-	-	0.85 ± 0.01	-0.01 ± 0	0.08
% Body Fat			-	-	-			
Test	-	39.7 ± 1.0	-	-	-	38.8 ± 1.1	-0.9 ± 0.6	0.13
Control	-	40.8 ± 1.0	-	-	-	40.2 ± 1.0	-0.6 ± 0.6	0.31

Values are mean ± SEM
-Waist, waist/hip ratio, and % body fat were measured on days 0 and 84

Food and Energy Intake

There were no significant differences in the mean energy, macronutrient or amount of food consumed in the test group when compared with the control group (Table 4.4). Based on within group analyses, on Day 0, there was no significant change in the energy, macronutrient, or amount of food consumed in the test group, as compared with their intake, on Day -7. The results were similar for the lunch, dinner, and the total (lunch + dinner) meal intake.

Subjective Ratings

No significant treatment effects were found for any of the appetite and satiety measures over the various time periods. There was no significant difference in VAS ratings of pleasantness, palatability, desirability, and capacity to satiate between the test and control yogurt served at the food intake tests.

Adverse Events

Fifty-eight adverse events were reported (test group: 26, control group: 32). Forty adverse events were resolved (test group: 20, control group: 20). There were 18 adverse events ongoing at the end of the study. Six were reported in the test group and 12 in the control group (Table 4.5). There were no serious adverse events (life threatening, requiring hospitalization, or significantly disabling).

6-n-propylthiouracil Test

There were 24.2% supertasters, 57.6% medium tasters, and 18.2% non-tasters in the test group as compared with 21.6% supertasters, 62.2% medium tasters, and 16.2% non-tasters in the control group. Taster status did not indicate a differential response to food intake, or an influence on body weight.

Table 4.4 Energy, macronutrient, and food intake determined at lunch and dinner, including the combined (lunch + dinner) intake, pre- and post- intervention (Between group P value = non-significant)

	Day -7		Day 0		Day 28[a]	
	Test	Control	Test	Control	Test	Control
Lunch	n = 34	n = 37	n = 34	n = 37	n = 30	n = 35
Energy Intake (kcal)	654.2 ± 47.8	588.9 ± 45.8	639.5 ± 47.8	606.7 ± 45.8	639.2 ± 49.2	601.1 ± 46.4
Food Intake (g)	700.4 ± 36.3	663.5 ± 34.8	661.4 ± 36.3	613.2 ± 34.8	637.2 ± 37.9	549.2 ± 35.5
Fat (g)	27.9 ± 2.7	23.4 ± 2.2	26.2 ± 2.7	23.7 ± 2.2	27.5 ± 2.3	25.7 ± 2.2
Cho (g)	70.8 ± 5.6	65.7 ± 5.4	71.5 ± 5.6	69.1 ± 5.4	69.5 ± 5.8	66. 8 ± 5.4
Protein (g)	28.4 ± 2.0	27.3 ± 1.9	27.9 ± 2.0	27.6 ± 1.9	27.0 ± 2.0	24.5 ± 1.9
Dinner	n = 34	n = 35[c]	n = 34	n = 35[c]	n = 29[b]	n = 32[c]
Energy Intake (kcal)	948.9 ± 58.3	915.3 ± 57.4	838.0 ± 58.3	788.9 ± 57.4	720.2 ± 60.9	662.8 ± 58.9
Food Intake (g)	419.7 ± 30.0	418.9 ± 29.6	383.3 ± 30.0	380.4 ± 29.6	342.0 ± 31.2	326.8 ± 30.2
Fat (g)	44.7 ± 3.3	46.6 ± 3.3	39.0 ± 3.3	39.5 ± 3.3	32.5 ± 3.5	32.2 ± 3.4
Cho (g)	102.4 ± 6.4	88.0 ± 6.3	91.3 ± 6.4	77.1 ± 6.3	80.5 ± 6.7	69.0 ± 6.5
Protein (g)	36.9 ± 2.7	36.5 ± 2.7	32.4 ± 2.7	31.9 ± 2.7	27.2 ± 2.8	25.0 ± 2.7
Lunch + Dinner	n = 34	n = 35	n = 34	n = 35	n = 29	n = 32
Energy Intake (kcal)	1603 ± 91.2	1484.1 ± 89.8	1477.5 ± 91.2	1376.1 ± 89.8	1350.7 ± 94.8	1239.7 ± 91.1
Food Intake (g)	1120.1 ± 56.0	1074.8 ± 55.2	1044.7 ± 56.0	992.8 ± 55.2	988.6 ± 58.2	867.1 ± 56.4
Fat (g)	72.6 ± 4.8	69.4 ± 4.8	65.2 ± 4.8	62.5 ± 4.8	59.9 ± 5.0	57.0 ± 4.9
Cho (g)	173.2 ± 9.9	150.7 ± 9.8	162.9 ± 9.9	143.3 ± 9.8	148.7 ± 10.6	132.6 ± 10.0
Protein (g)	65.3 ± 3.9	63.3 ± 3.9	60.3 ± 3.9	59.1 ± 3.9	53.8 ± 4.1	48.7 ± 4.0

Values are mean ± SEM

[a] 1 subject (control group) missed visit

[b] 1 subject missed dinner,

[c] Outliers in the data (all dinner records of 2 subjects and 1 dinner record of 1 subject, that could not be verified) removed from analysis

Table 4.5 Adverse events reported during the study period, including those resolved and those ongoing at the end of the study

Effect	Resolved		Ongoing at End of Study	
	Test Group	Control Group	Test Group	Control Group
Neurological				
Headache	6	4		2
Insomnia	1			
Musculoskeletal				
Muscle Pain	1			
Back Pain	2	2		1
Gastrointestinal				
Diarrhea	1	1		1
Abdominal Pain	1	1		
Nausea / Vomiting	1	1		
Heartburn/Indigestion		1		2
Oral Complaints	2		1	
Dermatologic				
Foot Infection	1			
Rash			1	
Pruritus				1
Respiratory				
Cough /Cold	1	2		1
Sinus Infection		1	1	1
Allergy		2		1
Other		1		
Cardiovascular				
Hypertension				1
Chest Pain				1
Dizziness		1		
Genitourinary				
Menstrual Cramps		1		
Urinary Tract Infection		1		
Non-specific				
Viral Infection	1			
Fatigue		1		
Anxiety			1	
Special Senses/Other	2		2	
Total:	20	20	6	12

Four adverse events in the control group (2 indigestion, 1 diarrhea, and 1 dizziness were reported as possibly related to the treatment. No treatment related adverse events were reported in the test group

Eating Inventory

There were no significant changes in the scores for dietary restraint and disinhibition, however, hunger scores were significantly reduced in the test group as compared with the control group (P=0.0082) (Figure 4.2).

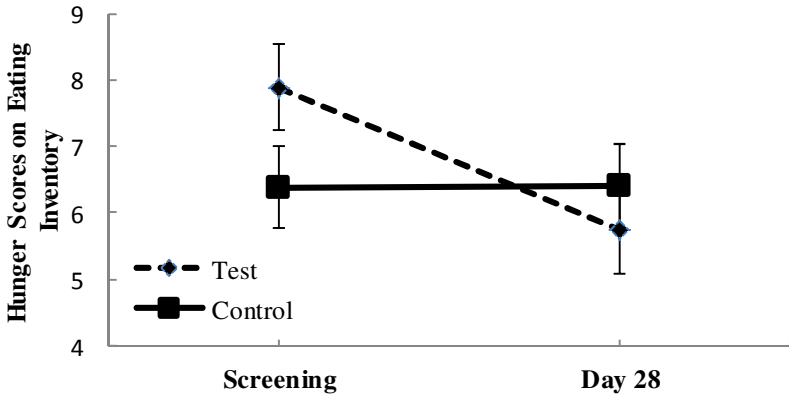

Figure 4.2 Hunger scores on Eating Inventory (EI) collected at screening and prior to food intake test, on Day 28(P = 0.0082). Values are mean ± standard error of the mean.

Discussion

At the end of 12 weeks, a reduction in body weight and waist circumference did occur but the differential reduction was not statistically significant between the groups. EI scores for hunger, which reflect an individual's perception of hunger feelings, were significantly reduced in the test group as compared with the control group, however, no significant treatment effects were observed on energy intake, food intake, and appetite and satiety ratings after four weeks of Olibra consumption.

Earlier studies[23-25] all crossover designs, reported a reduction in energy, macronutrient and total weight of food intake, following consumption of the Olibra™ emulsion. The suppressive effects on appetite ratings (hunger, desire to eat, and preoccupation with thoughts of food or perceived fullness) in the short term were only demonstrated in one study[24] and one part of another.[23] In the present study, there was no significant reduction in energy, macronutrient or total weight of food intake four hours or nine hours after consumption of Olibra™, based on within and between group analyses. Crossover designs minimize the errors of individual variability, hence the present study was designed to evaluate the acute effects of Olibra™ using a

within subjects analysis, in addition to its effects on two different groups. Using self-reported food intake data, Burns *et al*[25] concluded that the treatment effects of Olibra™ were maintained up to 36 hours. However, self-reported data are notorious for their susceptibility to misreporting and altered feeding behavior.

Two subsequent studies failed to confirm the reduction in energy intake,[45, 46] though a suppressive effect on appetite ratings (hunger, fullness, desire to eat, and prospective intake or preoccupation with thoughts of food) was demonstrated.[46] No effect on body weight, body composition or waist circumference was observed after three weeks consumption of Olibra™.[45] A meta-analysis[147] of the short term effects of Olibra™ on food intake attributed the differences in findings partly to the manufacture, processing, or preparation of Olibra™. It has been speculated that the functional integrity of the Olibra™ emulsion structure is affected when it is subjected to processing such as homogenization and pasteurization, along with the yogurt. The emulsion used in the present study was added after the yogurt, served at the food intake tests, was manufactured. It was therefore not subjected to further processing. The demonstrated efficacy of unprocessed as compared with processed Olibra™, in reducing energy and food intake[148] at eight hours was not observed. However, these investigators also found no effects on hunger, fullness and satiety.

All of the studies that investigated the effects of oral ingestion of Olibra™ used between four and five grams of the emulsion, except for one study[25] that investigated the dose response using 2, 4, and 6 g, and found no difference between the doses. Eating behavior comprises a large learned and anticipatory component.[127] Behavioral and environmental factors can overcome physiological drives and influence feeding behavior.[153] Therefore, a physiological impetus would have to be sufficiently large to consistently correlate with altered energy and

nutrient intakes. Additionally, the relatively small sample sizes used in all the studies resulted in divergent results since the actual difference was much smaller than the expected difference.

The beneficial effects of Olibra™ on body composition and weight maintenance after weight loss have been demonstrated,[149] however, Olsson *et al*[150] observed no effect on weight, but body fat mass decreased, after an initial weight loss period. In these studies, the calorie restriction imposed during the weight loss period may have had a role to play in the demonstrated effects. In humans, it has been shown that exposure to a high fat or high energy diet decreases sensitivity to the GI mechanisms involved in appetite regulation.[22, 141, 151] High fat diets have been shown to modify appetite perceptions, increasing hunger and decreasing fullness.[152] If the subjects in the present study usually consumed a high fat or high calorie diet the effect of Olibra™ could have been attenuated. Nevertheless, the ultimate goal of altering appetite and satiety signals is to correct energy imbalance and reduce weight, which as demonstrated in this study, was far from accomplished with the consumption of Olibra™.

A 45 minute delay in intestinal transit time following consumption of Fabuless™ (also known as Olibra™) has been reported[30] but, the computation of orocecal transit time has been questioned.[41] Using an intragastric administration technique to infuse Fabuless, Knutson *et al*[22] concluded that the palmitic acid crystals observed in the jejunal samples of subjects caused a reduction in intestinal digestion and absorption rates. Both studies used a single dose of 8.5 g of Olibra™ to produce these effects which is about twice the daily dose used in the present study. While it is important to demonstrate that Olibra™ produces conditions conducive to stimulation of the ileal brake mechanism, such manipulation must also produce the directional changes in feeding behavior consistent with the activation of this mechanism.

The present study is limited by the non-availability of information related to subjects' usual intake, to determine if previous patterns of nutrient exposure were related to the results of the study. A review of published human studies that investigated the effects of Olibra™ is presented in Table 4.6.

Conclusion

The Olibra™ emulsion had no significant effect on food intake, appetite and satiety ratings, body weight, or body composition. The results of studies indicating the beneficial effects of Olibra have not been confirmed in separate studies. A review of the available evidence indicates that further investigation of Olibra™ as a means of regulating appetite, satiety, food intake, and thereby body weight is not warranted.

Table 4.6 Review of Published Studies that Investigated the Effects of Olibra

Source	Study Overview	Summary of Results	Conclusions
Burns et al, 2000[23]	*Aim:* To investigate the short term effects of Olibra on energy and macronutrient intake in non-obese subjects *Subjects*: 59 total participants Study 1:15 females, 14 males Study 2: 16 females,14 males Age: 18-65 years BMI: ≤ 30 *Study Design*: Two RDBPC[a] WS[b] crossover studies three months apart. *Intervention*: An emulsion in yogurt to provide 5 g of fat as Olibra (1 treatment) *Length of Each Study:* 2 visits with a one week interval between crossover *Food intake test:* 4 h after consumption of test or placebo product. Free living weighed intake recorded in food diaries for rest of day *Subjective Ratings:* VAS[c] before and after eating yogurt and at hourly intervals until 2100h on test days	*Food Intake*: Lower mean energy, macronutrient, and total weight of food, intake after consuming test product Energy Intake: P < 0.001 (Study 1) P < 0.001 (Study 2) P < 0.001 (Combined studies) *Subjective Ratings*: Reduced hunger, desire to eat and preoccupation with food in Study 1 but not in Study 2 or combined studies Study 1: P = 0.002 (Hunger) P = 0.006 (Desire to eat) P < 0.001 (Preoccupation with food)	*Conclusions*: The physicochemical characteristics of small amounts of dietary fat affect short term satiety
Burns et al, 2001[24]	*Aim:* To investigate the effects of Olibra on energy and macronutrient intakes up to 8 h in non-overweight, overweight, and obese subjects. *Subjects*: 60 total participants Non-overweight: 20 (10 females, 10 males) Overweight: 20 (10 females, 10 males) Obese:20 (13 females, 7 males) Age: 18-65 years BMI: 20 - 30+ *Study Design*: RDBPC, WS, crossover *Intervention*: An emulsion in yogurt to provide 5g of fat as Olibra (1 treatment) *Length of Study:* 2 visits with a one week interval between crossover *Food intake test*: 4h and 8h after consumption of test or placebo product. Free living weighed intake recorded in food diaries for rest of day, and following day to 2100 h *Subjective Ratings:* VAS before and after eating yogurt and at hourly intervals until 2100h on test days	*Food Intake*: Lower mean energy and macronutrient intake in non-overweight, and overweight after consuming test product at 4h, and in all groups after consuming test product, at 8h. No overcompensation in next 24h Energy Intake, 4h/8h: P < 0.01/p < 0.001 (non-overweight) P < 0.001/p < 0.001 (overweight) P > 0.05/p < 0.01 (obese) P < 0.001 (total group at 24h) *Subjective Ratings*: Reduced hunger, desire to eat, and preoccupation with food, and greater perceived fullness P < 0.05	*Conclusions*: Effects of Olibra were maintained at least until 8h and were evident in non-overweight, overweight and obese subjects

Table 4.6 (continued)

Source	Study Overview	Summary of Results	Conclusions
Burns et al, 2002[25]	*Aim:* To investigate if the energy and macronutrient intake responses to Olibra are dose-dependent, and are maintained up to 36h *Subjects*: 50 total participants 30 females, 20 males Age: 18 - 65 years BMI: 20 – 25 kg/m^2 *Study Design*: RSBPC[d], WS, crossover *Intervention*: 5, 10, 15g emulsions in yogurt to provide 2, 4, and 6g of fat respectively as Olibra (3 treatments) *Length of Study:* 4 visits with a one week interval between visits *Food intake test*: 4h after consumption of test or placebo product. Free living weighed intake recorded in food diaries for rest of day and following day to 2100 h *Subjective Ratings:* VAS before and after eating yogurt and at hourly intervals until 2100h on test days	*Food intake*: Lower mean energy (21, 25, and 30% with 2,4, and 6 g of Olibra fat emulsion, respectively) macronutrient, and total weight of food, intake after consuming test product. Lower energy and macronutrient intakes up to 36h Energy Intake: P < 0.001 (at each dose) P < 0.001 (at each dose at 36h) *Subjective Ratings:* No effect between doses, and with control	*Conclusions:* Effects of Olibra were dose dependent but results were not consistent across gender or proportional across dose levels. Effects were maintained at 36h
Logan et al, 2006[26]	*Aim:* To investigate the medium term effects of Olibra on appetite and food intake in non-obese subjects. *Subjects:* 28 total participants 14 females, 14 males Age: 20 – 55 years BMI: < 30 kg/m^2 *Study Design:* RDBPC, WS, crossover *Intervention:* A 12.5g emulsion in yogurt drink to provide 5g of fat as Olibra (22 treatments) *Length of Study:* 2 x 3 weeks study phases separated by a 3 week wash out phase. *Food intake test*: 4 h after consumption of test or placebo product on days 1, 8, and 22. Free living weighed intake recorded in food diaries for rest of day and following day *Anthropometry:* Body weight and body composition measured on days 1, 8, and 22. *Subjective Ratings:* VAS before and after eating yogurt and at hourly intervals until 2100h on test days	*Food Intake:* No treatment effect on energy, macronutrient, and total weight of food, intake 4h after consuming test product. No treatment effect on intake during remainder of day and post-test day *Anthropometric Indices*: No treatment effect on body weight, body composition or waist circumference *Subjective Ratings*: No treatment effect *Blood Parameters:* No effect on lipid levels but reduction in fasting blood glucose during test treatment P = 0.018	*Conclusions:* There was no evidence of short or medium term effect of Olibra on food intake or appetite

Table 4.6 (continued)

Source	Study Overview	Summary of Results	Conclusions
Diepvens et al, 2007[28]	*Aim*: To investigate the effects of Olibra on weight maintenance after a very low calorie diet. *Subjects*: 50 female participants Age: 18 – 58 years BMI: 25 – 32 kg/m^2 *Study Design*: RDBPC, parallel *Intervention*: 5g emulsion in yogurt to provide 2g fat as Olibra (twice daily = 252 treatments) *Length of Study*: 26 weeks – 6 weeks weight loss period with a very low energy diet, followed by 18 week weight maintenance period with test product or placebo *Anthropometric Measurements*: Weeks 2, 8, and 26 *Satiety tests:* Test or placebo product consumption in the morning. VAS recorded hourly until 1300h, in weeks 1, 7 and 25 *Blood Tests:* Fasting, and 90 and 180 minutes after test or placebo product consumption at satiety tests *REE Measurement*: Weeks 2, 8, and 26	*As Compared with Placebo Group:* *Weight*: There was no significant increase in body weight in test group $P < 0.001$ *Body Composition:* Decrease in fat mass and increase in fat free mass in test group. $p < 0.05$ *BMI/Waist circumference:* No increase in test group. $p < 0.05$ *REE[e]:* Measured REE as a function of fat free mass was higher than predicted REE in test group $P < 0.05$ *Blood Parameters*: Increase in GLP-1 values 180 min after test product consumption. $p < 0.05$ *Subjective Ratings*: Decrease in hunger 4 h after test product consumption. $p < 0.05$	*Conclusions*: Long term consumption of Olibra had beneficial effects on weight maintenance and body composition after initial weight loss
Diepvens et al, 2008[27]	*Aim:* To investigate the short term effects of Olibra on satiety and energy intake *Subjects*: 41 female participants 21 junior normal weight 20 senior overweight Age: 18 – 50 years BMI: 20 – 30 kg/m^2 *Study Design:* RDBPC, WS crossover *Intervention:* 10g emulsion in yogurt to provide 4g fat as Olibra (1 treatment) *Length of Study*: 2 visits with a one week interval between crossover *Food intake test*: 4 h after consumption of test or placebo product *Subjective Ratings*: VAS at hourly intervals 4 times after consumption of test or placebo product	*Food intake:* No treatment effect *Subjective Ratings:* Suppressive effect over appetite ratings at 3 h, and lower return to baseline hunger in normal weight women aged between 18 and 30 years $P < 0.05$ (hunger) $P < 0.05$ (desire to eat) $P < 0.05$ (return to baseline hunger)	*Conclusions:* Olibra exerted a suppressive effect on appetite ratings in the short term and may prevent overeating

Table 4.6 (continued)

Source	Study Overview	Summary of Results	Conclusions
Haenni et al 2009[30]	*Aim:* To investigate the effects of Fabuless[f] on orocecal transit time *Subjects*: 15 male participants Age: 20 – 59 years BMI: 22 – 28 kg/m^2 *Study Design:* RDBC[g]crossover *Intervention:* An emulsion in yogurt to provide 8.5g of fat as Fabuless (1 treatment). . *Length of Study*: 2 visits with a one week interval between crossover *Food Intake:* Nutritional drink with 1000mg salazopyrine 3h after consumption of test or control product, followed by lunch 4h later. Dinner was served 4h after lunch *Blood Tests:* Before lunch and every hour until 11h after lunch	*Blood parameters*: A delay in the appearance of serum sulfapyridine (a metabolite of salazopyrine), in the test group compared with the control group, corresponded to a 45 minute delay in orocecal transit time. $P < 0.05$	*Conclusions:* Fabuless may stimulate the ileal brake mechanism by increasing GI transit time
Knutson et al 2010[22]	*Aim*: To investigate the differences in digestion and absorption of Fabuless compared with milk fat *Subjects:* 16 total participants 12 females, 4 males Age: 23 – 36 years BMI: 19 – 29 kg/m^2 *Study Design:* RDBPC, crossover *Intervention:* An emulsion in yogurt to provide 8.5g of fat as Fabuless (1 treatment) *Length of study*: 3 months – 2 visits with $\geq$ 5 day interval between crossover *Route of administration*: Intragastric perfusion of test or control yogurt. *Intestinal Samples:* Collected every 30 minutes following intragastric perfusion of test or control yogurt	*Jejunal sample:* Test group had higher lipids mainly as free fatty acids, than control group. Needle shaped palmitic acid crystals were observed only in test group $P < 0.05$ (total lipids) $P < 0.05$ (free fatty acids)	Conclusions: Higher amount of lipids in the proximal jejunum, and crystallization of lipids, after infusion of Fabuless, makes it possible for sufficient lipids to reach the ileum and activate the ileal brake.

Table 4.6 (continued)

Source	Study Overview	Summary of Results	Conclusions
Olsson et al 2011[29]	*Aim:* To investigate the effects of Fabuless on body weight and body composition after initial weight loss *Subjects:* 43 females Age; 18 – 60 years BMI: 26 - 31 kg/m^2 *Study Design:* : RDBC, parallel *Intervention*: A 12.5g emulsion in ready to use portion packs, added to meal replacement drink, to provide 5.2 g of fat as Fabuless (84 treatments) *Length of Study*: 18 weeks – 6 week weight loss period with calorie restricted diet, followed by 12 week weight maintenance period with test or control product *Anthropometric measurements:* Baseline and weeks 4, 8, and 12.	*Weight*: Significant reduction in both groups but no difference between groups *Body Fat Mass:* Decrease in body fat mass in test group as compared with control group $P < 0.05$ *Waist circumference*: Significant reduction in test group but no differences between groups *Muscle mass and hip circumference:* No treatment effects	*Conclusions:* The addition of Fabuless to a meal replacement diet plan resulted in a 0.9% decrease in body fat mass with no change in body weight between the groups.
Smit et al 2011[39]	*Aim:* To investigate the effects of Fabuless on appetite and food intake and to establish the impact of processing on its efficacy *Subjects*: 24 total participants 16 female, 8 male Age: 18 – 43 years BMI: 18 – 37 kg/m^2 *Study Design*: RDBPC, crossover *Intervention:* A 12.5g emulsion in yogurt-based beverage to provide 5 g of fat as Fabuless (2 treatments –1 processed,1 unprocessed) *Length of Study*: 4 weeks – 3 testing days over a 2 week period *Food intake test*: 4h and 8h after consumption of test or placebo product *Subjective Ratings*: VAS at baseline and every 30 minutes post-treatment until after dinner, on test days	*Food intake:* Reduced food intake 8h after treatment, only if active ingredient was added at the end of manufacture $P < 0.01$ *Subjective Ratings:* No treatment effect on appetite and satiety	*Conclusions:* Unprocessed Fabuless had a modest effect on food and energy intake. No effect when active ingredient was added to yogurt prior to homogenization and pasteurization

[a]Randomized double blind placebo-controlled, [b]Within subject, [c]Visual analog scales [d]Randomized single blind placebo-controlled, [e]Resting energy expenditure, [f]Also known as Olibra, [g]Randomized double blind controlled

CHAPTER 5

SUMMARY

The studies showed that oatmeal enhanced satiety, as compared with a RTEC in the four hour period following consumption, however the Olibra™ fat emulsion had no effect on satiety or food intake in the four or eight hour period following consumption. Additionally, regular consumption of Olibra™ had no effect on food intake after four weeks, or body weight and body composition at the end of 12 weeks.

Appetite sensations arise out of a convergence of several factors related to biology and the environment. It seems unlikely that biological imperatives and environmental cues will in all instances lead to exactly the same outcome. Manipulation of nutritional components may elicit a behavioral response when certain physiologic, psychologic, or contextual conditions are present. Thus, it is futile to imagine that anything other than a multifaceted relationship exists between food intake (the expression of appetite) and appetite control. If consumption of a particular food results in an increase in satiety in the short term, the question arises as to whether it causes a reduction in energy intake at a subsequent meal and a sufficient restraint is demonstrated over energy compensation mechanisms during the course of the day. The crux of the issue however, is whether repeated consumption of a particular food, has enduring effects on energy intake that translate into a loss of body weight.

Hunger, fullness, desire to eat, and prospective intake are indices of the drive to eat, and these sensations can be reliably measured through subjective or behavioral tests of satiety.[4] The desired directional changes in these indices are quite plainly not the same as a reduction in food intake. Nevertheless, they have immense value if consumption of healthier foods, recommended alterations in nutrient profile, or adherence to calorie restriction is the outcome, even if there is

no effect on body weight. However, a predictive decrease in energy intake and body weight may be attributed to a food only after studies have successively established its satiety enhancing effects first on food intake and then on body weight in various populations (normal, overweight, and obese individuals), through a staging of the proof of a concept.[166]

While oatmeal has in a past study,[50] and in the present study been demonstrated to increase satiety at a single exposure, its effects on repeated exposures, food intake, and body weight remain to be established. Studies evaluating the effects of Olibra™, on satiety and food intake however, have been unable to replicate the effects on satiety or food intake demonstrated in early studies. In the present Olibra™ investigation, a pre-load test meal paradigm, a parallel design with double blind conditions that permitted within subject analyses, and products that were matched for taste, appearance, energy and macronutrient content, were used. The results of the study add to the mounting evidence provided through a multi-step proof of concept that Olibra™ is ineffective as a satiety enhancing or weight loss strategy.

Differences in the macronutrient composition of foods produces differing effects on satiety, as each component has different interactions with the multitude of processes influencing satiety, described in the satiety cascade. From reviews that have been conducted,[15, 27, 64, 65, 167] it appears to be well established that high-protein foods and diets can exert a potent effect on appetite regulation. In the study investigating the satiety effects of oatmeal and a popular oat-based RTEC, the protein content of the meals differed by an amount that was far less than the proportion that has been demonstrated to facilitate an increase in satiety. Nevertheless, the overwhelming evidence related to protein-induced satiety presented in the literature[15] precludes the exclusion of protein as a mediating factor in the increase in satiety observed following consumption of the oatmeal breakfast as compared with the RTEC.

The Gi of oatmeal and the RTEC did not differ despite the higher fiber content of oatmeal as compared with the RTEC, which led to the inference that the difference in the satiety enhancing effects of the two products was not mediated by the Gi. The characteristics of a food and other dietary factors affecting food digestibility, GI motility, or insulin secretion influence the Gi.[92] Therefore, Gi values cannot be interpreted in isolation. However, inconsistencies in the data,[17, 18] and considerations of practicality render the clinical relevance of the concept of Gi debatable.

Consumption of viscous soluble fiber delays gastric emptying and intestinal transit. Prolonged exposure of the intestinal mucosa to nutrients stimulates the release of peptides which then function as satiety hormones or activate neural pathways.[29] Oats contain significant amounts of ß-glucan, a viscous soluble fiber which displays a high viscosity at relatively low concentrations.[119] Viscosity is an exponential function of the concentration of ß-glucan in solution and its molecular weight.[131] The main factors affecting solubility are temperature, moisture content, and any other factors that interfere with penetration of water and diffusion of the dissolved material.[129] Variations in the source, processing treatments, and interactions with other components in the primary source or the composite food matrix affect the amount, solubility, molecular weight, and structure of ß-glucan.[130] Thus, the physiologic action in the gastrointestinal tract and thereby the functionality of ß-glucan differs from one product to another. Oatmeal had a higher content of ß-glucan (2.3g) than the RTEC (1.7g), but it is possible that ß-glucan delivered through oatmeal may also be more bioavailable.

Relatively high levels of insoluble fiber (18-33g) in a meal have been shown to increase satiety.[87, 105] The insoluble fiber content of the oatmeal and the RTEC was only a fraction of these amounts and may have been too small to influence satiety. Although the energy density of

a food is largely determined by the water content, fiber does play a lesser role. Foods with a higher energy density are more satiating than foods with a lower energy density.[33] The total fiber content of oatmeal was higher than the RTEC which would have contributed to lowering its energy density and may have had a role to play in its greater effect on satiety as compared with the RTEC. Thus, it appears that the major role in enhancing satiety appears to have been played by the total fiber content especially the ß-glucan content of oatmeal.

Fat is higher in energy density than carbohydrate or protein yet it can generate potent satiety signals. Thus, despite its paradoxical nature, the satiating effects of fat may be exploited as a means of regulating food intake, making it an attractive target for the development of functional foods. Fats have been shown to reduce hunger when present in the GI tract by eliciting satiety signals.[22] Delaying lipolysis results in the exposure of more distal parts of the small intestine to fats and fatty acids. Exposure of the ileum to lipids activates the ileal brake, a distal to proximal feedback mechanism,[35] that delays gastric emptying,[36, 138] prolongs GI transit time [37] and influences satiety.[38, 39, 139] The inhibitory effects of the activation of the ileal brake are a result of the interaction of neural and humoral signals.[31]

The extent to which the ileal brake has a role in satiety and food intake under physiologic conditions is influenced by the physicochemical properties of fat. The effects are more pronounced with LCT (≥12 carbons) than shorter chain fatty acids.[22, 40, 41] whereas the role played by the degree of saturation in modulating the effects of fat on the GI tract has not been resolved fully.[43, 44] However, digestion to fatty acids is an essential step.[141] After ingestion of a regular meal only a small proportion of ingested nutrients reach the ileum. Thus, delaying lipolysis and reducing the absorption rate is crucial for stimulation of the ileal brake. It has been

shown that galactolipids reduce the rate and extent of lipolysis by sterically hindering the penetration of pancreatic colipase and lipase at the oil-water interface in the duodenum.[145]

Olibra™ is a fat emulsion comprised of fractionated palm, and oat oil in the proportion of 95:5. The palm oil is emulsified by hydrophilic galactolipids derived from oat oil.[146] Early studies,[23-25] all crossover designs, reported a reduction in energy intake and suppressive effects on appetite ratings in the short term, following consumption of the Olibra™ emulsion. Two subsequent studies failed to confirm the reduction in energy intake,[45, 46] though a suppressive effect on appetite ratings was demonstrated.[46] The beneficial effects of Olibra™ on body composition and weight maintenance, after weight loss, were demonstrated in one study,[149] however, in another study[150] no effect on weight was observed, but body fat mass decreased, after an initial weight loss period.

Studies that employed methods of delivering the emulsion directly into the GI tract demonstrated a delay in GI transit.[146, 159] However, when ingested orally, this fat emulsion may not elicit the GI responses manifested by an intragastric or intraduodenal administration. The lack of reproducibility of the beneficial effects of Olibra™ demonstrated in early studies suggests that in the dynamic environment of the GI tract, the emulsion may not resist digestion which is necessary for stimulating an increase in satiety and a reduction in food intake. A review of published studies investigating Olibra™ provided overwhelming evidence that further investigation of Olibra™ as a means of regulating appetite and satiety, and thereby food intake, is not warranted.

The studies had some limitations. Although the effects on satiety have been associated with hormonal action, hormone levels were not measured in either study; hence, it is difficult to draw any definitive conclusions as to the effects of hormones on appetite and satiety. Subjects in

both studies were asked to maintain a 10-12 hour overnight fast, but no control was exercised over subjects' food intake prior to each test day which may have influenced the results. The samples in both studies were relatively small, convenience samples, including predominantly female subjects, thus the generalizability of the results was compromised. The effects of oatmeal or the RTEC preload on subsequent food intake were not measured thus; the effects on regulation of food intake are unknown. Only short term satiety was measured, thus, the possibility of recurrent activation of the satiating mechanisms was not assessed. Further, the nutrient contents of the two breakfast cereals were not matched therefore; the effects of each nutrient on satiety could not be clearly differentiated. Lastly, in the study investigating the effects of Olibra™ on satiety, no information on subjects' usual intake was obtained, to determine if previous patterns of nutrient exposure were related to the results.

Postponing lipolysis and lipid absorption through manipulation of the physicochemical properties of fat, or increasing the viscosity of food products, so as to stimulate appetite and satiety mechanisms appears to be biologically plausible. Development of functional foods that target these physiologic responses may have a role in improving adherence to diet plans by prolonging the interval between meals, and perhaps reducing energy intake. However, it is possible that the satiety response at one exposure may be different at other exposures considering the learned and conditioning responses, and myriad factors affecting satiety.

Thus, studies that demonstrate the satiety enhancing effect of foods or the lack of it, contribute to the literature exploring the field of functional food development. Additionally, claims to satiety are different from claims to reduction in food intake or body weight. Any irrational expectations implied in satiety claims may thus be verified.

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APPENDIX

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You replied on 5/2/2012 11:34 AM.

Candida Rebello

From: Dan Shilstone [shilstone@diabetestechnology.org] **Sent:** Wed 5/2/2012 11:17 AM
To: Candida Rebello
Cc:
Subject: Re: Copyright release request (REBELLO)
Attachments:

Hi Candida,

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Best wishes,

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Dan Shilstone
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From: "Candida Rebello" <Candida.Rebello@pbrc.edu>
Subject: Olibra Study
Date: April 30, 2012 6:04:59 AM PDT
To: "Vanessa Ta" <vanessa@diabetestechnology.org>
Cc: "Frank Greenway" <Frank.Greenway@pbrc.edu>

Vanessa,

The article, entitled 'Efficacy of Olibra: A 12 week randomized controlled trial, and a review of prior studies' was part of my thesis for the Master's program in Human Nutrition at Louisiana State University. I am the first author on the paper and I will be defending my thesis in the first week of June. I am writing to request for a copyright release from the Diabetes Technology Society, so I can include the paper in my thesis.

I have attached a letter requesting permission. Please let me know if there is anything else I need to do to obtain permission from the Diabetes Technology Society.

I would appreciate your help in this matter.

Thank you,

Candida Rebello

VITA

Candida Rebello was born in Mumbai, India. She received her Bachelor of Law degree from the University of Mumbai in March 1986. She began the Didactic Program in Dietetics at Louisiana State University, Baton Rouge in June 2005 and completed the program in May 2009. She became a registered dietitian in August 2010, following completion of a dietetic internship program and achieving success in the Registered Dietitian examination administered by the Commission on Dietetic Registration, the credentialing agency of the Academy of Nutrition and Dietetics, Chicago, Illinois. Candida began the Master of Science program with a concentration in human nutrition in June 2011, at Louisiana State University, School of Human Ecology. She completed her research at the Pennington Biomedical Research Center in Baton Rouge, Louisiana.