# THE EFFECTS OF VISCOUS DIETARY FIBERS ON THE PARAMETERS OF APPETITE AND FOOD INTAKE REGULATION

by

Pearl Laurie Breitman

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Graduate Department of Nutritional Sciences University of Toronto

*Your file Votre référence*
*ISBN: 978-0-494-52598-2*
*Our file Notre référence*
*ISBN: 978-0-494-52598-2*

# THE EFFECTS OF VISCOUS DIETARY FIBERS ON THE PARAMETERS OF APPETITE AND FOOD INTAKE REGULATION

Doctor of Philosophy, 2009
Pearl Laurie Breitman
Department of Nutritional Sciences
University of Toronto

## ABSTRACT

Obesity results in significant morbidity and mortality. Hypocaloric diets lead to hunger, discontinuation of diet and weight re-gain. Soluble dietary fiber may control hunger, however the evidence is inconsistent; possibly from fiber property differences. **PURPOSE**: To examine soluble fiber blend (SFB) rheological and gravimetric properties and physiological mechanisms. **METHODS**: Healthy participants arrived fasted and randomly consumed study treatments. Glucose, insulin, growth hormone, acetaminophen (marker of gastric emptying time), symptoms, appetite and food intake were assessed. Treatments: Study 1: Four glucomannan particle sizes; Study 2: Two, 4 or 6g of SFB; Study 3: High (SFB), medium (glucomannan) or low (cellulose) viscosity fibers; Study 4: SFB or cellulose. Studies 3 and 4: food intake and satiety were also assessed at a pizza lunch. All studies used insoluble fiber controls. **RESULTS**: Study 1: In N=15 (29.5±2.3yrs; BMI:22.1±0.8kg/m$^2$) glucose iAUC was lower ($p=0.005$) with large(199.6±23.1min.mmol/l) vs. medium(257.7±45.6min.mmol/l) and control(256.9±35.3min.mmol/l) particle sizes. Insulin iAUC was higher ($p<0.01$) in control (19130.5±3834.0min.pmol/l) vs. all particles. Satiety was greater ($p=0.04$) after large (-0.27±0.25cm) vs. control (-1.08±0.34cm). Study 2: In N=9(33.4±4.2yrs; BMI:24.4±1.5kg/m$^2$) glucose was lower ($p<0.05$) at 15, 30and 60min with 4 and 6g vs. 2g and control. Glucose iAUC was higher ($p=0.0001$) in control(341.3±0.34min.mmol/l) vs. all doses. Study 3: N=35(16.2±0.1yrs; BMI:22.2±3.6kg/m$^2$) pizza intake was lower ($p=0.047$) after SFB(264±20g) vs. glucomannan(317±18g). Study 4: N=19(39.0±2.6yrs; BMI:28.5±0.6kg/m$^2$), satiety was numerically higher after SFB, however not significantly. Gastric emptying AUC was slower ($p=0.004$) after control(18330.13±1570.0umol/l.min) vs. SFB(19201.4±1479.5umol/l.min). Glucose and insulin iAUC were lower ($p<0.0001$) after SFB (125.6±7.9min.mmol/l, 8751.3±3256.4min.pmol/l, respectively) vs. control (181.2±7.8min.mmol/l, 57661.6±3321.4min.pmol/l, respectively). **CONCLUSIONS**: Concentration and rheological variations in viscosity and particle size affected glucose, insulin, appetite and food intake, such that larger particle sizes of glucomannan and highly viscous SFB doses of 4-6g reduced postprandial glucose and insulin and lead to greater reductions in appetite and food intake. Longer term studies are required to further define the dose and viscosities of fiber to consistently reduce appetite and further maintain healthy body weight. The current study suggests that larger particle size and greater than or equal to 4-6g doses of fiber intake may aid in glycemic control.

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Dr. Vladimir Vuksan, for providing me with the opportunity to work on this degree in his lab. While working with him I was able to experience multiple aspects of research there, including attending conferences, industry talks and teaching. I learned a great deal under his supervision.

I would also like to thank several other professors who helped me.

First, I would like to thank Dr. Pauline Darling, a member of my committee who encouraged me to apply for the combined dietetic internship and research program, taught me in a directed readings course and has been a mentor to me throughout the process of my PhD. She has always treated me with the respect of a colleague and because of these things I am extremely grateful to her.

I would also like to thank Dr. David Jenkins for agreeing to be part of my committee. I was honoured to have him as an advisor and to work with someone who is such an expert in this field.

I would also like to thank Dr. Valerie Tarasuk in her role as graduate coordinator for her dedication to this task and her kind encouragement and her professionalism during my time as a PhD student in the department.

In addition, I am grateful to the two external appraisers for my thesis. Dr. Anthony Hanley, as my external departmental appraiser and Dr. James Anderson, as my senate external appraiser. Both were very positive in their appraisals and provided me with very helpful suggestions for my thesis. In addition, they were fair and considerate, which made the defenses enjoyable.

I would also like to thank Louisa Kung, Gladys Lim, Agnes Lee and Asima Nadeem who provided a significant amount of technical help with guidelines and procedures. In addition, the support of friends and colleagues both in my lab (John, Mark, Alexandra, Anamaria, Uljana Shirin, Adish, Elena, Dana, Leanne and Amy) and in other labs in the department enriched my experience during the program. I would also like to acknowledge the many volunteers who dedicated hours of their time working in our lab and the research participants, who gave their time to advance science.

Many people in my personal life helped me find a balance between my degree and my personal life and for this I am very appreciative. I would like to thank my parents, for their welcomed advice and for providing me with a foundation from which I drew the strength I needed to complete this degree, my sisters and their husbands and children for their love and support, my in-laws and my grandmother for their kindness and encouragement and my friends who provided me with fun distraction throughout this time.

I would also like to thank my husband, who has provided me with knowledge, advice and love, while modeling an exceptional ability to balance hard work with personal enjoyment.

TABLE OF CONTENTS

TITLE PAGE ..... i
ABSTRACT ..... ii
ACKNOWLEDGEMENTS ..... iii
TABLE OF CONTENTS ..... iv
LIST OF TABLES ..... vii
LIST OF FIGURES ..... viii
LIST OF APPENDICES ..... ix
LIST OF ABBREVIATIONS ..... x
**CHAPTER 1: INTRODUCTION ..... 1**
INTRODUCTION ..... 2
**CHAPTER 2: LITERATURE REVIEW ..... 5**
**2.1 OBESITY ..... 6**
**2.1.1 Obesity and Weight Loss ..... 7**
**2.1.1.2 Pharmacological Approaches to Weight Loss ..... 7**
**2.1.1.3 Dietary Approaches to Weight Loss ..... 8**
**2.2 APPETITE AND FOOD INTAKE REGULATION ..... 10**
**2.2.1 Mechanisms of Appetite Regulation ..... 12**
**2.2.1.1 Mechanical Mechanisms of Appetite Regulation ..... 12**
**2.2.1.2 Metabolic Mechanisms of Appetite Regulation ..... 12**
**2.3 DIETARY FIBER ..... 14**
**2.3.1 Soluble Dietary Fiber and Physico-Chemical Properties ..... 14**
**2.3.2 Soluble Dietary Fibers and Glycemic Index ..... 15**
**2.3.3 Soluble Dietary Fiber, Satiety and Energy Intake ..... 16**
**2.3.4 Highly Viscous Soluble Fibers, Appetite and Energy Intake ..... 17**
**2.3.5 Soluble Fiber Blend ..... 18**
**2.3.5.1 Soluble Fiber Blend and Chronic Disease Risk Factors ..... 19**
**2.3.5.2 Soluble Fiber Blend, Glucose, Insulin and Lipid Control ..... 19**
**2.3.5.3 Soluble Dietary Fiber Blend and Appetite Regulation ..... 21**
**RATIONALE, OBJECTIVES AND HYPOTHESES ..... 22**
**2.4 RATIONALE ..... 23**
**2.5 OBJECTIVES ..... 25**
**2.6 HYPOTHESES ..... 26**
**CHAPTER 3: INVESTIGATION OF THE EFFECT OF FIBER PARTICLE SIZE ON GLUCOSE, INSULIN AND APPETITE REGULATION ..... 27**
**3.1 ABSTRACT ..... 28**
**3.2 INTRODUCTION ..... 29**
**3.3 SUBJECTS AND METHODS ..... 30**
**3.3.1 SUBJECTS ..... 30**
**3.3.2 TEST MEALS ..... 31**
**3.3.3 STUDY DESIGN ..... 31**
**3.3.4 LABORATORY ANALYSES ..... 32**
**3.3.4.1 Glucose ..... 32**
**3.3.4.2 Insulin ..... 35**
**3.3.4.3 Satiety Symptom and Ratings ..... 35**
**3.3.5 STATISTICAL ANALYSIS ..... 35**
**3.4 RESULTS ..... 36**
**3.4.1 SYMPTOMS ..... 36**
**3.4.2 LABORATORY ANALYSES ..... 36**
**3.4.2.1 Glucose ..... 36**
**3.4.2.2 Insulin ..... 37**
**3.4.2.3 Satiety ..... 37**
**3.5 DISCUSSION ..... 41**

CHAPTER 4: THE EFFECT OF DOSE OF A VISCOUS FIBER BLEND ON GLYCEMIC AND APPETITE REGULATION ..... 45
4.1 ABSTRACT ..... 46
4.2 INTRODUCTION ..... 47
4.3 SUBJECTS AND METHODS ..... 49
4.3.1 SUBJECTS ..... 49
4.3.2 TEST MEALS ..... 49
4.3.3 STUDY DESIGN ..... 50
4.3.4 LABORATORY ANALYSES ..... 51
4.3.4.1 Plasma Glucose ..... 51
4.3.4.2 Satiety Ratings and Symptoms: ..... 51
4.3.5 STATISTICAL ANALYSES: ..... 51
4.4 RESULTS ..... 52
4.4.1 SYMPTOMS ..... 55
4.4.2 LABORATORY ANALYSIS ..... 55
4.4.2.1 Glucose: ..... 55
4.4.2.2 Satiety: ..... 55
4.5 DISCUSSION ..... 58
CHAPTER 5. THE EFFECT OF A VISCOUS FIBER BLEND ON FOOD INTAKE AND APPETITE REGULATION IN HEALTHY ADOLESCENTS ..... 61
5.1 ABSTRACT ..... 62
5.2 INTRODUCTION ..... 63
5.3 SUBJECTS AND METHODS ..... 64
5.3.1 SUBJECTS ..... 64
5.3.2 TEST MEALS ..... 65
5.3.3 STUDY DESIGN: ..... 66
5.3.4 STUDY ANALYSES ..... 66
5.3.4.1 Anthropometric Assessment: ..... 66
5.3.4.2 Questionnaires ..... 67
5.3.5 STATISTICAL ANALYSES ..... 69
5.4 RESULTS ..... 71
5.4.1 SYMPTOMS ..... 71
5.4.2 STUDY ANALYSES ..... 71
5.4.2.1 Appetite Ratings: ..... 71
5.4.2.2 Short Term Food Intake: ..... 71
5.4.2.3 Longer Term Food Intake: ..... 71
5.5 DISCUSSION ..... 78
CHAPTER 6. THE EFFECT OF A VISCOUS FIBER BLEND ON THE MECHANISMS OF APPETITE AND FOOD INTAKE ..... 83
6.1 ABSTRACT ..... 84
6.2 INTRODUCTION ..... 85
6.3 SUBJECTS AND METHODS ..... 86
6.3.1 STUDY SUBJECTS ..... 86
6.3.2 TEST MEALS ..... 87
6.3.3 STUDY DESIGN ..... 87
6.3.3.1 Study Environment ..... 89
6.3.4 EXPERIMENTAL ANALYSES ..... 90
6.3.4.1 Visual Analog Scales: ..... 90
6.3.4.2 Appetite scales: ..... 90
6.3.4.3 Symptoms ..... 90
6.3.4.4 Pizza Intake ..... 92
6.3.4.5 Long Term Symptom and Appetite Records ..... 92
6.3.4.6 Gastric Emptying ..... 92
6.3.4.7 Glucose ..... 93

6.3.4.8 Insulin and Growth Hormone ..... 94
6.3.5 STATISTICAL ANALYSES ..... 95
6.4 RESULTS ..... 96
6.4.1 EXPERIMENTAL ANALYSES ..... 96
6.4.1.1 Appetite ..... 96
6.4.1.2 Symptoms: ..... 102
6.4.1.3 Food Intake: ..... 102
6.4.1.4 Twenty Four Hour Symptoms, Appetite and Intake ..... 102
6.4.1.5 Gastric Emptying ..... 102
6.4.1.6 Glucose ..... 102
6.4.1.7 Insulin ..... 110
6.4.1.8 Growth Hormone ..... 110
6.5 DISCUSSION ..... 110
CHAPTER 7. MAIN FINDINGS, GENERAL SUMMARY, LIMITATIONS AND FUTURE DIRECTIONS ..... 118
7.1 MAIN FINDINGS ..... 119
7.2 GENERAL SUMMARY ..... 120
7.3 LIMITATIONS ..... 122
7.4 FUTURE DIRECTIONS ..... 126
CHAPTER 8. REFERENCES ..... 132
CHAPTER 9. APPENDICES ..... 146
APPENDIX 1 ..... 147
APPENDIX 2 ..... 154

LIST OF TABLES

**TABLE TITLE** **PAGE**

Table 3.1. Nutrient Profile of Preload Treatments 34
Table 3.2. Preload consumption times among treatments 34
Table 4.1. Nutrient Profile of Preload Treatments 54
Table 5.1. Nutrient Profile of Preload Meals 70
Table 5.2. Nutrient Profile of Pizza Lunch 70
Table 5.3. Consumption Time of the Three Breakfast Preloads. 72
Table 5.4 Long-Term Nutrient Intake 77
Table 6.1. Nutrient content of Breakfast Meal 88
Table 6.2. Nutrient content of Pizza lunch 88
Table 6.3. 24-Hour Symptoms 104
Table 6.4. 24 Hour Food Intake 108

LIST OF FIGURES

**FIGURE TITLE** **PAGE**

Figure 2.1. Glycemic and Insulinemic Response to Soluble Fiber Blend Biscuits. 20
Figure 2.2. Glucose, Insulin Acute and Prolonged Effect of Prolonged Consumption of SFB. 20
Figure 3.1. Study Day Protocol 33
Figure 3.2. Plasma Glucose 38
Figure 3.3. Serum Insulin 39
Figure 3.4 Satiety 40
Figure 4.1. Study Day Protocol. 53
Figure 4.2. Plasma Glucose Response 56
Figure 4.3. Satiety Ratings. 57
Figure 5.1. Study Day Protocol 68
Figure 5.2. Appetite ratings during the study period. 75
Figure 5.3. Pizza Intake 76
Figure 6.1. Study Day Protocol. 91
Figure 6.2. Absolute and Incremental Appetite 100
Figure 6.3 Average Appetite Scores 101
Figure 6.4. Pizza Intake 103
Figure 6.5. Long-Term Appetite 107
Figure 6.6. Serum Acetaminophen Response 109
Figure 6.7. Plasma Glucose 111
Figure 6.8. Serum Insulin 112
Figure 6.9. Growth Hormone 113

LIST OF APPENDICES

**APPENDIX** **PAGE**

Appendix 1
1. Particle size and Dose Study appetite, palatability and side effect scale 148
2. Clinical Questionnaire Adolescent study 149
3. Subjective Physical Comfort Adolescent study 150
4. Telephone Screening Questionnaire Mechanistic Study: 151
5. Rating of study food Enjoyment Mechanistic and Adolescent Study 152
6. Clinical Questionnaire Mechanistic Study 153

Appendix 2
Table A2.1: Mean Symptom Ratings for Study 1 155
Table A2.2 Mean Symptom Ratings for Study 2 155
Table A2.3 Mean Symptom Ratings for Study 3. 156
Table A2.4 Mean Symptom Ratings for Study 4. 157
Inclusion and Exclusion Criteria: 158

LIST OF ABBREVIATIONS

**WHO**: WORLD HEALTH ORGANIZATION
**BMI**: BODY MASS INDEX
**CVD**: CARDIOVASCULAR DISEASE
**DM**: DIABETES MELLITUS
**T2DM**: TYPE 2 DIABETES MELLITUS
**TG**: TRIGLYCERIDES
**LDL**: LOW DENSITY LIPOPROTEIN
**CNS**: CENTRAL NERVOUS SYSTEM
**RIO**: RIMONABANT IN OBESITY
**CCK**: CHOLOCYSTOKININ
**HBAIC**: HEMOGLOBIN AIC
**HDL**: HIGH DENSITY LIPOPROTEIN
**GI**: GASTROINTESTINAL
**GLP-1**: GLUCOSE-LIKE PEPTIDE 1
**AUC**: AREA UNDER THE CURVE
**GM**: GLUCOMANNAN
**SFB**: SOLUBLE FIBER BLEND
**TC**: TOTAL CHOLESTEROL
**IV:** INTRAVENOUS
**SPSS**: STATISTICAL SOFTWARE FOR THE SOCIAL SCIENCES
**SEM**: STANDARD ERROR MEAN
**SD**: STANDARD DEVIATION
**VAS**: VISUAL ANALOG SCALE
**Q1 – Q4**: QUESTION 1 – QUESTION 4
**PYY**: PEPTIDE YY
**CV:** COEFFICIENT OF VARIATION
**SCID**: STRUCTURED CLINICAL INTERVIEW FOR DSM (DIAGNOSTIC AND STATISTICAL MANUAL) DISORDERS
**GE**: GASTRIC EMPTYING
**ISI**: INSULIN SENSITIVITY INDEX
**MRI**: MAGNETIC RESONANCE IMAGING

# **CHAPTER 1:** INTRODUCTION

INTRODUCTION

Overweight and obesity are significant health concerns in North America. While the prevalence and incidence of obesity continue to rise so do the serious comorbidities that are attributable to weight gain. Because the causes of obesity are multifactorial, interrelated and complex, efforts from research, government and health care sectors aimed at reducing weight gain continue to be multifaceted.

Several dietary factors have been examined as potential areas of interest for weight regulation. Macro and micronutrients have been extensively studied for their ability to control appetite through a variety of mechanisms. Dietary fiber may impart multiple health benefits, including potential for weight regulation. Although many health benefits have been shown to be related to dietary fiber intake, the North American population still consumes half the fiber proposed by national recommendations of 25-38g/d[1-3]. A possible explanation could be discomfort associated with adding large quantities of fiber too quickly to the diet, which leads to abdominal discomfort, bloating and gas. Therefore, advice in this area may have limited practical implications if individuals are not willing to increase fiber intake. However, given the recent obesity epidemic the population is seeking weight loss methods that are acceptable and sustainable. Hypocaloric diets have been shown to reduce body weight; however they strongly rely on willpower and can lead to eventual discontinuation due to hunger and boredom. Therefore, a dietary modality that requires the addition of small amounts of fiber to the diet and results in hunger regulation and improvements in obesity-related comorbidity risk factors may be an acceptable addition to hypocaloric diets.

Dietary fiber has shown promise in terms of its ability to affect appetite through a combination of mechanical and metabolic mechanisms. For instance, it may augment the individual abilities of co-ingested macro and micronutrients to control hunger and fullness by slowing gastrointestinal transit time and thereby increasing the chances of nutrients to trigger gut hormones for a longer period of time at lower serum levels.

Despite promising findings, the literature provides inconsistent results on the effects of soluble dietary fibers on appetite, food intake and the physiological mechanisms that control these parameters. For instance, some studies demonstrate reduction in appetite and slowed gastric emptying time, while

others do not show any differences. One possible explanation for these inconsistencies is that the soluble fibers studied differ in variety, batch and physico-chemical properties. These differences may have a large impact on the outcomes being measured. For instance, differences in particle size may affect the rate at which dietary fibers with viscous properties solubilize in water and form viscous gels. Small particle sizes, compared to large particles, have greater surface area that can come into contact with surrounding fluids. A faster rate of contact and penetration from water molecules may lead to faster forming gels and greater viscosity. Gels made from smaller particle sizes could potentially trap coingested nutrients faster and lead to a slower transit through the gastrointestinal tract and greater opportunity for those nutrients to influence the mechanisms that control hunger and food intake. When fiber isolates are processed, they can be separated into particle size through a series of mesh sieves. If these separations do not occur, fiber isolates are packaged as a mix of particle sizes. If particle size is not accounted for in studies investigating the effects of viscous fibers on appetite and food intake, there may be variation in findings in the literature due to differences in fiber properties.

Dose is another property that has been previously investigated. Given the reluctance of the population to increase dietary fiber intake, finding a dose of dietary fiber that confers the greatest reduction in postprandial glucose, insulin and maximizes the hormonal responses involved in appetite and food intake regulation is crucial. Previous studies have found that greater doses of dietary fiber lead to greater effects, such as glycemic response, however some researchers have demonstrated a threshold, beyond which greater doses do not elicit greater effects[4]. When the physico-chemical properties of dietary fibers are considered the dose required to meet this threshold may be reduced. For instance, a combination of dietary fibers that act synergistically could be used to develop a highly viscous gel. If the combination of these dietary fibers leads to a more viscous gel than individual fibers alone, perhaps the physiological benefits could be achieved at a lower dose and the amount of this fiber that is recommended for the population to consume daily for health benefits could be reduced to a more acceptable amount.

To date, there have been no studies that have examined the effect of various particle sizes of a viscous soluble dietary fiber blend on glucose, insulin and appetite regulation. In addition, although the dose-response effect has been investigated, the effects of a synergistic blend of viscous fibers on the

parameters of glucose, insulin and appetite regulation have not. The investigation of both physico-chemical and gravimetric properties of fibers on these parameters is a step towards determining their impact on appetite and food intake and eventually long-term weight regulation using pre-established methodology. Controlling for variability in fiber investigations is of great importance given that research involving appetite and food intake includes so many extraneous sources of variability, such as psychological factors, cues and belief that may confound findings. A more thorough knowledge of these characteristics may allow previous findings in the literature to be better interpreted and future findings to be more comparable.

Therefore, the objective of the current research was to examine the relationship between physical characteristics of soluble dietary fibers, appetite, food intake and the mechanical and metabolic parameters by which they are controlled.

In this research, four randomized control trials were conducted on a synergistic blend of highly viscous dietary fibers, including glucomannan, xanthan and alginate. The first of these studies investigated the effects of 4 different particle sizes of the most viscous fiber in the blend on glucose, insulin and appetite while the second study used the most efficacious particle size from the first study to examine whether there was a dose-response effect. Following these two studies, a study designed using pre-established preload methodology was conducted to explore the effects of the most effective particle size and dose on subjective appetite and food intake in a healthy population. A fourth study further explored the mechanisms behind the findings in the third study to try to elucidate physiological explanations for the findings.

Although future work is still required to replicate these findings and further explore the rheological and gravimetric properties of viscous dietary fibers, these studies are a continuation of steps taken in the literature to elucidate the characteristics of fiber that must be controlled as science approaches a greater understanding of the use of soluble dietary fiber in physiological responses.

# **CHAPTER 2:** LITERATURE REVIEW

# LITERATURE REVIEW

## 2.1 OBESITY

The obesity epidemic is currently the most prevalent nutritional problem in the world. The International Obesity Task Force estimates that globally, 1.7 billion adults are overweight and 312 million are obese[5]. In North America, the prevalence of obesity has increased by 131% since the 1960s[6]. The World Health Organization (WHO) defines overweight as a body mass index (BMI) greater than 25.0 $kg/m^2$ and obesity as a BMI over 30 $kg/m^2$ [5]. Data from the most recent Canadian Community Health Survey indicates that the percentage of Canadians with a measured BMI of 24.9-29.9 $kg/m^2$ (overweight) is 59%, while the percentage with a measured BMI above 30 $kg/m^2$ (obese) is 23%[7].

Obesity is associated with the development of multiple comorbidities, including stroke, arthritis, dyslipidemia, osteoarthritis, certain cancers, cardiovascular disease (CVD), and type 2 diabetes mellitus (T2DM)[8-10]. For instance, it has been projected that for each kilogram of weight gained annually over 10 years, the risk of developing T2DM over those 10 years rises by 49%[11]. Moreover, BMI and waist circumference have been shown to be among the strongest predictors of T2DM development[12-16]. This relationship was supported by data demonstrating that over a 7 year period between 1990 and 1998 the incidence of obesity increased over 50% in United States and, in the same population over the same time period, the prevalence of T2DM increased by 33%[17].

The health complications that can develop from obesity and its comorbidities are severe. For instance, diabetes is the leading cause of several micro- and macrovascular complications, including coronary artery disease, peripheral vascular disease, diabetic nephropathy, neuropathy and retinopathy. Diabetes also increases the risk of death from cardiovascular causes, including myocardial infarction and stroke, by 3-8 fold compared to individuals without diabetes who have a history of a myocardial infarction[18].

Despite the established relationship between obesity and DM, the cause and effect relationship has not been fully elucidated. It is unknown whether elevated insulin results in obesity or whether obesity results in increased insulin resistance. In general, the greater the severity of obesity, the higher the fasting and postprandial serum insulin concentrations[19-21]. Insulin resistance and compensatory hyperinsulinemia

in T2DM is proposed to be a pathogenic factor in obesity due to the development of a lipogenic state. In an insulin resistant state, glucose uptake is reduced in muscle and liver and there is increased hepatic glucose output[22, 23]. During this time, adipose tissue retains some insulin sensitivity and it is thought that unused nutrients are therefore shunted to the adipose tissue, where they are stored in adipocytes, which grow and multiply and further contribute to insulin resistance[22].

### 2.1.1 Obesity and Weight Loss

Regardless of the cause-effect relationship between obesity and diabetes, there is evidence to suggest that a reduction of 10% of body weight can lead to a 30-40% reduction in diabetes-related complications and mortality[24, 25].

#### 2.1.1.2 Pharmacological Approaches to Weight Loss

Many options exist for achieving weight loss. Currently, two medications have been approved for long-term use in Canada as antiobesity agents; Orlistat (Xenical) and Sibutramine (Meridia).

Orlistat is a pancreatic lipase inhibitor which prevents hydrolysis of most triglycerides (TG) into free fatty acids and leads to excretion of undigested TG in the feces. A meta-analysis of 11 clinical trials demonstrated that Orlistat lead to 21% and 12% more participants achieving a 5% or 10% (respectively) weight loss compared to placebo[26, 27]. It also found a reduction in blood pressure by 1.8mmHg systolic and 1.6mmHg diastolic, a 0.27mmol/l reduction in LDL cholesterol and a 0.8mmol/l reduction in fasting glucose in participants with diabetes. Despite these findings, Orlistat was found to be associated with unpleasant side effects, such as fatty, loose and oily stool (steatorrhea), fecal urgency, flatulence and fecal incontinence[26]. Furthermore, there is potential for Orlistat to reduce the absorption of ingested fat-soluble vitamins.

Sibutramine is a monamine-reuptake inhibitor that acts by increasing serotonin and norepinephrine levels in the brain; leading to increased satiety due to the reuptake of serotonin, norepinephrine and dopamine. The randomized control trials of sibutramine in overweight or obese patients demonstrated that 34% and 15% of individuals experienced weight loss of 5% and 10% (respectively) of body weight. Despite these positive findings, long-term studies have shown small to no effect on LDL or glucose[27]. Sibutramine was also shown to be associated with insomnia, nausea, dry

mouth and unusual tastes, upset stomach, constipation, dizziness, headache, flushing and joint/muscle pain, as well as increased blood pressure and pulse.

Rimonabant (Acomplia) is a new drug that is still awaiting approval in Canada. It is an endocannabinoid receptor antagonist that blocks one of the two major receptors of the endocannabinoid system that in turn prevents orexigenic pathways within the CNS that increase motivation to eat and food intake[28-31]. The potential mechanisms proposed are increased thermogenesis by skeletal muscle oxygen consumption[32], diminished hepatic and adipocyte lipogenesis[33], increased concentrations of adiponectin[34] and CCK-induced satiety[28, 35]. It has also been shown to inhibit pre-adipocyte proliferation and maturation[36]. There have been 4 clinical trials as part of the Rimonabant in Obesity (RIO) trial examining its effectiveness. Rimonabant has been shown to lead to 29-39% and 17-25% of patients achieving 5% and 10% weight loss (respectively)[34, 37, 38]. Rimonabant also reduced HbA1c by 0.7% yet LDL and blood pressure were unchanged or reduced minimally[34, 37, 38]. Adverse side effects of Rimonabant include nausea, dizziness, diarrhea and insomnia and in some cases depression. In many trials, over 40% of participants discontinued use of the drug before 1 year.

Despite the benefits of pharmacological agents, the drawbacks make this option undesirable for many people. Side effects, significant financial costs and contraindication/interaction with other medications are all factors that impact the decision to initiate pharmacotherapy for weight regulation. In addition, drug discontinuation can lead to weight regain.

#### 2.1.1.3 Dietary Approaches to Weight Loss

In the United States, $33 billion is spent annually on alternatives to pharmacotherapy for weight loss. This market is comprised of diet related products and services, including merchandise related to fad diets[39]. Although the health effects of these diets and products have not all been clinically investigated in randomized control trials, individuals continue using them in hopes of fast, effective weight loss. Several weight loss dietary regimens are now being investigated in controlled trials and the evidence is promising, however, many long-term concerns must be resolved before these diets become more widely accepted by clinicians.

Recently, a clinical study by Dasinger *et al* (2005) compared the effectiveness of 4 popular diets (Atkins, Zone, Weight Watchers and Ornish) for weight loss and cardiac risk factors over a 12 month period in 160 overweight or obese patients[40]. The nutrient goals for each diet were as follows: Atkins: 20g of carbohydrate daily with gradual increase towards 50g daily; Zone: 40-30-30 balance of percentage calories from carbohydrates, fat and protein, respectively; Weight Watchers: 1200-1600kcal/day and Ornish: vegetarian diet containing 10% of calories from fat. The study results demonstrated that weight loss at 1 year was 4.8kg for Atkins, 3.2kg for Zone, 4.9kg for Weight Watchers and 7.3kg for Ornish. Each diet significantly reduced LDL/HDL ratio by 10% in association with weight loss. Although some studies have reported low overall long term adherence rates, two recent studies have reported very high adherence rates, making these diets more desirable in the long-term[41, 42].

Besides the question of adherence rates, these diets have been further criticized. For instance, Atkins diet has been questioned for the potential to increase risk factors associated with heart disease in the long term and that dieters experience more diarrhea, general weakness, have little dietary fiber and potential for ketosis and protein toxicity in individuals with preexisting kidney problems[43, 44]. The Zone diet has been criticized by the American Heart Association due to low levels of essential nutrients and very little long-term information on its health effects. Although Weight Watchers diet has been recognized for teaching individuals healthy lifestyle patterns, it may be difficult for some to maintain due to the costs of enrolment and annual dues. Fad diets have many benefits but the major consistent drawback to each is that they are typically discontinued within 6 months to 1 year and long-term effects are difficult for clinicians to evaluate because of the scarcity of data.

Conventional advice from health care providers has been to follow a diet that restricts caloric intake and increases energy expenditure. Current clinical weight loss recommendations advise achieving a 500-1000kcal/day energy deficit by caloric restriction and/or exercise in order to result in 1-2 lbs of weight loss per week and achieving long-term lifestyle habits and healthy weight maintenance[45].

This strategy is, however, often difficult to maintain because it relies strongly on self-discipline and can lead to uncomfortable episodes of hunger and eventual weight regain[46, 47]. Additionally, restriction of certain foods may reduce the potential for the nutrients in those foods to promote satiety.

For instance, a review of the literature demonstrates evidence for satiating factors in foods with: high protein content[48, 49], low glycemic index carbohydrates[50-52], high dietary fiber[53-55], low calorie/high volume[56, 57] and with minerals such as calcium[58].

Compounding the problem is that many weight-loss approaches, including pharmacological and dietary strategies target a single aspect of hunger. Hunger and energy intake regulation is, however, extraordinarily multidimensional and complex, involving cognitive, environmental and physiological mechanisms that are often interrelated. The additional effects of nutrients and the interactions of co-ingested nutrients and timing of ingested nutrients adds a level of complexity that illustrates the reasons many approaches have been met with resistance. Thus, an approach that can influence multiple control mechanisms involved in appetite and food intake regulation may offer a means to prevent and/or treat weight gain while minimizing diet-induced hunger episodes. In addition, a modality that can positively affect glucose response to a meal would be ideal, since a large proportion of overweight and obese individuals have impaired glucose tolerance. Dietary fiber has been examined as one modality due to the potential to augment the effects of individual coingested nutrients on appetite in intake regulation.

## 2.2 APPETITE AND FOOD INTAKE REGULATION

The ingestion of dietary fiber has been theorized to reduce the neuro-hormonal signals that lead to consumption of food[59], possibly due to the effect of the physico-chemical properties of fiber on the multiple mechanisms of appetite regulation. Before examining the specific physical and chemical properties of dietary fiber on appetite, it is important to consider the factors involved in appetite regulation and the methods used to investigate the effects of various foods and food components on appetite.

Appetite and food intake regulation is a balanced process that is influenced by metabolic parameters as well as cognitive and environmental factors, such as beliefs about food, time of day, food availability, smells and taste. Metabolic parameters of appetite regulation involve an integration of interrelated responses to cognitive and environmental cues and physiological responses to ingestion of nutrients. The processes involved in appetite have been conceptualized by Blundell et al (1991) as a cascade that includes 4 categories: sensory, cognitive, pre-absorptive and post-absorptive effects[60].

Sensory components are associated with the physical characteristics of foods, such as smell, taste, texture, appearance and auditory cues. Cognitive factors involve the socio-cultural and personal beliefs held about food. Preabsorptive elements include physiological processes that occur prior to absorption of nutrients in the gastrointestinal (GI) tract, such as gastric distention and gastric emptying time, while the post-absorptive category refers to the effects occurring from and in conjunction with absorption of nutrients and presence of their metabolites in the blood, such as changes in glucose, counterregulatory hormones, fatty acid metabolism and the expression of digestive and appetite-related hormones. The complexity of this cascade is compounded by its influences on neurocognitive factors in the enteric nervous system, including the vagal nerve, hypothalamus and meso-limbic centers in the hindbrain. In addition, each of these neurocognitive factors in turn, influences the cascade.

In order to assess this cascade, the most commonly used experimental measurable markers of appetite and intake regulation are: hunger (the signal for the onset of eating), satiation (the process which develops during eating and which brings an episode of eating to a close) and satiety (the state of inhibition over future eating which follows the end of an eating episode)[61] and food intake[59, 62].

The capacity of a food to cause a reduction in subsequent food intake is termed the "satiating efficacy" and is generally studied using the preload method[63]. The preload method involves manipulating a defined amount of food and/or nutrient and comparing the effects of this variation on hunger, satiation and satiety to a control food. This "gold standard" method involves subjective ratings of appetite and hunger and a subsequent meal that is presented at a predetermined time period after the preload is consumed. During the meal the research participant is instructed to eat as much as desired.

Satiation is generally influenced by stimuli that are involved in the preabsorptive phase of the appetite cascade, such as gastric emptying rate. Conversely, satiety is largely induced by metabolic signals in the post-absorptive phase, such as postprandial serum insulin and glucose concentrations and appetite-related gastrointestinal hormones (e.g. CCK, GLP-1).

In order to optimize the digestion and absorption of food for energy, the gut has a variety of mechanical and metabolic mechanisms to stop ingestion of food when satiation has been reached and to prolong the time between eating episodes when satiety is experienced.

### 2.2.1 Mechanisms of Appetite Regulation

#### 2.2.1.1 Mechanical Mechanisms of Appetite Regulation

Entry of food into the stomach and proximal small intestine activates mechano-receptors [64]. Mechano-receptors relay information about the quantity of food in the stomach via the vagal nerve to the hindbrain where the information is processed[65, 66]. Results from animal trials indicate the rate of discharge along the vagus nerve increases as the stomach distends[67, 68]. This pathway is where the physical and chemical properties of food can elicit short-term regulation of food intake and limit the size of a meal [69]. Gastric distension for instance, is thought to cause a feeling of fullness and contribute to satiation during meals and satiety in the postmeal period in humans[70-72]. The impact of physical stimuli such as gastric distension by water, air or viscosity has been shown in several clinical trails[57, 73]. Viscous substances, for instance, have shown delayed gastric emptying and food intake in the short-term[74, 75].

Although it is generally thought that these afferent transmissions are responsible only for short-term regulation of food intake at a meal (satiation), they may also affect subsequent energy intake in a later meal (satiety). For instance, meals that are high in volume but low in energy can decrease food intake[76-78]. Within 2-4 hours after a meal, the stomach contents completely empty into the duodenum (gastric emptying)[79]. As the food enters the proximal small intestine, neural and hormonal reflexes ensure that the stomach does not release more chyme to the small intestine than it can process (i.e. regulates gastric emptying). The composition of the chyme and the distension caused by presence of chyme in the duodenum initiates the enterogastric reflex of nerve impulses from the duodenum to the medulla, where they inhibit activity in the stomach and stimulate secretion of hormones such as CCK and GLP-1, which inhibit gastric motility and emptying[80, 81]. In vagotomy studies, the satiating effect of food is not blocked from the stomach, suggesting that additional factors, besides gastric distension affect food intake[82]. Moreover, if gastric distension were the only factor controlling food intake, the sensation of satiety would dissipate with gastric emptying.

#### 2.2.1.2 Metabolic Mechanisms of Appetite Regulation

There are many theories regarding the mechanisms that regulate appetite and food intake, such as the glucostatic and lipostatic theories and their interaction with central and peripheral regulatory

processes in the hypothalamus and the enteric nervous system, including the orexigenic and anorectic neuropeptides they affect. This review concentrates on the glucostatic theory of appetite and food intake regulation. The glucostatic theory of food intake regulation postulates that a decline in plasma glucose concentration results in an increase in appetite[83, 84]. However, high plasma glucose does not necessarily result in satiety and low plasma glucose does not necessarily result in hunger. Conversely, it is the rate of glucose utilization and the slope or shape of the plasma glucose curve that appears to affect appetite and food intake rather than absolute plasma levels at any time point[85]. Following a meal rich in carbohydrates, plasma glucose rises to reach a peak in 30-60 minutes and then falls back to baseline in healthy individuals. This postprandial glycemic response has been found to differ depending on the source of carbohydrate consumed and the rate at which they are digested[44]. The glycemic index is a tool used to classify the glycemic responses of various carbohydrates, as defined by the incremental area under the blood glucose response curve (AUC), and ranks them relative to a standard, such as white bread or glucose[86]. Rapidly absorbed carbohydrates result in a blood glucose curve that tends to peak abruptly and subsequently fall below the baseline glucose level. This fall below baseline is thought to stimulate hunger and eating due to the counterregulatory hormone response it provokes[87]. Counterregulatory hormones, such as cortisol, growth hormone and glucagon, are released in response to a low serum glucose level. They are secreted in order to increase gluconeogenesis, glycogenolysis and appetite so that the concentration of plasma glucose will be replaced. By slowing carbohydrate absorption with low glycemic index foods, such as viscous dietary fiber, plasma glucose is maintained above baseline for a longer time period[88]. It is thought that this may prevent the hunger that accompanies glucose levels that fall below baseline and lead to a longer feeling of satiety. Glycemic index is often used as an indication of the rate of digestion and absorption of food. Therefore, a rapid rise in the blood glucose curve signifies fast digestion, absorption, large insulin secretion, and fast peripheral glucose utilization and subsequent drop in plasma glucose below baseline, whereas a slow rise in the blood glucose curve signifies the opposite.

Although many studies suggest that low glycemic index foods may be more satiating than high glycemic index foods[50], there is evidence that the glucostatic theory alone does not translate to differences in subjective satiety ratings or in food intake. For instance, Holt et al (1996) reported no connection

between the satiety scores and area under the glucose and insulin curves on 38 different foods[89]. They also found that foods with higher insulin response elicited a greater subjective satiety rating. Therefore, low glycemic index foods may affect satiety and food intake but the role of plasma glucose response in conjunction with other mechanistic factors, such as approximately 24 gut hormones, gastric distension, gastric emptying rate and gastric transit time is not yet fully understood.

Therefore, several sites of appetite and food intake and weight regulation must be addressed in the development of modalities used for appetite, intake and weight regulation.

## 2.3 DIETARY FIBER

Epidemiological and cross-sectional evidence has suggested that there is a relationship between the amount of daily dietary fiber intake and prevalence of obesity and obesity related comorbidities [90-92]. For instance, in countries where dietary fiber intake is significantly higher than in North America, obesity rates are much lower than in North American countries. In a Canadian study in an Aboriginal population with very low fiber intake (1.2g/MJ), increases in fiber by 1 standard deviation were associated with a reduction in risk of having diabetes by 39%[93]. The current daily recommended intake (DRI) for adequate intakes of dietary fiber are 25-38 grams of fiber per day for adults[2] however the average American and Canadian diets contain less than half of these levels[1, 3].

### 2.3.1 Soluble Dietary Fiber and Physico-Chemical Properties

The means by which dietary fibers influence satiation, satiety, and consequently weight reduction and maintenance are thought to be due to their physico-chemical properties, particularly their bulking and viscosity-producing capabilities[94, 95]. Soluble fibers can form a dispersion when mixed with water. This dispersion creates a matrix that is swollen with water and is typically viscous[96]. The viscous gel that is produced allows the fiber to entrap hydrophilic molecules such as carbohydrates thus delaying their absorption[97]. This may also be true for the emulsion phase of the lipid portion of a meal, suggesting that the nutrient flux in the small bowel could be delayed[98]. Therefore, soluble fiber may control appetite by reacting with water to form a viscous gel that traps nutrients and delays their gastric emptying rate and intestinal transit time[59], thus affecting postprandial plasma glucose and serum insulin responses[94, 99]. The reasons for this effect include the hypothesis that the gel forms a layer or a barrier along the intestinal

wall, often referred to as the "unstirred layer". This unstirred layer slows absorption of nutrients and results in a delayed and flattened glycemic response. In addition, it is hypothesized that digestive enzymes, such as pancreatic amylase, are unable to penetrate the gel; leading to a slower digestion and absorption of nutritive substrates within the gel and flattened glycemic response[4].

**2.3.2 Soluble Dietary Fibers and Glycemic Index**

It is well established that when soluble fiber is present or added to a test food it reduces the glycemic index of the meal, an effect that is closely related to rheological characteristics of soluble fiber, especially the level of viscosity.

Dietary fiber that develops viscosity in the gastrointestinal tract is capable of addressing various sites of hunger regulation, throughout the gastrointestinal tract thus representing a potential treatment modality for multiple mechanisms of appetite regulation and/or weight loss. Viscous dietary fiber has the potential to entrap coingested nutrients and lead to the development of a viscous gel in the gastrointestinal tract, thereby slowing the digestion and absorption of nutrients. A food bolus that is able to traverse the gastrointestinal system more slowly could increase the opportunity for nutrients to traverse a greater portion of the GI tract, thereby triggering metabolic and mechanical mechanisms of appetite regulation for a longer period of time. Therefore, addition of a viscous dietary fiber to the diet may be attractive to individuals, who cannot or do not want to use pharmacologic strategies or short term diets to lose weight. This strategy could be an effective adjunct to a conventional diet since it may lead to greater satiety on a hypocaloric diet.

Studies of foods containing highly viscous fibers such as guar gum[100], and other low glycemic index foods[101, 102] have shown reduction in the rate of intestinal digestion and absorption of nutrients[65, 92, 103] and lower postprandial plasma glucose and insulin concentrations[104, 105]. Therefore, after consumption of viscous dietary fiber, the plasma glucose and insulin curves appear flattened and the fall of glucose levels below baseline that triggers hunger is prevented[106]. This observation has been demonstrated in numerous studies[53] and has also been shown to influence glycemic responses at subsequent test meals (second-meal effect)[104, 107]. Moreover, several investigators have demonstrated that over time, consumption of low glycemic index dietary components[108-110] such as guar gum[111, 112] and glucomannan[113,

[114], results in improved glycemic control and improved insulin sensitivity in subjects with insulin resistance, type 2 diabetes and the metabolic syndrome.

### 2.3.3 Soluble Dietary Fiber, Satiety and Energy Intake

Acute clinical interventions demonstrate that soluble dietary fiber is inversely related to satiety and energy intake[59]. In particular, purified soluble dietary fibers, such as psyllium and guar gum, have been found to increase feelings of fullness and satiety [115] and result in reduced energy intake and weight loss[116, 117]. In a comprehensive review by Howarth et al (2001), the authors found that consumption of an additional 12g of fiber per day over 3.8 months was associated with a 1.9 kg reduction in body weight and a 10% decrease in energy intake[53]. A more pronounced effect of high fiber diets was seen in studies of obese and overweight individuals (energy intake reduced to 82% of control with 2.4 kg of weight loss).

Soluble fiber has been shown to influence energy intake though its effects on gut hormones. Although the precise mechanisms have not been fully investigated, it is thought that the delayed absorption of macronutrients in the proximal small intestine results in an increased contact of nutrients later with the distal small bowel surfaces, where they are able to stimulate appetite related hormones[53]. This, in turn results in the "ileal break" and delays gastric emptying. Ileal break is a term used to describe the mechanism that is activated by the presence of nutrients in the ileal lumen and leads to inhibition of gastric motility and secretion[65, 107, 118, 119]. GLP-1, for instance, is among many gut hormones that are thought to mediate the ileal break and is secreted in response to nutrients. Animal studies have shown that fermentable fibers can increase secretion of GLP-1[120-127], however only a few recent studies have demonstrated this in humans[128-132]. It is unknown whether the response to fermentable fibers is due to an absolute increase in GLP-1 concentration or a longer secretion of GLP-1. The hormone stimulates reduction in gastric emptying rate, hunger and appetite when provided exogenously[133-136]. Although GLP-1 secretion is reduced in obese individuals[136, 137], it is unclear if consumption of fermentable soluble fibers reduces intake due to stimulation of GLP-1 in this population.

### 2.3.4 Highly Viscous Soluble Fibers, Appetite and Energy Intake

Numerous investigators have examined the effects of the highly viscous soluble dietary fiber, glucomannan (GM), on body weight and appetite in rodents[138-141] and humans[142-147]. Despite the findings that no differences existed in food intake or weight after consumption of GM in rodents, every study examining the effects of GM on weight loss in humans has demonstrated a decrease in body weight.

In a landmark double-blind study by Walsh et al. (1984), 20 obese women (mean BMI: 32.8 $kg/m^2$) each consumed 1 gram of purified GM, 3 times per day with 8 oz of water, 1 hour before each meal[148]. The results were compared to a placebo group under the same conditions, with the exception that the capsules contained 500mg of starch instead of GM. After 4 weeks, participants in the GM group lost 4.5 lbs more ($p<0.02$) than placebo and after 8 weeks GM group lost 7.0 lbs more ($p<0.005$) than placebo[148]. Although this study did not address the effect of the GM on appetite, many subjects indicated that they had a "full" feeling after consuming the GM.

In another study by Biancardi et al. (1989) 20 overweight men (N=3) and women (mean BMI: 29.3 $kg/m^2$) consumed 1.5 g of GM or placebo before breakfast and dinner[149]. After 2 months, participants in the GM group lost 3.6 lbs from baseline ($p<0.02$) and 8.9 lbs more than placebo, although these results were not significant.

Despite the relationship between GM and body weight, the mechanisms of the highly viscous dietary fiber on appetite regulation and related metabolic parameters that control food intake have not yet been fully investigated.

Although the previously described studies of GM on glycemic control and weight loss demonstrate promising results, there was no standardization of the soluble fiber, which can vary among batches. Moreover, studies in the literature that have examined the effects of viscous soluble dietary fibers on appetite regulation and related mechanisms have found inconsistent effects[70, 74, 94, 150-167]. For instance, some studies found reductions in appetite and slowed gastric emptying time[70, 74, 150, 153, 157, 161, 163, 167, 168], while others did not show any differences in these parameters[152, 155, 160, 162, 166]. It is possible that these inconsistencies are due to the variety of dietary fiber type and/or batches used among studies.

In addition to the differences in fiber batch variations, there are inconsistencies in the physicochemical properties of dietary fiber, such as particle size. For instance, differences in particle size may affect the rate at which dietary fibers with viscous properties solubilize in water and form viscous gels. Small particle sizes, compared to large particles have greater surface area that can come into contact with surrounding fluids and form gels and viscosity more quickly. Gels made from smaller particle sizes could potentially trap coingested nutrients faster and lead to a slower transit through the gastrointestinal tract and greater opportunity for those nutrients to influence the mechanisms that control hunger and food intake. If particle size is not accounted for in studies investigating the effects of viscous fibers on appetite and food intake, there may be great variation in findings in the literature due to differences in fiber properties, not due to type of fiber.

Dose is another property that has been previously investigated. Given the reluctance of the population to increase dietary fiber intake, finding a dose of dietary fiber that confers the greatest reduction in postprandial glucose, insulin and maximizes the hormones responsible for appetite and food intake regulation is crucial. Previous studies have found that greater doses of dietary fiber lead to greater effects, such as glycemic response, however a threshold exists, beyond which greater doses do not lead to greater effects[4]. When the physico-chemical properties of dietary fibers are considered, the dose required to meet this threshold may be reduced. For instance, a combination of dietary fibers could be used that act synergistically to develop into a viscous gel. If the combination of these dietary fibers leads to a more viscous gel than individual fibers alone, perhaps the amount of this fiber that is recommended for the population to consume for health benefits could be reduced to a more acceptable amount.

Inter and intra-fiber variations in batch, dose and particle size may affect physiological outcome. Therefore, a dietary fiber model in which these and the properties that have the greatest impact on physiological response can be controlled would be ideal to help standardize fiber and make results in the literature more comparable.

**2.3.5 Soluble Fiber Blend**

Based on investigation of the rheological properties of various viscous soluble dietary fibers, a soluble fiber blend (SFB) (commercially available as Polyglycoplex (PGX), InovoBiologic, Coquitlam,

British Columbia), comprised of highly viscous dietary fibers was created. The blend is mixed in proportions that lead to standardized viscosity across batches. Standardized viscosity is important for future research so that inter and intra-fiber variability in viscosity due to fiber type and batch may be minimized or eliminated. Since viscosity is the property that is thought to elicit the physiological responses of soluble dietary fibers on glucose and insulin and appetite regulation, standardizing the viscosity of all fibers in research studies would enable a better comparison of study results across the scientific literature.

Because the SFB is composed of soluble fibers that act in a synergistic, complementary manner when combined, it is able to achieve a greater maximum viscosity than any of the individual viscous fibers currently known are able to achieve independently. GM fiber, one of the constituents of the blend, is a polysaccharide chain of glucose and mannose in the molar ratio of 1:1.6 with β-1-4 linkages [169-172]. Studies in humans and in rodents have demonstrated that GM forms a soluble gel and increases the moisture content of the food bolus during digestion[173]. One gram of GM can absorb up to 100 ml of water in vitro[174]. When properly selected, the viscosity of GM is approximately five times higher than guar gum and considerably higher than pectin and psyllium[173, 174]. Xanthan, a constituent of the SFB, is a highly viscous fiber produced under controlled conditions from bacterial cultures, and is complementary to GM.

#### 2.3.5.1 Soluble Fiber Blend and Chronic Disease Risk Factors

Several acute and long-term investigations of a blend of GM with other highly viscous dietary fibers on risk factors for chronic diseases (i.e. glucose, insulin, dyslipidemia) have been conducted and results of these studies provide a rational for further exploration into the effects on appetite regulation mechanisms[113, 114, 175]. The highly viscous nature of SFB has conferred upon it physiological effectiveness in terms of postprandial glycemia (Figures 2.1, 2.2), lipid lowering properties and mild blood pressure lowering effects in individuals with T2DM and insulin resistance[113, 114].

#### 2.3.5.2 Soluble Fiber Blend, Glucose, Insulin and Lipid Control

In a randomized crossover, placebo-controlled study on individuals with impaired glucose tolerance, SFB was added to biscuits and participants consumed SFB biscuits or control biscuits (wheat bran) for 3 weeks with a 2 week crossover period. SFB to biscuits resulted in the simultaneous reduction

in postprandial glucose and insulin response as well as improvements in blood lipid profile (TC:HDL reduced by 10%) and systolic blood pressure (reduced by 6.9%). In addition, serum fructosamine was reduced by 5.7%[113].

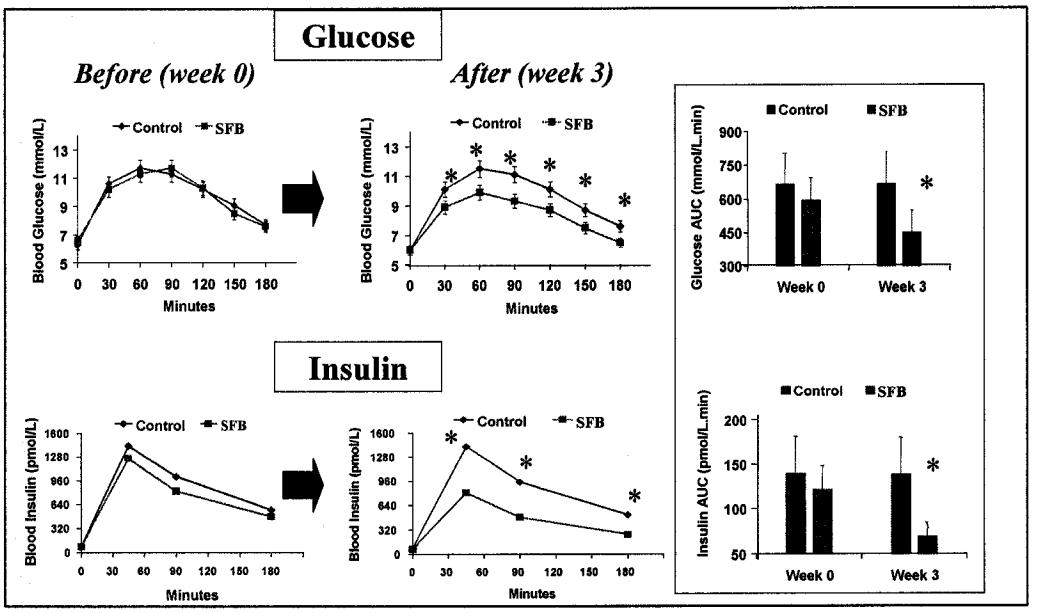



Figure 2.1. Glycemic and Insulinemic Response to Soluble Fiber Blend Biscuits.
Acute postprandial glucose (top left) and insulin (bottom left) baseline and 3 week responses in individuals with the insulin resistance on an NCEP diet plus consumption of a biscuit with either soluble fiber blend (SFB) or control (wheat bran). The figure on the right represents the corresponding acute baseline and 3 week glucose and insulin areas under the curve (AUC). Unpublished data.

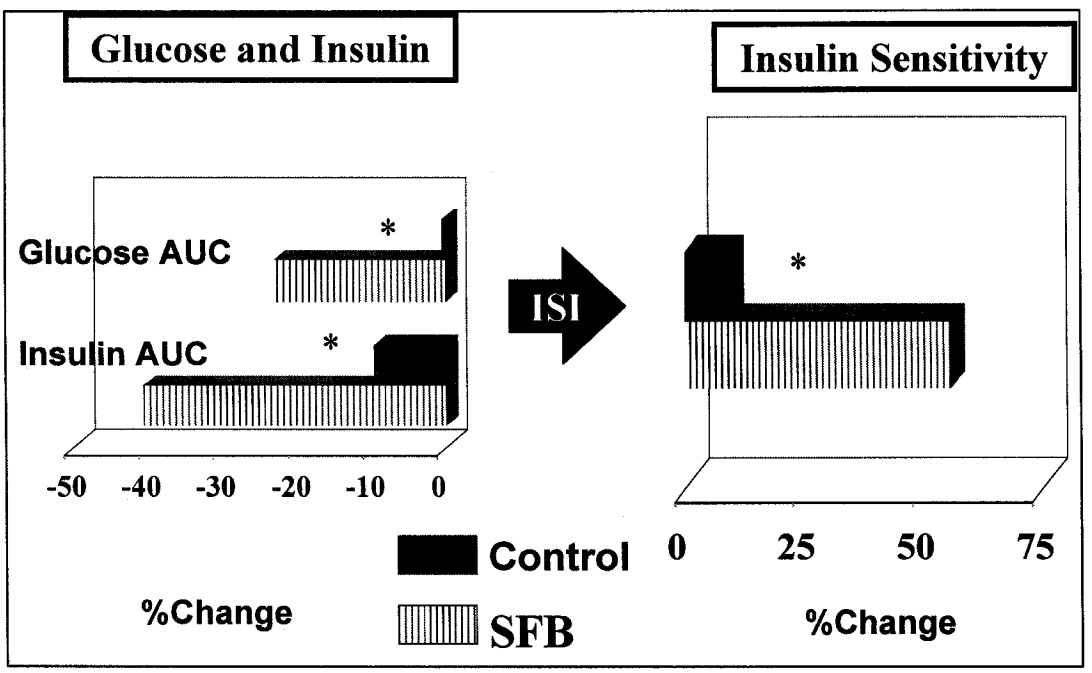



Figure 2.2. Glucose, Insulin Acute and Prolonged Effect of Prolonged Consumption of SFB.
Acute postprandial glucose (top left) and insulin (bottom left) area under the curve (AUC) responses (% change) from baseline to 3 weeks in individuals with the insulin resistance on an NCEP diet plus consumption of a biscuit with either soluble fiber blend (SFB) or control (wheat bran). The figure on the right represents the corresponding change in insulin sensitivity index (ISI) over 3 weeks, which was calculated using the Matsuda and DeFronzo method[176]. Unpublished data.

In a later study with an identical design, SFB-enriched biscuits were given to subjects with insulin resistance. Similarly to the first study, addition of SFB resulted in significant improvements in serum cholesterol, apolipoprotein B and fructosamine after 8 weeks of treatment[113, 114]. In the same study, whole-body insulin resistance was reduced by 45% following 3 weeks of SFB feeding (Figure 2.2)[113, 114].

**2.3.5.3 Soluble Dietary Fiber Blend and Appetite Regulation**

It was hypothesized that the >40% reduction of insulin resistance following a 3-week consumption of SFB may have a role in appetite suppression. Therefore, a post-study analysis was conducted on the effects of SFB on markers of appetite regulation and anthropometric measurements.

Between week-0 and week-3 an increase in self reported satiety and reduction of body fat from 34.2±2% to 31.4±3%, $p<0.05$ were found in a post hoc analysis. Subsequently, post-ingestive (pre-absorptive) signals were measured in a group of 11 type 2 diabetic individuals for 4 hours following a standard breakfast control and then again after the same breakfast supplemented with SFB.

Since SFB has indicated promising results in preliminary investigations of insulin resistance and appetite regulation, the current research will investigate the effect of the fiber blend on glucose, insulin, satiety and food intake and attempt to elucidate the potential role of mechanical and metabolic parameters affected by its supplementation. SFB may represent an ideal agent for examining and/or treating the diverse etiology of obesity and the constellation of risk factors for obesity-related chronic diseases, such as type 2 diabetes mellitus. If addition of small quantities of a highly viscous blend are able to achieve significant risk-factor reduction, SFB could be added to the diet to impart similar benefits at current North American intake amounts so that individuals would not have to make drastic increases in amounts of dietary fiber consumed.

# RATIONALE, OBJECTIVES AND HYPOTHESES

## 2.4 RATIONALE

Dietary fiber may affect appetite through a combination of mechanical and metabolic mechanisms. For instance, it may augment the abilities of individual nutrients to control hunger and fullness by slowing gastrointestinal transit and increasing the opportunity for nutrients to trigger gut hormones for a longer period of time.

Despite promising findings, the literature provides inconsistent results on the effects of soluble dietary fibers on appetite, food intake and the physiological mechanisms that control these parameters. These inconsistencies may be due to differences in the fibers studied. Small differences may have an impact on the outcomes being measured. For instance, differences in particle size may affect the rate at which dietary fibers with viscous properties solubilize in water and form viscous gels. Small particle sizes, compared to large particles have greater surface area that can come into contact with surrounding fluids and form gels and viscosity more quickly. Gels made from smaller particle sizes could potentially trap coingested nutrients faster and lead to a slower transit through the gastrointestinal tract and greater opportunity for those nutrients to influence the mechanisms that control hunger and food intake. If particle size is not accounted for in studies investigating the effects of viscous fibers on appetite and food intake, there may be great variation in findings in the literature due to differences in fiber properties, not due to type of fiber.

Dose is another property that has been previously investigated. Given the reluctance of the population to increase dietary fiber intake, finding a dose of dietary fiber that confers the greatest reduction in postprandial glucose, insulin and maximizes the hormones responsible for appetite and food intake regulation is crucial. Previous studies have found that greater doses of dietary fiber lead to greater effects, such as glycemic response, however a threshold exists, beyond which greater doses do not lead to greater effects. When the chemical properties of dietary fibers are considered the dose required to meet this threshold may be reduced. For instance, a combination of dietary fibers could be used that act synergistically to develop into a viscous gel. If the combination of these dietary fibers leads to a more viscous gel than individual fibers alone, perhaps the amount of this fiber that is recommended for the population to consume for health benefits could be reduced to a more acceptable amount.

To date, there have been no studies that have examined the effects of various particle sizes of viscous soluble dietary fibers on glucose, insulin and appetite regulation. In addition, although dose-response effect has been investigated, the effects of a synergistic blend of viscous fibers on the parameters of glucose, insulin and appetite regulation have not. The investigation of both chemical and gravimetric properties of fibers on these parameters is the first step in determining their impact on appetite and food intake and eventually long-term weight regulation using pre-established methodology in this area. Controlling for variability in studies of fibers is of great importance given that research involving appetite and food intake includes so many extraneous sources of variability, such as psychological factors, cues and belief that may confound findings. A more thorough knowledge of these characteristics may allow previous findings in the literature to be better interpreted and future findings to be more comparable.

In this research, four randomized control trials were conducted on a synergistic blend of highly viscous dietary fibers, including glucomannan, xanthan and alginate. The first study investigated the effects of 4 different particle sizes of the most viscous fiber in the blend on glucose, insulin and appetite while the second study used the most efficacious particle size from the first study to examine the whether there was a dose-response effect. Following these two studies, a study designed using pre-established preload methodology was conducted to explore the effects of the blend on subjective appetite and food intake. A fourth study further explored related physiological mechanisms.

These studies are a step towards elucidating the characteristics of fiber that must be controlled as science approaches a greater understanding of the use of soluble dietary fiber for the reduction of risk factors for chronic diseases.

## 2.5 OBJECTIVES

The overall objective of the current research was to assess the role of physicochemical and gravimetric properties of SFB on appetite and food intake regulation and to elucidate the related mechanisms of action. More specifically, each of the following 4 studies was designed to address a different aspect of this objective.

**Study 1**: To determine the most efficacious particle size in a constituent of SFB to affect postprandial glucose, insulin and appetite regulation.

**Study 2:** Using the most effective particle size from study 1, to determine the most effective dose of SFB in glucose and appetite regulation.

**Study 3**: To explore the effects of various viscosities of SFB on subjective and objective appetite and food intake using pre-established preload methodology in healthy participants.

**Study 4:** To elucidate the mechanisms of action responsible for appetite and/or intake regulation, such as the metabolic parameters of appetite regulation, namely glucose and insulin and how they relate to gastric emptying time, subjective appetite ratings and the objective appetite indicator of food intake.

## 2.6 HYPOTHESES

The general hypothesis of this research was that consumption of the SFB, as compared to a non-viscous dietary fiber alone, would elicit greater metabolic, mechanical and subjective and objective indicators of appetite regulation and that physicochemical and gravimetric properties would both affect metabolic responses, satiety and food intake.

**Study 1**: It was hypothesized that the smallest particle size of the glucomannan fiber in the blend would lead to more blunted and sustained glucose and insulin responses and lead to reductions in appetite ratings compared to larger particle sizes.

**Study 2:** It was hypothesized that plasma glucose response would be lower after the greater doses of the SFB and that lower postprandial plasma glucose would be inversely correlated with postprandial satiety.

**Study 3:** It was hypothesized that the preload containing the highest viscosity would lead to a reduction in food intake and an increase in satiety ratings compared to the preload containing either glucomannan alone or cellulose.

**Study 4:** It was hypothesized that subjective and objective indicators of satiety would be greater after consumption of soluble fiber blend (SFB), and would be correlated with a combination of metabolic and mechanical parameters and that SFB consumption would elicit slower gastric emptying time. In addition, it was hypothesized that delayed gastric emptying, and transit times would correlate with subjective and objective scores of satiety and with postprandial concentrations of gut peptides, glucose, and insulin.

# **CHAPTER 3:** INVESTIGATION OF THE EFFECT OF FIBER PARTICLE SIZE ON GLUCOSE, INSULIN AND APPETITE REGULATION

## 3.1 ABSTRACT

**Background**: Both inter and intra-fiber variations in soluble dietary fibers exist and must be considered when evaluating physiological responses. To date, physical characteristics, such as particle size of soluble dietary fibers have not been examined. Knowledge of particle size, which affects the degree and speed of viscosity and gel development, could contribute to more consistent rheological properties and physiological results and more comparable interpretation of studies in the literature. **Objective**: To determine the most efficacious particle size in a constituent of SFB to affect postprandial glycemic, insulinemic and appetite regulation. **Design**: The effects of preload breakfast drinks (Glucodex plus either: gelatin control, large (mesh size: 40-80), medium (mesh size: 80-120), small (mesh size: 120-250) or mixed particle size on postprandial glucose, insulin and appetite were examined in an acute, randomized, crossover study design. Appetite, plasma glucose and serum insulin were analyzed at time points 0, 15, 30, 45, 60, 90, 120, 150 and 180 minutes. **Results**: In N=15 (11 female) healthy individuals (29.5 ± 2.3yrs, BMI: 22.1 ± 0.8 $kg/m^2$), plasma glucose was higher ($p<0.022$) in control compared to large, and small particle size at 30 and 45min. At 150min absolute glucose was lower in control compared to large and small particles. Incremental glucose area under the curve (iAUC) was lower ($p=0.005$) after the large (199.6±23.1 min.mmol/l) compared to control (256.9±35.3 min.mmol/l; $p=0.005$) and medium particle size (257.7±45.6 min.mmol/l; $p=0.003$). Incremental insulin response was higher ($p=0.0001$) in control (315.2±63pmol/L) compared to all particle sizes at 30 min but was higher ($p=0.012$) only compared to small particle size at 45 minutes and higher ($p=0.045$) than medium and small particle sizes at 60 minutes. Incremental area under the insulin curve was significantly higher ($p=0.0001$) in the control compared to all particle sizes. Satiety was higher after large particle size compared to control at 150 minutes. **Conclusion**: These results demonstrate that the glucose AUC was lowest with the largest particle size in the SFB, illustrating the importance of identifying the particle size and other physical properties of soluble dietary fibers before examining their physiological responses.

## 3.2 INTRODUCTION

There is strong evidence to support that viscous fibers affect postprandial glucose, insulin, appetite and various related metabolic and mechanistic mechanisms. Despite this evidence, studies do not always show consistent results; possibly due to inherent physico-chemical variations between (inter-fiber variability) and within (intra-fiber variability) the fibers used.

The concept of inter-fiber variability was first demonstrated in a study by Jenkins et al. in 1978 [94]. In this study a comparison of a 6 different dietary fiber and fiber analogs (guar, pectin, wheat bran, gum tragacanth, cholestyramine and methylcellulose) with different viscosities but similar quantities was consumed. The study found that postprandial glucose and insulin responses were lower with highly viscous fibers compared to low-viscosity fibers[94], identifying the need to control for fiber type and viscosity so that studies across the literature could be more comparable. Therefore, due to inter-fiber variability, standardization of viscosity of fiber may be as critical as the quantity of fiber used and evaluation of the physiological responses to dietary fiber on a strictly quantitative (gravimetric) basis may be limited.

In an unpublished study by Vuksan, 10 healthy participants consumed 3 different fibers; xanthan, glucomannan and psyllium. Although the quantities of each of these fibers were not matched, the viscosities were matched. The study found that standardized viscosity of different fibers lead to equivalent postprandial glucose AUC. This study further supports the concept that rheological properties must be considered in future studies. Furthermore, variations in viscosity can also occur within the same type of fiber when samples from different batches are used (intra-fiber variability). In another unpublished study from Vuksan et al., the viscosities of various fiber types and batches were examined. As expected, there were differences in viscosity among different fiber types. In addition, however variation in viscosity existed between different batches of the same fiber type (glucomannan).

These study results suggests that both inter and intra-fiber variations exist and must be considered when making meaningful conclusions from physiological study results.

In the presence of fluids, some fibers form very viscous gels and some form looser gels. Physico-chemical properties that affect the degree of viscosity are related to the fiber: side chain solubility, pH,

interaction with impurities or other fibers in a mixture and fiber structure (e.g. particle size). Alterations in physical structure, such as the size of the molecule, can occur during processing and can impact the intra- or intermolecular actions of fibers that lead to viscosity development and the subsequent physiological response. It is thought that since smaller fiber particles have greater surface area than larger particles, they will go into solution with fluid molecules more readily than larger particles. Faster solubilization and greater dispersion, in turn, may lead to the development of viscosity and formation of gels more quickly. For example, by processing oat hull fiber into discrete fiber strands, the surface area is enhanced and the water holding capacity and speed at which the smaller particles are dissolved (i.e. more rapidly) of the fiber is increased [177].

Currently, there is little evidence in the literature to demonstrate the role of soluble fiber particle size on glycemic and insulinemic responses. It is suggested that full physiological impact requires soluble dietary fibers to enter the alimentary system dissolved or in form that will dissolve during digestion [177], however the specific physical characteristics, such as particle size have not been examined. Therefore, knowledge of particle size, which affects the degree and speed of viscosity and gel development, could contribute to more consistent rheological properties (e.g. viscosity and hydration rate), more consistent biological results and more comparable interpretation of results of studies in the literature. In addition, awareness of fiber physico-chemical properties and the effects of modification of these properties on physiological response may make it possible to predict the physiological actions of various dietary fibers and foods containing them.

This study was designed to determine the effect of various soluble fibre particle sizes on postprandial appetite, glucose and insulin.

## 3.3 SUBJECTS AND METHODS

### 3.3.1 SUBJECTS

Healthy participants were recruited by an advertisement posted at the University of Toronto. Information sessions were provided for individuals interested in participating in the research. A detailed questionnaire regarding medical history, drug, medication and supplement use, smoking, alcohol, exercise and diet patterns was used for screening purposes. Fifteen healthy individuals (11 female, age 29.5 ±

2.3years, BMI: 22.1 ± 0.8 kg/m$^2$) who met inclusion/exclusion criteria (Appendix 2) were recruited and completed the study.

Power analysis indicated that in order to detect a difference of 33mmol/l.min for glucose iAUC with a power of 90% and alpha level of 0.05, 17 participants were required to participate in the study[178].

Informed consent was obtained from all participants. The study was approved by the Research Ethics Board at St. Michael's Hospital.

### 3.3.2 TEST MEALS

Four different particle sizes of glucomannan were assessed: large (mesh size: 40-80), medium (mesh size: 80-120), small (mesh size:120-250) and mixed particle sizes. Xanthan gum (Sigma. Aldrich Corporation, St. Louis, MO) was mixed with the glucomannan in order to achieve a synergistic effect that would lead to a maximized viscosity for physiological response.

The control treatment consisted of 3 grams of gelatin (Knox Gelatin, NBTY, Inc., Kraft). The test treatments were a soluble fiber blend of glucomannan (GM) and xanthan. The GM particle size differed for each treatment and was either: large (Fiber Tech Co. Gyeonggi, Korea); medium (ChongQuin Foreign Trade IMP&EXP corp., Chong Qing, China); small (Fiber Tech Co. Gyeonggi, Korea) or mixed (Opta RS Propol; Opta Food Ingredients Corporation, Chicago). Xanthan source and mesh size was constant (Sigma. Aldrich corporation, St. Louis, MO). The total carbohydrate content of the control was matched with the SFB treatments. Control and test fibers (granulated form) were mixed into 200 ml of Glucodex® to prevent lumps and consumed. Following consumption, 100-200 ml of tap water (same volume for each test) was consumed. Nutrient profile of breakfast is detailed in Table 3.1.

### 3.3.3 STUDY DESIGN

Participants were asked to arrive at The Risk Factor Modification Center after a 10-14 hour overnight fast on five separate occasions. A minimum 1 day washout period separated each visit to minimize carryover effects. Participants were instructed to maintain the same dietary and exercise patterns the evening before each test and consume a minimum of 150 g of carbohydrate each day over the three days prior to the test. To ensure instructions were followed, participants were provided with examples of what constitutes 150g of carbohydrate and complete a questionnaire detailing pre-session

information about their diet and lifestyle patterns. Upon commencement of the test, subjects' body weight was assessed and a catheter was inserted into a forearm vein secured by tape and kept patent by saline. From this device a 7ml blood sample was obtained in a tube containing fluoride oxalate. A registered intravenous (IV) nurse performed blood collections. The first sample represented zero (fasting). One of the 5 dietary treatments was randomly selected using computer generated random numbers and administered at each of the 5 study visits. The 50g Glucodex® challenge was used as a source of nutrient given with the test or control fiber (Table 3.1). After the fasting blood sample was taken, one of the treatments was consumed (in random order) over 5-10 minutes. Additional blood samples were drawn at 15, 30, 45, 60, 90, 120, 150 and 180 minutes (Figure 3.1). During the test, participants indicated on the testing questionnaire whether they experienced any adverse symptoms, including: bloating, belching, nausea, headache, diarrhea, flatulence, hyperurination. The symptoms were rated using a 7-point Likert scale (Appendix 1). Palatability of test meals was assessed during the study; participants were asked to rate each of the test foods on a scale ranging from "extremely dislike" to "delicious" (Appendix 1).

### 3.3.4 LABORATORY ANALYSES

#### 3.3.4.1 Glucose

Blood samples were taken in 7ml grey top BD Vacutainer® Fluoride Tubes containing potassium oxalate and sodium fluoride additives for glycolytic inhibition. Tubes were centrifuged at 2000 rpm for 15 minutes and the plasma was divided into 3 aliquoits of 500-750µl each. Aliquoits were sent to the Banting and Best Laboratory for glucose and insulin analysis. Total blood taken per participant was 224ml. Plasma glucose was analyzed using glucose oxidase method and a Cobas Inegra Analyser (Roche Diagnositcs). The interassay coefficients of variation for this test were 3.5% and 1.7% at 4.0mmol/l and 15.5mmol/l, respectively.

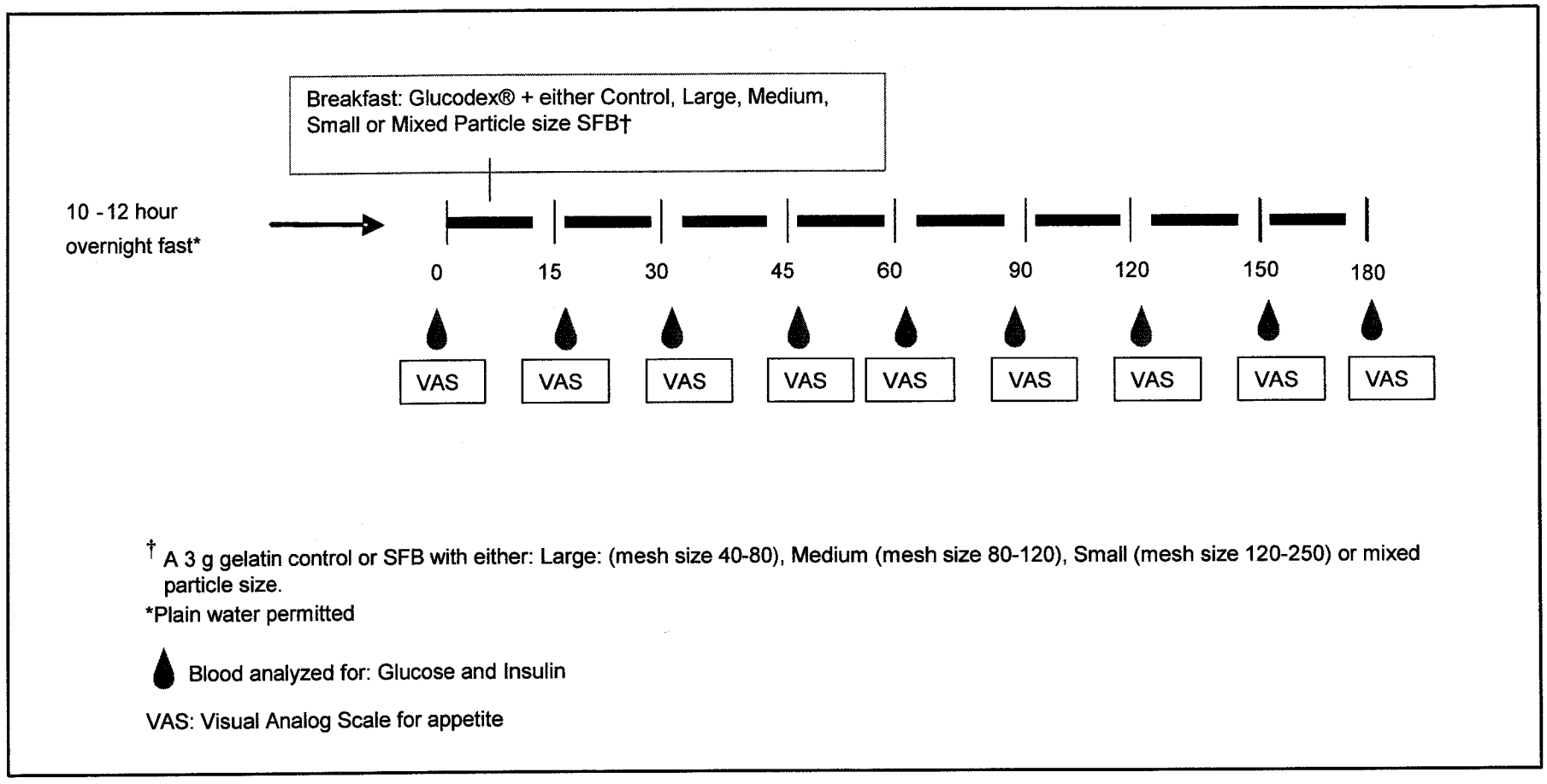



Figure 3.1. Study Day Protocol

The effects of preload breakfast drinks on postprandial glucose, insulin and appetite were examined in an acute, randomized, crossover study design in healthy participants. Breakfast drinks were180ml of Glucodex® plus either control (3g of gelatin) or granulated fiber with various particle sizes (large: 40-80; medium: 80-120; small: 120-250 or mixed). Participants were instructed to consume drinks within 5 minutes. Appetite, symptoms, plasma glucose and serum insulin were analyzed at time points 0, 15, 30, 45, 60, 90, 120, 150 and 180 minutes. Time "0" represents the fasting time point.

**TABLE 3.1. NUTRIENT PROFILE OF PRELOAD TREATMENTS**

The nutrient profiles of preload treatments (200ml Glucodex®) with either 3g of gelatin added as control or test treatments of granulated soluble fiber blend (SFB). The particle size of the glucomannan in the SFB was either: large (mesh size 40-80), medium (mesh size 80-120), small (mesh size 120-250) or mixed. These preload treatments were given fasting and serum glucose and insulin and satiety ratings were assessed for 180 minutes after.

| Nutrient | Control | Large | Medium | Small | Mix |
|---|---|---|---|---|---|
| Energy (kcal) | 209.9 | 200.0 | 200.0 | 200.0 | 200.0 |
| Protein (g) | 2.6 | 0.0 | 0.0 | 0.0 | 0.0 |
| Fat (g) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Carbohydrate (g) | 50.0 | 50.0 | 50.0 | 50.0 | 50.0 |
| Fiber (g) | 0.0 | 3.0 | 3.0 | 3.0 | 3.0 |

**TABLE 3.2. PRELOAD CONSUMPTION TIMES AMONG TREATMENTS**

Preloads were provided fasting and consisted of 200ml of Glucodex® plus control (3g gelatin) or a granulated soluble fiber blend (SFB), of which the glucomannan particle size was varied to be either: large, medium, small or mixed. Participants were provided with timers and instructed to consume the drink within 5 minutes.

| Treatment | Meal Consumption Time (minutes) |
|---|---|
| Control | 4.88 ± 0.1 |
| Large | 4.74 ± 0.1 |
| Medium | 4.91 ± 0.1 |
| Small | 4.87 ± 0.1 |
| Mix | 4.94 ± 0.1 |

Values represent means ± SEM

#### 3.3.4.2 Insulin

Samples were analyzed for insulin using a double antibody radioimmunoassay (Livesey et al., 1980), where insulin competes with a fixed amount of 121-labeled insulin for the binding sites on the specific antibodies. Bound and free insulin are separated by addition of a second antibody immunoadsorbent followed by centrifugation and decanting. The radioactivity in the pellet is then measured. The radioactivity is inversely proportional to the quantity of insulin in the sample. The interassay coefficients of variation for the method at different levels were 7.2, 6.6 and 8.8% at insulin concentrations of 72, 316 and 753pmol/l respectively. The lower detection limit of the assay was 22pmol/l.

#### 3.3.4.3 Satiety Symptom and Ratings

Satiety was assessed using a 7-point equilateral category Likert scale rating system of -3 to +3 at each time point[179, 180]. Participants were instructed to rate satiety as "extremely hungry" (-3) or "uncomfortably full" (+3) at each time point corresponding with a blood collection. Symptoms were identified using a 7 point scale in which participants rated the presence of bloating, belching, nausea, headache, diarrhea, flatulence, hyperurination as "yes" or "no" and the severity on a 7 point scale, where 1 = "low" and 7 = "high"(Appendix 1).

### 3.3.5 STATISTICAL ANALYSIS

Statistical analyses were performed using the Statistical Software for the Social Sciences (SPSS Inc, Version 15.0 for Windows, Chicago, Ill). A Linear Mixed Models design was used with treatment and time as repeated measures to determine the interactive and independent effects of treatment and measurement time on parameters measured over time. If the interaction terms were significant, then pairwise comparisons between treatments were performed at each time point using the Sidak post hoc test. Data points for insulin and glucose that were considered outliers (± 2 standard deviations) were removed prior to analyses. All results are expressed as mean ± SEM, unless stated otherwise. Differences between means were considered statistically significant if $p<0.05$. Curves were plotted as the absolute values, incremental change over time and the positive incremental area under each curve (iAUC) was calculated geometrically for each participant, ignoring areas below the fasting value.[44, 181]

Incremental values were used so that baseline/fasting difference among treatments were controlled for and values at future time points could be compared.

## 3.4 RESULTS

All participants followed the study protocol safely and completed all treatments without difficulty. According to the questionnaires, the evening activities and morning events prior to test sessions did not deviate from their usual lifestyle pattern. Neither body weight (data not shown) nor meal consumption time (Table 3.2) differed significantly among the treatments.

### 3.4.1 SYMPTOMS

Mean symptom ratings were reported to be low in magnitude. There were no significant differences among treatments for bloating, belching, nausea, headache, diarrhea, flatulence, hyperurination (Appendix 2).

### 3.4.2 LABORATORY ANALYSES

#### 3.4.2.1 Glucose

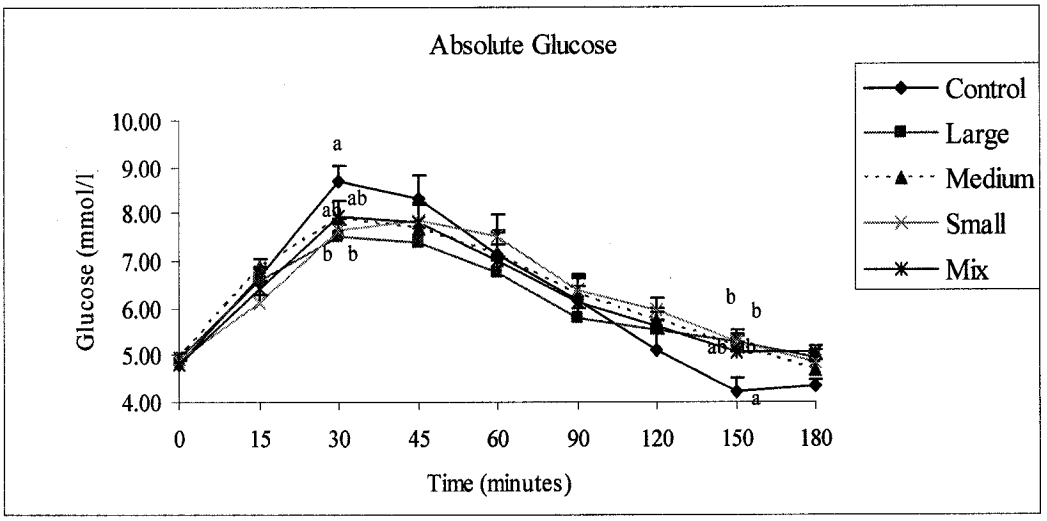
After 30 minutes there was a significantly higher blood glucose response in control (8.7±0.3 mmol/l) compared to large (7.5±0.3 mmol/l; p=0.006) and small particle size (7.6±0.3 mmol/l p=0.022). At 150 minutes there was a significantly lower absolute blood glucose response in control (4.2 ± 0.3 mmol/L) compared to large (5.3 ± 0.2 mmol/l p=0.022) and compared to small (5.3 ± 0.2 mmol/l; p=0.024). Similarly, after 30 minutes there was a significantly lower (p=0.001) incremental glucose response in large (2.5 ± 0.3 mmol/l) and small particle size (2.7±0.4 mmol/l; p=0.005) compared to control (3.9 ± 0.3 mmol/l). After 45 minutes there was also a significantly lower (p=0.016) incremental glucose response after large particle size (2.4 ± 0.3 mmol/l) compared to control (3.5 ± 0.6 mmol/l). Incremental glucose area under the curve (iAUC) was significantly lower (p=0.005) after the large particle size (199.6±23.1 min.mmol/l) compared to control (256.9±35.3 min.mmol/l; p=0.005) and compared to medium particle size (257.7±45.6 min.mmol/l; p=0.003) (Figure 3.2).

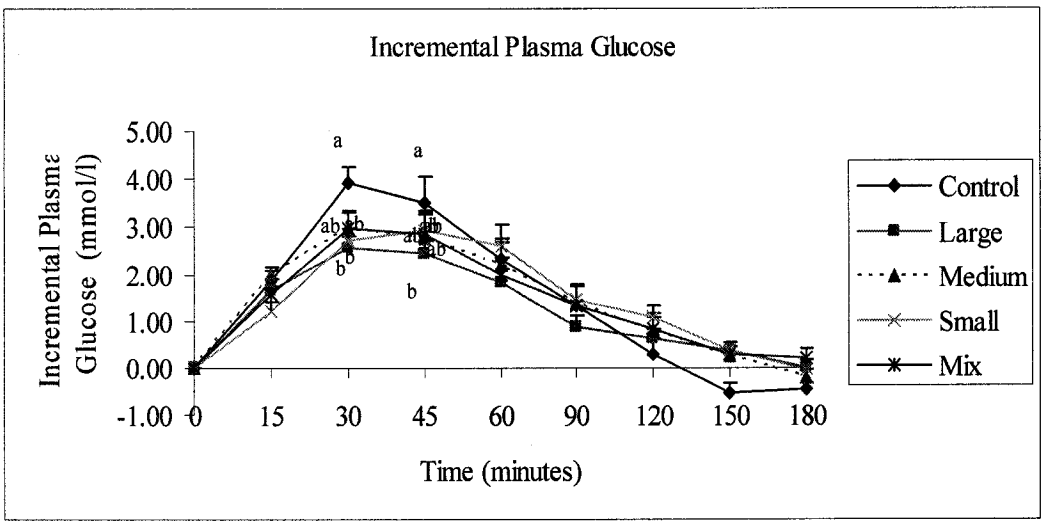
### 3.4.2.2 Insulin

After 30 minutes there was a significantly higher serum insulin response from control (361.5 ± 64.3pmol/l) compared to the large (212.3 ± 24.6; pmol/l; p=0.0001), the medium (230.5 ± 32.4pmol/l p=0.0001), the small (176.4± 17.3pmol/l; p=0.0001) and to the mix of particle sizes (254.9±33.6pmol/l; p=0.001). At 45 minutes there was also a significantly higher serum insulin response in control (264.6 ± 49.2 pmol/l) compared to large (187.4 ± 20.4 pmol/l; p=0.0.046), medium (183.5 ± 23.3 pmol/l; p=0.034), small (171.3 ± 14.9 pmol/l; p=0.0.008) and mixed particle size (188.1 ± 20.0 pmol/l; p=0.050). Similarly, at 60 minutes there was a significantly higher serum insulin response in control (239.0 ± 43.7pmol/l) compared to large (162.2 ± 19.1 pmol/l; p=0.048), medium (160.8 ± 30.5 pmol/l; p=0.041) and small particle sizes (146.8 ± 14.5 pmol/l; p=0.007). Incremental insulin response was similar to absolute insulin response. After 30 minutes there was a significantly higher serum incremental insulin response from the control meal (315.2 ± 63.0 pmol/l) compared to the large (169.8 ± 22.8; p=0.0001), the medium (189.2 ± 33.0; p=0.0001) the small (134.8 ± 16.1 p=0.0001) and to the mixed particle size (209.0 ± 33.2 pmol/l; p=0.001). At 45 minutes there was also a significantly higher incremental serum insulin response in control (219.0 ± 27.8 pmol/l) compared to small particle size (129.6 ± 13.9 pmol/l; p=0.012) but not compared to the larger particle sizes. At 60 minutes there was a significantly higher incremental serum insulin response in control (193.4 ± 43.1 pmol/l) compared to medium (115.0 ± 31.9 pmol/l; p=0.045) and to small particle size (104.2 ± 13.7 pmol/l; p=0.011) but not compared to large particle size or mixed particle size. Incremental area under the curve was significantly higher (p=0.0001) in the control (19130.5 ± 3834.0 min.pmol/l) compared to large (12960.5 ± 1528.8 min.pmol/l), medium (12486.5 ± 2158.8 min.pmol/l), small (13119.6± 1803.8 min.pmol/l), and mixed particle size (12160.3 ± 1634.1 min.pmol/l) (Figure 3.3).

### 3.4.2.3 Satiety

There was a greater (p=0.04) rating of satiety with larger particle size (-0.27 ± 0.25cm) compared to control (-1.08 ± 0.34 cm) at 150 minutes (Figure 3.4).



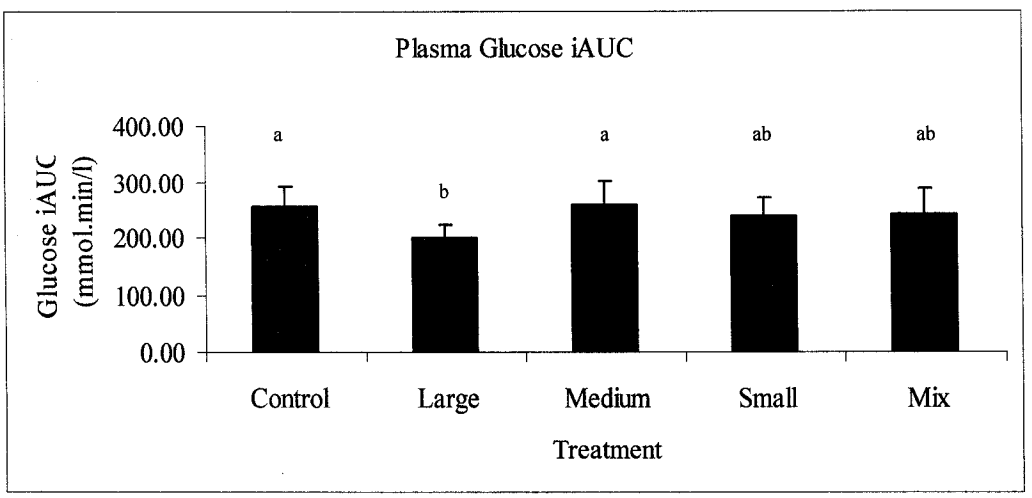




Figure 3.2. Plasma Glucose

Plasma glucose was collected from the antecubital vein at a fasting time point (0 minutes) and every 15-30 minutes after the study treatment was consumed. Study treatments were Glucodex plus either Control (3g of gelatin) or granulated fiber blend with glucomannan particle sizes of either large(40-80 mesh), medium (80-120), small (120-250) or mixed.

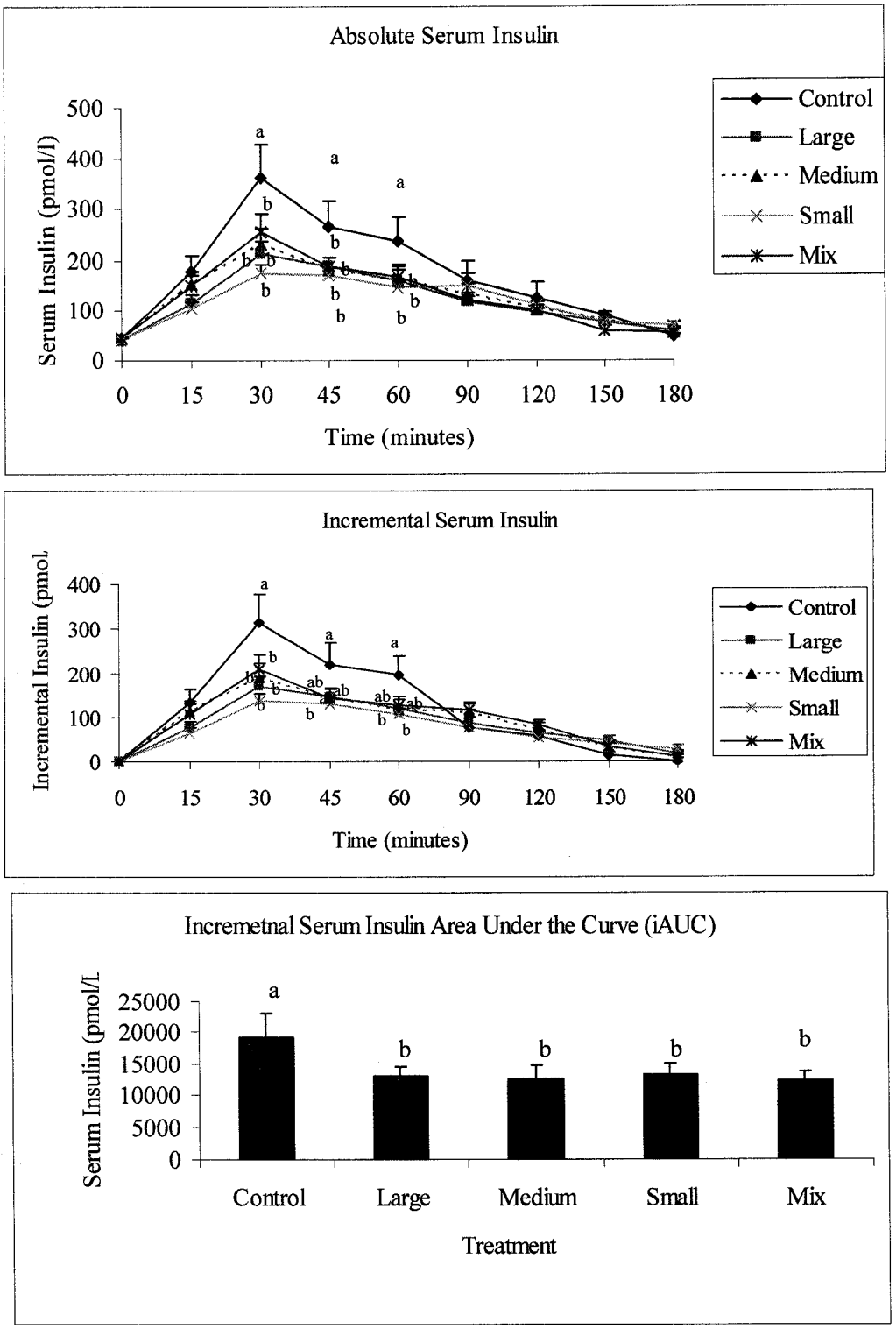
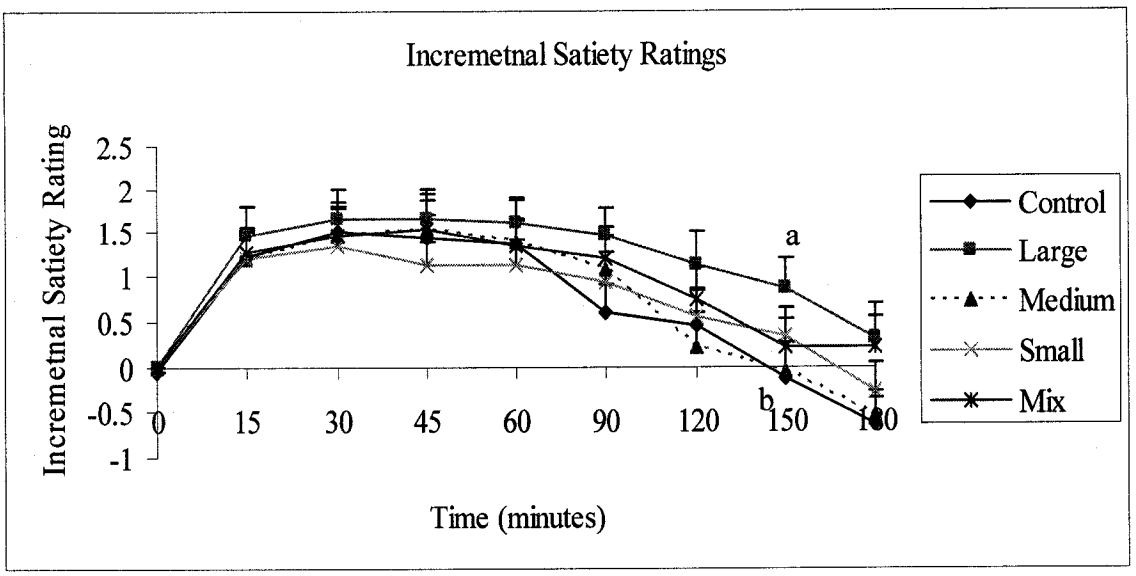



Figure 3.3. Serum Insulin
Serum insulin was collected from the antecubital vein at a fasting time point (0 minutes) and every 15-30 minutes after the study treatment was consumed. Study treatments were Glucodex plus either control (3g of gelatin) or granulated fiber blend with glucomannan particle sizes of either large (40-80 mesh), medium (80-120), small (120-250) or mixed.



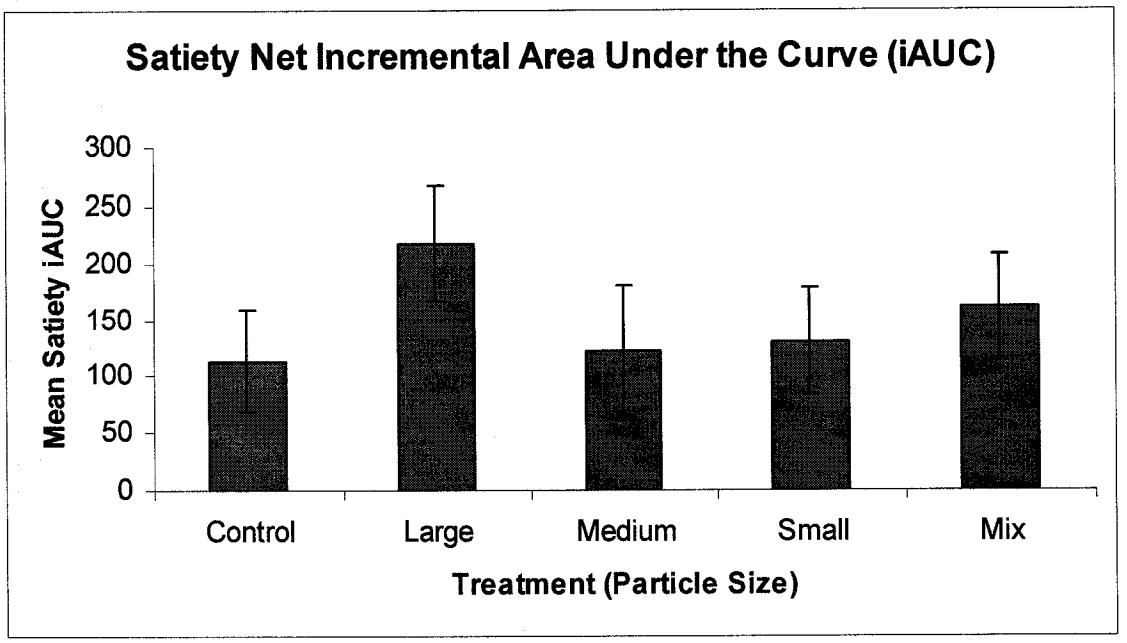




Figure 3.4 Satiety

Satiety ratings were assessed using a Likert scale at a fasting time point (0 minutes) and every 15-30 minutes after the study treatment was consumed. Study treatments were Glucodex® plus either control (3g of gelatin) or granulated fiber blend with glucomannan particle sizes of either large (40-80 mesh), medium (80-120), small (120-250) or mixed.

## 3.5 DISCUSSION

The objective of the current study was to determine the effect of dietary fiber particle size on glucose, insulin and appetite ratings. It was hypothesized that smallest fiber particle size would lead to a faster forming gel and, in turn, more blunted glycemic, insulinemic and appetite responses. This hypothesis was based on the theory that the greater surface area of smaller particles would have increased contact with fluid, allowing greater hydration and faster gelling in the gastrointestinal tract. This would result in slower digestion and absorption of coingested, entrapped nutrients, which would then appear in the blood at slower rates compared to nutrients that are digested and absorbed into the blood quickly.

Contrary to this hypothesis, the results from this study demonstrate that consumption of the largest particle size leads to the lowest postprandial glycemic response at 30 and 45 minutes compared to control and other mesh sizes and to a similar response to the smallest particle size at 30 minutes. The large particle size lead to a lower glucose incremental area under the curve compared to medium and control but not compared to small and mixed particle size. Insulin incremental area under the curve was lower after all particle sizes compared control, however no differences existed among particle sizes.

Despite the hypothesis of this study, there is a contrary theory supported by literature of food particle size and insoluble fibers. For instance larger food particles have been shown to result in reduced digestion, absorption and glycemic and insulinemic responses[182-185]. In this theory, it is reasoned that since large food particles have less surface area, there is a reduced ability of enzymes, such as amylase, to contact the interior of the food particle. For instance, in a study where participants swallowed rice, maize, apple or lumps of potato without chewing, the glycemic response was lower than when it was chewed[185], supporting that larger food size may not facilitate access of amylase enzymes to the starch with a higher surface area:volume ratio. A study of obese individuals with ileostomies by O'Donnell et al (1989) demonstrated similar findings: coarse, whole-meal flour lead to lower glucose and insulin responses compared to fine ground flour [184]. In a further study where rice was ground into flour and compared to whole grains, it was found that whole grains evoked lower glycemic and insulinemic responses [183]. Although these studies examined whole food particle sizes, which are different than fiber particle size, they suggest a theory that may be further explored using dietary fiber particle size.

Few studies have examined the effects of soluble dietary fiber particle size on digestion and absorption markers. A study by Heaton et al. (1988), examined whole grains, cracked grains, coarse flour and fine flour of wheat, maize and oats and found that glucose peak-to-nadir swing was greater with flour (smaller particle sizes) than cracked or whole grains (larger particle sizes) [182]. Peak plasma insulin responses (peak concentration and AUC) increased stepwise, respectively, with wheat and maize only but were similar with whole grain oats, rolled oats and fine oatmeal. Despite the differences between wheat, maize and oats in vivo, in vitro starch hydrolysis by pancreatic amylase was faster with decreasing particle size with all three cereals (wheat, maize and oats). This study suggests that particle size may affect digestion rate and metabolism in wheat and maize, but only for in vitro digestion and not in vivo metabolism in oats, which are soluble fibers. The authors suggest that viscous properties of the soluble β-d-glucan in oats strongly influence digestion or absorption in vivo that was inoperative in vitro. The viscosity, they postulate, may lead to a greater viscosity in the intestinal lumen which would reduce the diffusion of amylase to starch or glucose and maltose towards the mucosa. They also suggest that these effects would have been greater in vivo compared to in vitro, since there is greater constant mechanical shaking in vivo. They further point out that the oats evoked a smaller glucose and insulin response compared to wheat and maize in vivo even though the maize and wheat was digested in vitro at equal speeds, supporting that the viscous fiber in oats may limit the rate of digestion and/or absorption in vivo.

Despite these findings demonstrating differences in soluble fiber particle size on digestion in vitro, other studies show that particle size of soluble fiber does not lead to different responses. Behall et al (2005) compared barley and oats in flour vs. flake and found that the soluble fiber content alone had more effect on glycemic response than did particle size [186].

Therefore, although there is compelling evidence that food size, specifically insoluble fiber particle size has an inverse relationship with glycemic and insulinemic responses, there is scarce evidence to demonstrate the role of particle size in soluble fibers on these physiological responses. The findings from this study are the first to suggest that soluble fiber with large particle size can lead to lower postprandial glucose response.

The results of the present study do not demonstrate a graded response of satiety, glucose and insulin to fiber particle size. The medium particle size reduced glycemic response to a greater extent than the smallest particle size and the largest particle size only differed compared to control and medium, not smallest particle size. Perhaps the dose of the fiber used was not great enough to show differences between medium and small particle sizes. Alternatively, larger differences in particle size than the ones in the current study may be needed to demonstrate variations. These results are clinically important, since recommendations based on particle size need to be consistent and graded. Further investigations into a dose-response and gradations of particle size are warranted to reveal any differences that may be evident in vitro.

Satiety was greater in the present study with larger particle size compared to control at 150 minutes. At this time point there was also a significant difference in serum glucose between large particle size and control. This is likely due to greater remainder of serum glucose with the larger particle size compared to the compensatory fall below baseline with control leading to a reduction in the hunger experienced at that time point. These findings support the glucostatic theory. There was also a trend toward the largest particle size leading to the greatest satiety. This trend was initiated by a divergence between the largest particle size and control after 60 minutes, where the differences in glucose and insulin occurred. It is possible that the lower glucose response in the large particle size leads to more stable serum glucose levels, precluding the need for increased insulin and further resulting in less hunger. Because this study was not designed as a satiety study, these trends should not be over-interpreted, however the trend provides a rationale for future investigations of the effects of this particle size on appetite and food intake.

This study supports that there is a need to standardize the physico-chemical characteristics of soluble dietary fiber prior to investigating their effects on physiological outcomes. Inconsistent findings in the literature may be due to discrepancies in these and other characteristics, such as batch variations. Once materials are standardized, the results of the literature may potentially be used to predict biological effectiveness of various species of dietary fibers and allow the development of the most efficacious fiber

products possible for health benefits, such as glycemic control and satiety for weight loss and for knowledge of structure-function relationship for regulatory evaluation.

In conclusion, this study is the first to demonstrate that there is a negative relationship between particle size and postprandial glycemic response in a blend of soluble dietary fibers. Future studies are required to examine the magnitude of differences in particle size required for maximal reduction in glucose and insulin and whether various particle sizes mix more thoroughly with preload meals. In addition, future investigation of the most appropriate dose of soluble fiber at each particle size would be relevant for planning examination of viscous dietary fibers on appetite, satiety and food intake.

# CHAPTER 4: THE EFFECT OF DOSE OF A VISCOUS FIBER BLEND ON GLYCEMIC AND APPETITE REGULATION

## 4.1 ABSTRACT

**Background**: Confusion exists over the ideal amount of fiber necessary for maximum physiological benefits and is compounded by variations in rheological properties and viscosity of fibers investigated. The epidemic of obesity and its comorbidities makes it essential to develop a dietary fiber model in which maximum health benefits can be obtained from an acceptable dose. Maximum benefits may come from fibers with superior rheological properties, such as particle size. To date, no study has investigated the dose-response relationship between a blend of synergistic, complimentary dietary fibers with a high viscosity and physiological responses. **Objective**: To use the most effective particle size from study 1, to determine the most effective dose of SFB in glucose and appetite regulation. **Design**: The effects of preload breakfast drinks (Boost™ plus either: wheat bran control, 2, 4 or 6 grams of soluble fiber blend) on postprandial glucose and appetite were examined in an acute, randomized, crossover study design. Plasma glucose, appetite and symptom ratings were analyzed at time points 0, 15, 30, 45, 60, 90 and 120 minutes. **Results**: In N=9 (7 female) healthy individuals ( 33.4 ± 4.2 yrs; BMI: 24.4 ± 1.5 $kg/m^2$), glucose was higher ($p=0.005$) after 15 minutes in control (1.6 ± 0.3mmol/l) compared to 4g (0.5 ± 0.1mmol/l) and 6g (0.7 ± 0.3 mmol/l) but not 2g. Similarly, at 30 and 60 minute glucose was higher ($p<0.05$) after control compared to the 4g and 6g treatments. Glucose incremental area under the curve was higher after control (341.3 ± 52.2 mmol.min/l) compared to 2g (235.3 ± 33.5 mmol.min/l $p<0.0001$), 4g (197.3 ± 32.7 mmol.min/l $p< 0.0001$) and 6g (176.6 ± 33.9 mmol.min/l $p<0.0001$). There were no differences at any of the time points among groups for satiety ratings. **Conclusions**: These results suggest that an amount of SFB greater than 4.0 g may be appropriate for reducing postprandial glucose response at certain time points; however, there were no differences between 4g and 6g in glycemic response or area under the glucose curve among the 3 doses. Future studies may be required to determine whether with greater doses, greater magnitudes of differences between doses or a greater sample size lead to greater differences among physiological responses, such as glucose.

## 4.2 INTRODUCTION

The previous study demonstrated that particle size affects postprandial glycemic and insulinemic response in soluble dietary fiber. However, the most appropriate dose of soluble fiber blend at each particle size must be elucidated for use in future studies of appetite, satiety and food intake and for future clinical advice to the population.

The current national recommended daily intake of total dietary fiber (soluble and insoluble) is 25-38 grams per day[2]. These recommendations stem from evidence demonstrating widespread benefits in risk-reduction for chronic disease markers with fiber intake. In North America, individuals generally consume half the recommended adequate intake of dietary fiber per day[1, 3]. A study by Davis et al. (2006) found that overweight/obese individuals consumed more total fat and less carbohydrate, complex carbohydrate and dietary fiber than age and height-matched normal weight controls and that fiber was the only nutrient that accounted for a significant amount of the variance in percent body fat, with and without controlling for age, physical activity-related energy expenditure, sex, total energy intake and macronutrients[187]. In preload studies examining the effects of dietary fiber on appetite, the dietary fiber may reduce hunger indirectly by causing gastrointestinal distress, rather than through metabolic responses such as glucose, insulin or GI stimulation of anorexigenic hormone cascades [164]. Therefore, it is plausible that the reasons for low fiber intake in the population may be partially due to side-effects.

The health benefits from dietary fiber, however, may be dose-dependent. For instance, it has been established that the glycemic response to meals can be attenuated by the consumption of viscous dietary fibers[94, 188] and that the relationship that exists between viscosity and fiber concentration and the glycemic and insulinemic effectiveness is dose-dependent[189] and strongly inversely related to viscosity[190]. Wood et al. (1990) supported this in a study that found that increasing the dose of oat gum, successively reduced the plasma glucose and insulin responses relative to a control without gum.[191] Later, Wood et al (2000) also found a significant relationship between changes in peak blood glucose and log oat β-glucan concentration[192]. In a study by Holt et al (1992), the satiety ratings of various breakfast cereals were compared. The highest dose of fiber (26.2g of Kellogg's All-Bran) prompted stronger ratings of satiety than control with 0.0g of fiber (white bread, bacon and eggs), supporting the theory that dietary fiber can

aid in satiety [193]. These positive findings, however, may be of limited practical value since the average range of dietary fiber intake (<15g/d) consumed in the North American population may have modest efficacy.

There is, however, wide variation in fiber intake in long-term studies in the literature, ranging from 4-50g/d [194, 195]. Makelainen et al (2007) found that there is a critical level of viscous fiber β-glucan, past which an inverse, linear relationship between dose and glucose response no longer occurred [4].

Therefore, despite the abundance of data in the literature on the dose-response and viscosity implications of dietary fiber on glycemic and insulinemic responses, confusion still exists over the ideal amount of fiber necessary for maximum physiological response. This confusion is compounded by variations in rheological properties and viscosity of fibers investigated.

In light of the current epidemic rise in obesity and related comorbidities, it is essential to explore a method of increasing fiber intake in an acceptable manner so that the maximum health benefits may be achieved without discomfort. Since rapid increases in soluble dietary fiber consumption can lead to unpleasant side effects, such as bloating, gas and abdominal discomfort; making the long-term high fiber dietary regimens unattractive, a dietary fiber model in which maximum health benefits can be obtained from an acceptable dose (e.g. 5g/d) that does not elicit these symptoms may be more realistic.

One potential method of obtaining maximum benefits with a small dose is with fibers that have superior rheological properties, such as high viscosity. The viscosity of a solution that includes random coil polysaccharides, where viscosity develops from coil entanglement, is dependent on physico-chemical properties, including concentration and distribution of fiber in solution [191]. It is postulated that at higher concentrations of dietary fiber viscosity development is augmented. For instance, viscosity development is dependent on the extent to which the chain units of fiber molecules can collide and form cross-links. Fiber molecules can bind in irregular associations due to the length of molecules and physical properties. The cross-link associations occur in specific regions termed "junction zones"[196]. Junction zone formation can continue to occur among molecules until the majority of the molecules in solution are formed in a three-dimensional network. Junction zones are dependent on numerous factors, including number, type and charge of fiber side chains. Higher doses of fiber molecules increase the number of random coils that

can form since the probability of fiber chains colliding together increases. When chains of polysaccharides form junction zones, a stronger viscous gel network occurs[197]. In addition, complimentary fibers at lower doses may interact and lead to a synergistic augmentation in junction zone formation and subsequent higher viscosity. If, however, complimentary fibers could provide greater benefit at lower doses than non-complimentary fibers at higher doses, then a model may be developed to aid in a more acceptable method of fiber consumption among the population. Therefore, it is important to determine if the effect of a blend of synergistic, complimentary dietary fibers, such as those in the SFB, which have already developed into a higher viscosity than the constituent fibers alone, have any physiological benefit at lower doses.

In previous investigations, SFB provided in quantities of 6g/day (0.3g/100kcal) has lead to significant improvements in cardiovascular disease risk factors (blood pressure, lipid profile) and diabetes markers (acute and long-term glucose and insulin regulation) [113, 114, 198]. To date, however, no study has investigated the most effective dose of the SFB. Therefore, this study aimed to evaluate the dose-response of a viscous fiber blend (SFB) on postprandial plasma glucose and satiety compared to an insoluble, wheat bran (WB) control and to determine whether there is a correlation between plasma glucose response and satiety. From these findings, the most efficacious dose of the SFB will be found for use in future research.

## 4.3 SUBJECTS AND METHODS

### 4.3.1 SUBJECTS

Healthy participants were recruited from the Faculty of Medicine and students at the University of Toronto. Nine participants (7 females, age 33 ± 4 years, BMI: 24.4 ± 1.5 kg/m$^2$) that met inclusion/exclusion criteria were recruited and completed the study. Informed consent was obtained from all participants. The study was approved by the Research Ethics Board at St. Michael's Hospital.

Power analysis indicated that in order to detect a difference of 30mmol/l.min for glucose iAUC with a power of 90% and alpha level of 0.05, 10 participants were required to participate in the study[199].

### 4.3.2 TEST MEALS

Participants received 4 different treatment meals in a randomized cross-over design. The test treatments (SFB) included 2g, 4g or 6g of a mixture of a large mesh size (40-80) glucomannan (ChongQuin Foreign Trade IMP&EXP corp., Chong Qing, China) and xanthan (Sigma. Aldrich corporation, St. Louis, MO). The placebo treatment consisted of 1.2 grams of wheat bran (American Association of Cereal Chemists (AACC), St. Paul, MN). The total carbohydrate content of the wheat bran control was matched with the 4 gram SFB treatment. Control and test fibers were mixed in a granulated form into 289ml of Boost™ prior to consumption to prevent the formation of lumps. Following consumption of the Boost™/fiber mix, 100-200 ml of tap water (the same volume of water for each test) was consumed. Nutrient profile of breakfast meals (Boost™) plus treatments is detailed in Table 4.1.

**4.3.3 STUDY DESIGN**

Participants attended The Risk Factor Modification Centre at St. Michael's Hospital, Toronto, on 4 separate mornings following a 10-12 hour overnight fast. A minimum 1 day washout period separated each visit to minimize carry-over effects. Participants were instructed to maintain the same dietary and exercise patterns the evening before each test and to consume a minimum of 150g of CHO each day over the 3 days prior to test (e.g. 3 servings of any of the following -2 slices of bread, 1 cup of cooked rice or pasta, 1 medium potato, 1 bowl of cereal w/ milk, 1 glass of juice/soft-drink, 3 oranges/apples, or 1 bowl of ice cream). To ensure that these instructions were followed, participants completed a questionnaire detailing pre-session information about their diet and lifestyle patterns. Before the beginning of each test, subjects' body weights were assessed using a beam scale. Each subject gave approximately 250 µl of a fasting finger-prick capillary blood sample, using a lancet (Monoject Lancet Device and Monolet Sterile Lancets; Sherwood Medical, St. Louis, USA). One of the 4 treatments was then mixed with 289mL of Boost™ which has 50 grams of available carbohydrates. A timer was set and participants were instructed to wait 10 minutes for the bubbles in the drink to settle and then stir the drink from time to time while consuming it over a 5 minute period. Each test began at the same time each morning and the meal and water were consumed over the same period of time for each test. After the test meal was consumed, participants consumed 100-200 ml of tap water within 10 minutes. Additional finger-prick blood samples were obtained at 15, 30, 45, 60, 90 and 120 minutes after the start of the meal (Figure 4.1). All blood

samples were collected in tubes containing fluoride oxalate and immediately frozen at -20$^0$ Celsius pending analysis.

### 4.3.4 LABORATORY ANALYSES

#### 4.3.4.1 Plasma Glucose

Analysis of plasma glucose of each sample was performed using the glucose oxidase method with a glucose/L-lactate analyzer (model 115; YSI 2300 Stat glucose/L-lactate analyzer, Yellow Springs, Ohio). Measurements were expressed in millimoles per liter (mmol/L) (to convert from mmol/L to milligrams per deciliter (mg/dl) multiply by 18). The inter-assay coefficient of variation of this method for 2 sample pools was 3.3% (n=91, 3.99±0.13 mmol/L, mean ± SD) and 1.8% (n=89, 14.35±0.26 mmol/L, mean ± SD).

#### 4.3.4.2 Satiety Ratings and Symptoms:

Satiety was assessed using a questionnaire that assessed using a rating system of -3 to +3 at each time point. Participants were instructed to rate satiety as "extremely hungry" (-3) or "uncomfortably full" (+3) (Appendix 1). Symptoms were identified using a 7 point scale in which participants rated bloating, belching, nausea, headache, dizziness and diarrhea as "yes" or "no" and the severity on a 7 point scale, where 1 = "low" and 7= "high"(Appendix 1).

### 4.3.5 STATISTICAL ANALYSES:

Plasma glucose and satiety curves were plotted as the incremental change in levels over time and the positive incremental area under the curve (AUC) was calculated geometrically for each participant, ignoring areas below the fasting plasma glucose value [200]. Incremental plasma glucose concentrations were used to control for baseline/fasting differences between the treatments. Statistical analyses were then performed using the Statistical Software for the Social Sciences (SPSS Inc, Version 15.0 for Windows, Chicago, Ill). A Linear Mixed Models design was used with treatment and time used as repeated measures to determine the interactive and independent effects of treatment and measurement time on parameters measured over time. If the interaction terms were significant, then pairwise comparisons between treatments were performed at each time point using the Sidak post hoc test. All

results are expressed as mean ± SEM, unless stated otherwise. Differences between means were considered statistically significant if $p<0.05$.

**4.4 RESULTS**

All participants followed the study protocol safely and completed all treatments without difficulty. The participants were instructed to finish drinking the meal within 5 minutes and all consumed the treatment meals in a self-standardized amount of time. According to the questionnaires, the evening activities and morning events prior to test sessions did not deviate significantly from their lifestyle

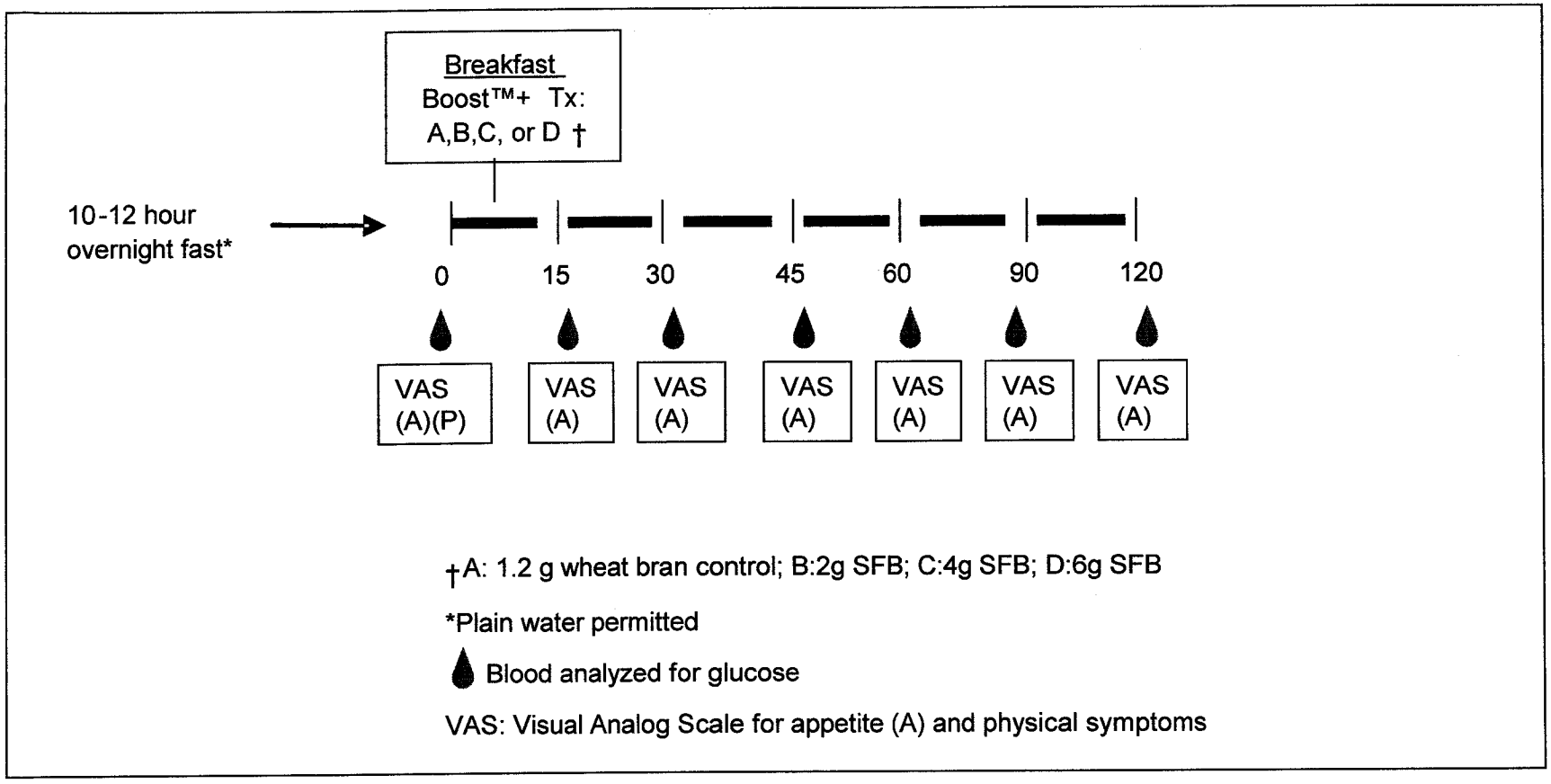



Figure 4.1. Study Day Protocol.
The effects of preload breakfast drinks on postprandial glycemia, appetite and physical symptoms were examined in an acute, randomized, crossover dose-response study design. Breakfast drinks were 289ml of Boost meal replacement plus either 1.2g of wheat bran (control) or soluble fiber blend (SFB) in either 2g, 4g or 6g doses of granulated fiber mixed into the Boost prior to consumption. Appetite and plasma glucose were analyzed at time points 0,15,30,45,60,90 and 120 minutes. Time "0" represents the fasting time point.

**TABLE 4.1. NUTRIENT PROFILE OF PRELOAD TREATMENTS**

Preload treatments consisted of 289ml of Boost™ meal replacement plus granulated fibers of either control (1.2g of wheat bran), or treatment soluble fiber blend (SFB) in 2 gram, 4gram or 6 gram doses. Fibers were mixed with Boost prior to consumption to prevent lump formation. After consumption, satiety ratings and serum glucose response were collected for 120 minutes.

| Nutrients | Preload Meal Replacement Profile | Control (1.2 g WB) | 2g SFB | 4g SFB | 6g SFB |
|---|---|---|---|---|---|
| Calories (kcal) | 292.8 | 292.8 | 292.8 | 292.8 | 292.8 |
| Calories from Fat (kcal) | 42.7 | 42.7 | 42.7 | 42.7 | 42.7 |
| Protein (g) | 12.2 | 12.2 | 12.2 | 12.2 | 12.2 |
| Fat (g) | 4.88 | 4.88 | 4.88 | 4.88 | 4.88 |
| Saturated fat (g) | 0.61 | 0.61 | 0.61 | 0.61 | 0.61 |
| Cholesterol (mg) | 6.1 | 6.1 | 6.1 | 6.1 | 6.1 |
| Available Carbohydrate (g) | 50.00 | 50.00 | 50.00 | 50.00 | 50.00 |
| Total Dietary Fiber (g) | 0 | 1.2 | 2.0 | 4.0 | 6.0 |
| Sugars (g) | 28.06 | 28.06 | 28.06 | 28.06 | 28.06 |
| Water (g) | 244 | 244 | 244 | 244 | 244 |
| Vitamin A (IU) | 1525 | 1525 | 1525 | 1525 | 1525 |
| (50% as β-carotene) | 756.4 | 756.4 | 756.4 | 756.4 | 756.4 |
| Vitamin D (IU) | 183 | 183 | 183 | 183 | 183 |
| Vitamin E (IU) | 36.6 | 36.6 | 36.6 | 36.6 | 36.6 |
| Vitamin K (μg) | 36.6 | 36.6 | 36.6 | 36.6 | 36.6 |
| Vitamin C (mg) | 73.2 | 73.2 | 73.2 | 73.2 | 73.2 |
| Folic Acid (μg) | 170.8 | 170.8 | 170.8 | 170.8 | 170.8 |
| Thiamin (mg) | 0.4636 | 0.4636 | 0.4636 | 0.4636 | 0.4636 |
| Riboflavin (mg) | 0.5246 | 0.5246 | 0.5246 | 0.5246 | 0.5246 |
| Niacin (mg) | 6.1 | 6.1 | 6.1 | 6.1 | 6.1 |
| Vitamin B6 (mg) | 0.854 | 0.854 | 0.854 | 0.854 | 0.854 |
| Vitamin B12 (μg) | 2.562 | 2.562 | 2.562 | 2.562 | 2.562 |
| Biotin (μg) | 91.5 | 91.5 | 91.5 | 91.5 | 91.5 |

WB: Wheat Bran

pattern. The body weight did not differ among the treatment sessions.

### 4.4.1 SYMPTOMS

Mean symptom ratings were reported to be low in magnitude. There were no significant differences among treatments for bloating, belching, nausea, headache, dizziness and diarrhea ratings. Means ± SEM are reported in Appendix 2.

### 4.4.2 LABORATORY ANALYSIS

#### 4.4.2.1 Glucose:

*Absolute Values*: There was a significantly lower ($p=0.044$) absolute glucose response at 15 minutes after consumption of 4grams (5.3 ± 0.2 mmol/l) compared to control (6.1 ± 0.2mmol/l). There was also a significantly higher glucose response in control (7.6 ± 0.3 mmol/l) compared to 4g (6.7 ± 0.3; $p = 0.036$) and 6g (6.2 ± 0.4 mmol/ l; $p<0.0001$)); treatments after 30 minutes. At 45 minutes there was a significantly higher ($p=0.008$) glucose response in control (7.0 ± 0.5 mmol/l) compared to 6g (5.9 ± 0.3 mmol/l). There were no differences in any other time points for absolute glucose values (Figure 4.2). *Incremental Values*: There was a significantly higher ($p=0.005$) incremental plasma glucose after 15 minutes for control (1.6 ± 0.3mmol/l) compared to 4g (0.5 ± 0.1mmol/l) and 6g (0.7 ± 0.3 mmol/l). At 30 minutes there was a significantly higher glycemic response after the control (3.1 ± 0.4mmol/l) compared to the 4g (2.0 ± 0.3mmol/l; $p=0.004$) and 6g treatments (1.5 ± 0.4mmol/l; $p<0.0001$). After 45 minutes control lead to significantly higher glucose response compared to all groups. At 60 minutes, glycemic response after control (1.6 ± 0.4 mmol/l) was significantly higher ($p<0.05$) than 4g (0.7 ± 0.3mmol/l) or 6g treatments (0.6 ± 0.2 mmol/l) (Figure 4.2). *Incremental Area Under the Curve*: iAUC was significantly higher after the control (341.3 ± 52.2 mmol.min/l) compared to 2g (235.3 ± 33.5 mmol.min/l $p<0.0001$), 4g (197.3 ± 32.7 mmol.min/l $p< 0.0001$) and 6g (176.6 ± 33.9 mmol.min/l $p<0.0001$) (Figure 4.2).

#### 4.4.2.2 Satiety:

There were no differences at any of the time points among groups for satiety ratings (Figure 4.3).

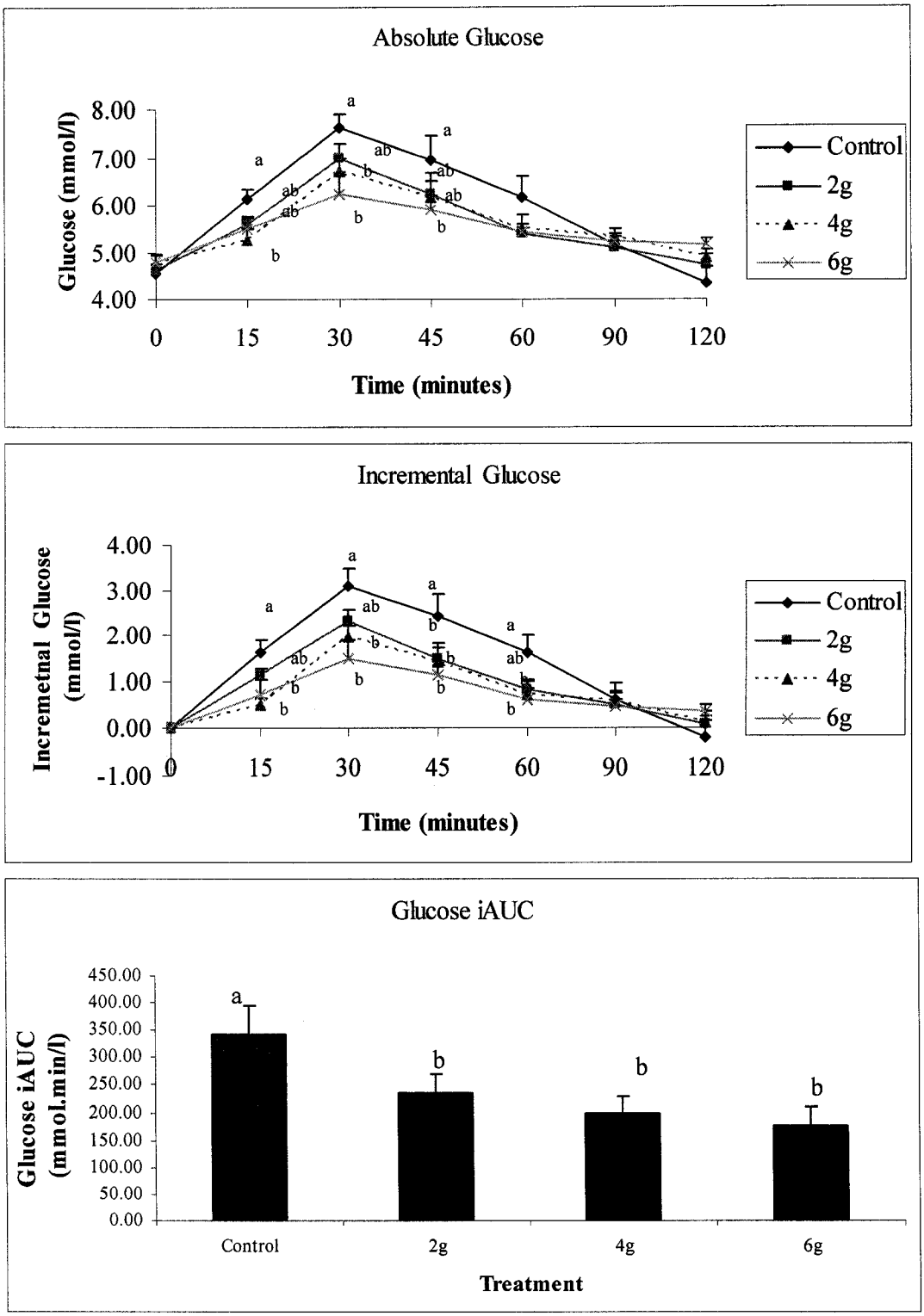
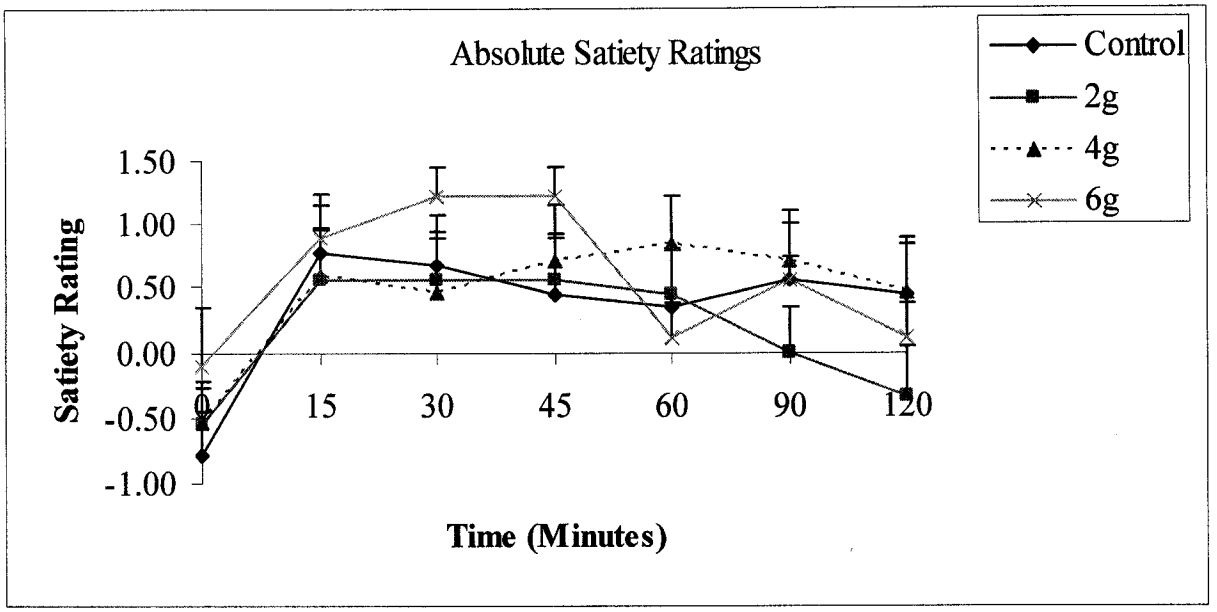



Figure 4.2. Plasma Glucose Response
In an acute, randomized, crossover design, plasma glucose was collected from the antecubital vein at a fasting time point (0 minutes) and every 15-30 minutes after the study treatment was consumed. Study treatments were Boost™ plus either 2g, 4g, or 6g of granulated soluble fiber blend or control (1.2g of wheat bran). iAUC: Incremental Area Under the Curve



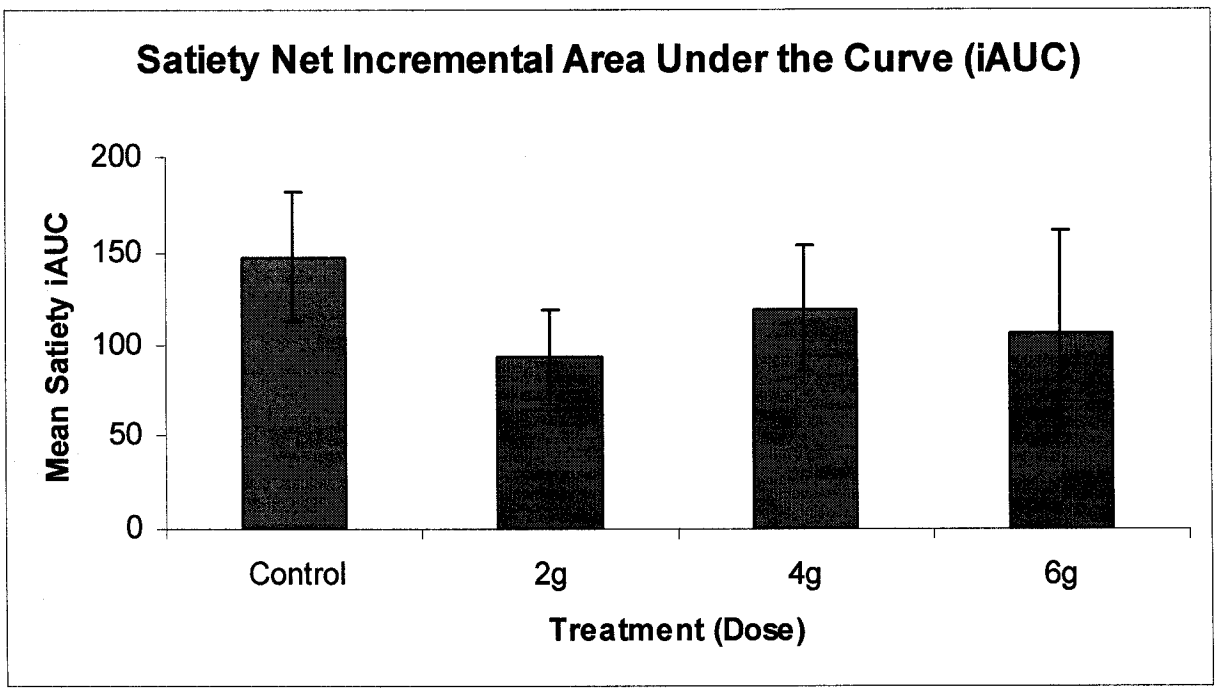




Figure 4.3. Satiety Ratings.
In an acute, randomized, crossover design, satiety ratings were assessed using a Likert scale fasting (0 minutes) and every 15-30 minutes after the study treatment was consumed. Study treatments were Boost™ plus either 2g, 4g, or 6g of granulated soluble fiber blend or control (1.2g of wheat bran).
iAUC: Incremental Area Under the Curve
Satiety was rated on a scale using -3 as "extremely hungry and +3 as "uncomfortably full".
Points and bars represent means ± SEM, respectively.

## 4.5 DISCUSSION

The current study aimed to evaluate the effects the SFB with the largest particle size (selected from the previous study) on glycemic response in three doses (2.0, 4.0, 6.0 grams).

The key findings from this study are that plasma glucose response was significantly lower at 15, 30 and 60 minutes with the 4.0 g and 6.0 g doses of SFB compared to control and the 2g dose. At 45 minutes, 4g and 6g were only significantly lower from control, not 2g dose. The incremental area under the glucose curve, however, showed no differences among doses. These results suggest that an amount of SFB equal to or greater than 4.0 g may be appropriate for aiding in glycemic control of a meal at various time points after meal ingestion. Since these results showed no differences between 4g and 6g in glycemic response, there may be no additional benefit of ingestion of amounts equal to or greater than this amount, however greater doses are required from those used in this study to determine if there is additional benefit beyond 6g. Moreover, a greater sample size may help reveal any differences that may have existed from dose but may have not been strong enough to be significantly different. Post study power analysis indicated that 44 subjects may have been required to find differences in incremental glucose response beyond what was demonstrated.

Similar results come from a study by Tappy et al (1996), where the dose-response of β-glucan (4.0, 6.0, 8.4 grams) on glucose response was investigated [201]. The results also demonstrated a difference between the low and medium doses, however the higher doses showed similar responses to each other. In addition, a study by Biorkland et al, (2005) found a response after 5 g of β-glucan but did not find an additional benefit from 10 grams [202]. Conversely, Liljenberg et al (1996) demonstrated that while 2 g of soluble fibre in a meal had no influence on postprandial glucose tolerance 8 g did [203]. Although the viscosities in these studies were not reported, the dose-response relationship of one single fiber type on glucose response is not consistent. One possible explanation for these discrepancies may be that different amounts of β-glucan were extracted from oats and barley and compared in these studies. In the current study, a blend of a variety of different fibers was used to achieve a constant viscosity so that the inconsistencies among fiber seen in the literature could be controlled while viscosity was held constant.

Although it is difficult to compare the results of the current study to the findings of the studies of individual fibers in the literature, there may be practical and clinically relevant implications to the amount of SFB required for a difference in glycemic response in addition to the viscosity. The study by Davis et al (2006) found that overweight/obese individuals consumed approximately 3 grams less dietary fiber than their healthy weight controls[187]. Therefore, adding a small specific amount of granulated dietary fiber to meals, such as 4-5 grams/meal may be more realistic for the population to accept compared to more general recommendations, such as increasing daily fiber intake by 15g/day to achieve closer to 25-38g/day.

In the current study, when the glucose incremental Area Under the Curve responses were compared, there were no differences among the 3 doses of SFB. Despite this, there were differences among doses at individual postprandial time points for serum glucose response, suggesting that gravimetric properties of soluble fiber may need to be combined with further investigation into more rheological properties before meaningful interpretation of study results can be made.

The glucostatic theory of food intake regulation postulates that a decline in plasma glucose concentration results in an increase in appetite [83, 84]. However, high plasma glucose does not necessarily result in satiety and low plasma glucose does not necessarily result in hunger. Following a meal rich in carbohydrates, plasma glucose rises to reach a peak in 30-60 minutes and then falls back to baseline in healthy individuals. It has been shown that it is the rate of glucose utilization and the slope or shape of the plasma glucose curve that affects appetite and food intake rather than absolute plasma levels at any time point [85].

In the current study, there were no differences in satiety ratings among the 3 doses of SFB or between any of the doses and control. There was, however a trend toward the 6g of SFB leading to greater satiety until 45 minutes, after which the 4g SFB tended to lead to greater satiety. These trends should not be over-interpreted since they were not significantly different from other doses, there were differences in fasting and the participants were not being studied in isolation from external cues related to appetite. Isolation is important since other participants in the study test room may have been receiving their lunch when other participants were rating their appetite and being influenced by sensory (visual,

olfactory and auditory) food cues. It does however justify future research to investigate whether there is a relationship between SFB and subjective measures of satiety and hunger.

There were several limitations to this study that must be considered. The SFB was added to a meal replacement drink, containing less than 300kcal. Therefore, although the results of the 4 treatments are comparable, they are not indicative of an average meal in the North American diet, which is approximately 500kcal. The amount of carbohydrate in the test meals, however, was equivalent to previous studies investigating the glycemic effect of foods. Future studies, are required to determine the effect of these amounts of SFB on postprandial glucose, insulin and satiety after an average North American meal to determine the practical implications of these doses.

Furthermore, a study that is planned to assess the effects of SFB on satiety as the main outcome is required where the study environment is controlled and validated visual analog scales are used to assess various parameters of motivation to eat (e.g. hunger, satiety, appetite). In the current study only one parameter of appetite was assessed, whereas, in validated appetite visual analog scales, multiple parameters are assessed. The importance of assessing these parameters was demonstrated in a recent study, where fullness was shown to be the strongest predictor of food intake [204]. Furthermore, previously established preload methodology that uses measures of appetite, such as food intake would have provided further information to demonstrate more objective effects of fiber on motivation to eat [63, 205].

The results of the current study suggest that SFB is effective at reducing the postprandial glycemic response. It appears that the effectiveness is related to the dose of the SFB used in the breakfast meal, where doses of 4-6 g appear more effective than 2g compared to wheat bran control at certain postprandial time points. Despite a lack of significant differences in satiety ratings, future research is warranted to determine whether a dose of 4-6g of SFB affects appetite ratings and food intake in a study designed using established preload methodology to examine these factors as primary outcomes.

In conclusion, these results suggest 4-6g of SFB may be appropriate for aiding in glycemic control of a meal at specified postprandial time points. Further research is necessary to investigate the effects of SFB on the trends of appetite differences seen in this study, using well-established preload methodology.

# **CHAPTER 5.** THE EFFECT OF A VISCOUS FIBER BLEND ON FOOD INTAKE AND APPETITE REGULATION IN HEALTHY ADOLESCENTS

## 5.1 ABSTRACT

**Background**: Messages to the population regarding dietary fiber principles are confusing because the optimum dose, administration time, form and physical properties (i.e. viscosity) of soluble fiber have not been fully elucidated. A blend of these soluble fibers may have synergistic and additive effects on appetite as they have been previously shown to augment the control of risk factors for type 2 diabetes, such as glucose control, that have been correlated with reduced appetite[114, 206]. In order to recommend consumption of soluble fiber and blends of soluble fiber it is essential that a comprehensive understanding of its effects on appetite regulation at various viscosities is established. **Objective:** To explore the effects of various viscosities of SFB on subjective and objective appetite and food intake using pre-established preload methodology in healthy participants. **Design**: The effects of 3 preload breakfast drinks ((low (cellulose), medium (glucomannan), or high viscosity (soluble fiber blend)) on subjective ratings of appetite and symptoms as well as pizza intake 90 minutes after preload were examined in an acute, randomized, crossover dose-response study design in healthy adolescents. Appetite and symptoms were assessed using visual analog scales at time points 0,15,30,45,60,90 and 120 minutes. **Results:** In N=35 (27 female) participants (16.2 ± 0.1 yrs; BMI: 22.2 ± 3.6 kg/m$^2$) there were no differences in the subjective appetite ratings among the three treatments. Pizza intake was significantly lower (p=0.047) after consumption of the highly viscous preload drink (mean pizza intake =264 ± 20g) compared to the glucomannan alone (317 ± 18g) but not control. This 53-gram difference translated to a caloric difference of 118.2 kcal. There were no differences in longer-term food intake among groups. **Conclusions**: Although no differences existed in subjective appetite ratings among different viscosities, the study demonstrate that the SFB has an augmented ability to reduce food intake compared to glucomannan alone but not cellulose, the fiber with the lowest viscosity. Therefore, given the lack of differences between the highest and lowest viscosities, these results are of interest but must not be over-interpreted, since this study was not designed to examine the physiological reasons for appetite and intake, future investigation must incorporate mechanistic markers that may explain differences in food intake seen in this study.

## 5.2 INTRODUCTION

Obesity is a growing concern in North American adults, leading to type 2 diabetes, cardiovascular disease and premature death [11, 13, 19-21, 207-226]. This trend is being mirrored in adolescents,[227] however research into safe, effective dietary treatment in this population is limited. In addition, a propensity for insulin resistance has been reported occur during puberty, making this population particularly vulnerable to uncontrolled caloric intake and weight gain[228]. Compounding this problem is an environment in which there has been a steady growth in meal portion sizes [229, 230]. Many common weight-loss diets rely on restriction of macronutrients (e.g. carbohydrates, fats or proteins) and restriction of calories. Although these diets have been shown to be successful in the short term, they are ineffective in long term weight regulation since resumption of old eating habits typically occurs after restrictive diets are discontinued [214, 226, 231-233]. This is particularly important in the current climate of growing portion sizes, highly caloric meals and sedentary lifestyles. A dietary regimen that targets appetite regulation without dietary restriction may be more appropriate for this population of adults and adolescents to prevent the development of comorbidities and premature death associated with obesity.

Addition of soluble fiber to the diet has been shown to lead to appetite regulation and weight loss [53]. In fact, consumption of dietary fiber has been shown to be related to risk of obesity. In a study by Hanley et al (2000) of 242 children and adolescents, previous day dietary fiber intake was associated with a decreased risk of overweight[234].

Although many of the principles underlying the mechanisms involved have been investigated, messages to the population are confusing because the optimum dose, administration time, form and physical properties (i.e. viscosity) of soluble fiber have not yet been elucidated. Moreover, there is very little information on the differences in appetite and food intake caused by consumption of a blend of highly viscous soluble fibers in comparison to a constituent viscous fiber alone or an insoluble fiber. A blend of these soluble fibers may have synergistic and additive effects on appetite as they have been previously shown to augment the control of risk factors for type 2 diabetes, such as glucose control, that have been correlated with reduced appetite [114, 206].

In order to make recommendations on the consumption of soluble fiber and blends of soluble fiber as an approach to reduce hunger and promote weight loss or maintenance, it is essential that a more comprehensive understanding of its effects on appetite regulation at various viscosities is established.

The design of the following study used the principles of the previous two studies and incorporated well-established preload methods and validated and controlled appetite and food intake parameters to assess appetite and subsequent food intake following consumption of meal replacement drink preloads containing high (SFB), medium (glucomannan) and low (cellulose) viscosity dietary fiber.

## 5.3 SUBJECTS AND METHODS

### 5.3.1 SUBJECTS

An information session to a group of 50 potential study participants was conducted during which study details were explained. Potential subjects were given a screening package consisting of a baseline information questionnaire, The Eating Habits Questionnaire[235, 236], a Beck Depression Inventory Scale[237] and a consent form. The baseline information questionnaire gathered information on medication use, including oral hypoglycemic agents, dietary supplements, vitamins, minerals and herbal remedies. The Eating Habits Questionnaire was used to measure dietary restraint, and the Beck Depression Inventory measured depression. Based on these and other inclusion/exclusion criteria (Appendix 2), eligible participants were invited to the clinic and screened for general health, study food enjoyment and body weight, height, waist circumference and body fat. Ratings of study food enjoyment were measured using a 100 mm linear visual analog scale. Only participants who rate ≥ 80% of the study foods ≥ 50mm on the visual analog scale were included in the study. Written informed consent to participate in the proposed study was obtained. Both potential participants and parents/guardians (if participants were under 18 years of age) were required to sign the consent form in order to participate. The study was approved by the St. Michael's Hospital Research Ethics Board. Thirty five healthy-weight adolescents (age: 16 ± 0.1 year; BMI: 22.2 ± 3.6 kg/m$^2$) participated in the study. Based on a power analysis by Warren et al (2003), a sample size of 37 would have sufficient power to detect differences in food intakes within a range of 54kcal. Therefore, a sample size of 35 was within a 5% drop out rate[52].

### 5.3.2 TEST MEALS

Meal Replacement Preload Drink: Each of the three breakfast meal replacement drinks was prepared by combining a powdered preparation (InovoBiologic, Coquitlam, British Columbia) with 350 mL water which was shaken vigorously immediately prior to serving. The strawberry flavoured drinks were identical in taste, texture, appearance and nutrient content (Table 5.1), and differed only in the fiber type (high viscosity (soluble fiber blend) vs. medium viscosity (glucomannan) vs. low viscosity (cellulose) fiber). The maximum viscosities of each drink were: high viscosity (70 cpsx1000), medium viscosity (40 cpsx1000), low viscosity (3 cpsx1000). The powder was weighed using an electronic scale (Mettler PM 6000, Zurich, Switzerland), and combined with 350 mL of tap water and was shaken vigorously in a tightly sealed drink container (945 ml Leak Resistant Chug Bottle, Rubbermaid), immediately prior to serving. Following completion of the fiber drink, participants consumed 350 mL of tap water. In vitro examination of viscosity was performed for 24 hours on samples of the preload drink using a Brookfield (RVT) Viscometer (D.W. Brookfield Ltd., Cooksville, ON) at a concentration of 1% and a shear rate of 1/30sec at spindle type "F".

Test Meal: Vegetarian pizzas (5-inch diameter) with mozzarella and cheddar cheese, onions, mushrooms, red and green pepper (Pizza Minis, Veggie Supreme, Pillsbury, General Mills Inc., Minneapolis, Minnesota) were purchased from local retailers and provided to participants following the completion of the 90-minute motivation to eat and physical symptoms questionnaires. Pizzas were cooked on a baking pan in an oven for 10 minutes at 450 degrees Celsius. For each participant, 4 pizzas were cut into quarters and the bite-sized pieces were randomly distributed on the tray so that participants were not able to estimate the number of pizzas they consumed. Cooked pizzas were weighed on an electronic scale (Mettler PM 6000, Zurich, Switzerland) before serving and the amount left on the tray after the meal was weighed and subtracted from the initial weight to provide a measure of food intake. Participants were given verbal and written instructions to eat the pizza until they were satisfied (not stuffed, but not still hungry). Four cups (1000 ml) of tap water was provided with the pizza. The total amount of pizza and water consumed was calculated. Ten minutes after participants received the pizzas they were provided

with another plate of pizza. Participants were not disturbed again for at least 10-15 minutes. Nutrient profile of whole pizzas is given in Table 5.2.

### 5.3.3 STUDY DESIGN:

In a randomized, crossover study, participants attended the clinic for 3 study visits, separated by a minimum 1 day washout period (Figure 5.1). Participants were asked to consume a usual dinner the night before each test. At each visit, participants arrived after a 10-12 hour overnight fast, completed a lifestyle and sleep questionnaire and were randomly assigned to consume one of the three meal replacement preload drinks, within 10 minutes, followed by 350 ml of water. Visual analog scales were completed fasting and every 15 minutes following completion of the breakfast meal to assess parameters of appetite and physical symptoms. Individual timers were provided to ensure that the breakfast drink was consumed in 10 minutes and the tap water was consumed within 5 minutes and that the questionnaires were completed at designated times. After 90-minutes, participants were provided with an *ad libitum* pizza meal and were instructed to eat the pizza until they were satisfied. The purpose of the pizza meal was used to assess the effects of the treatments on food intake. Following the pizza meal, another set of appetite and physical symptoms visual analog scales were completed. At the end of each visit, participants were given a food intake record to complete.

Participants were seated at private booths in a common room during consumption of the breakfast drink up to the completion of the 90 minute questionnaires. After completion of the questionnaires, participants were taken to a private room to consume the pizza meal and to complete the postprandial motivation to eat and physical symptoms questionnaires. The rooms were free of any visible food products, packaging, posters or anything related to food. Reading materials were allowed between zero and 90 minutes, however only reading materials screened by the study coordinator for food-related articles and advertisements were permitted.

### 5.3.4 STUDY ANALYSES

#### 5.3.4.1 Anthropometric Assessment:

Body Weight: Participants were asked to remove their shoes and any objects from their pockets and were weighed in lightweight clothing using a beam scale (Healtometer, USA). Height: Height was

measured using the built-in height bar on the beam scale. Waist Circumference was measured using a flexible tape measure at the midpoint between the distal rib and the anterior superior iliac crest and the hip circumference was measured at the widest part below the iliac crest. Percent Body Fat was measured using the Futrex® 5000 system (Futrex Inc, Gaithersburg, MD), which directs an infrared beam into the triceps.

**5.3.4.2 Questionnaires**

Clinical Questionnaire: The clinical questionnaire was provided at each visit and included a diary of their previous day activity, dinner, sleep, mode of transportation to the clinic, medications, and time since last void and last bowel movement (Appendix 1). Participants were given a copy of the completed questionnaire from their first visit and were asked to follow the previous day activity, dinner, sleep and mode of transportation as closely as possible for the next two visits. Compliance was assessed on subsequent visit clinical questionnaires and participants were rescheduled if the previous day's activity and food intake were not similar to first visit.

Visual Analog Scales (VAS): Subjective measurements of motivation to eat and physical comfort were assessed using visual analog scales (VAS). Each of the questions on the VAS was a 10 cm line anchored at each end with opposing statements [238]. For instance, fullness was assessed with the following statement on the left side of the line "not full at all" and the following statement to the right side of the line "as full as I have ever felt". Participants marked an "X" on the line at a point they felt reflected their feelings at the moment the test was taken. Scores were assessed by measuring the distance between the intersection of the "X" with the line and the left end of the line.

Subjective Appetite: Subjective appetite was assessed using the Motivation to Eat questionnaire[238], which included 4 questions:

Q1: How much do you think you could eat now? ("nothing at all" to "a large amount")

Q2: How full do you feel? ("not full at all" to "as full as I have ever felt")

Q3: How strong is your desire to eat? ("very weak" to "very strong")

Q4: How hungry do you feel? ("not hungry at all" to "as hungry as I have ever felt")

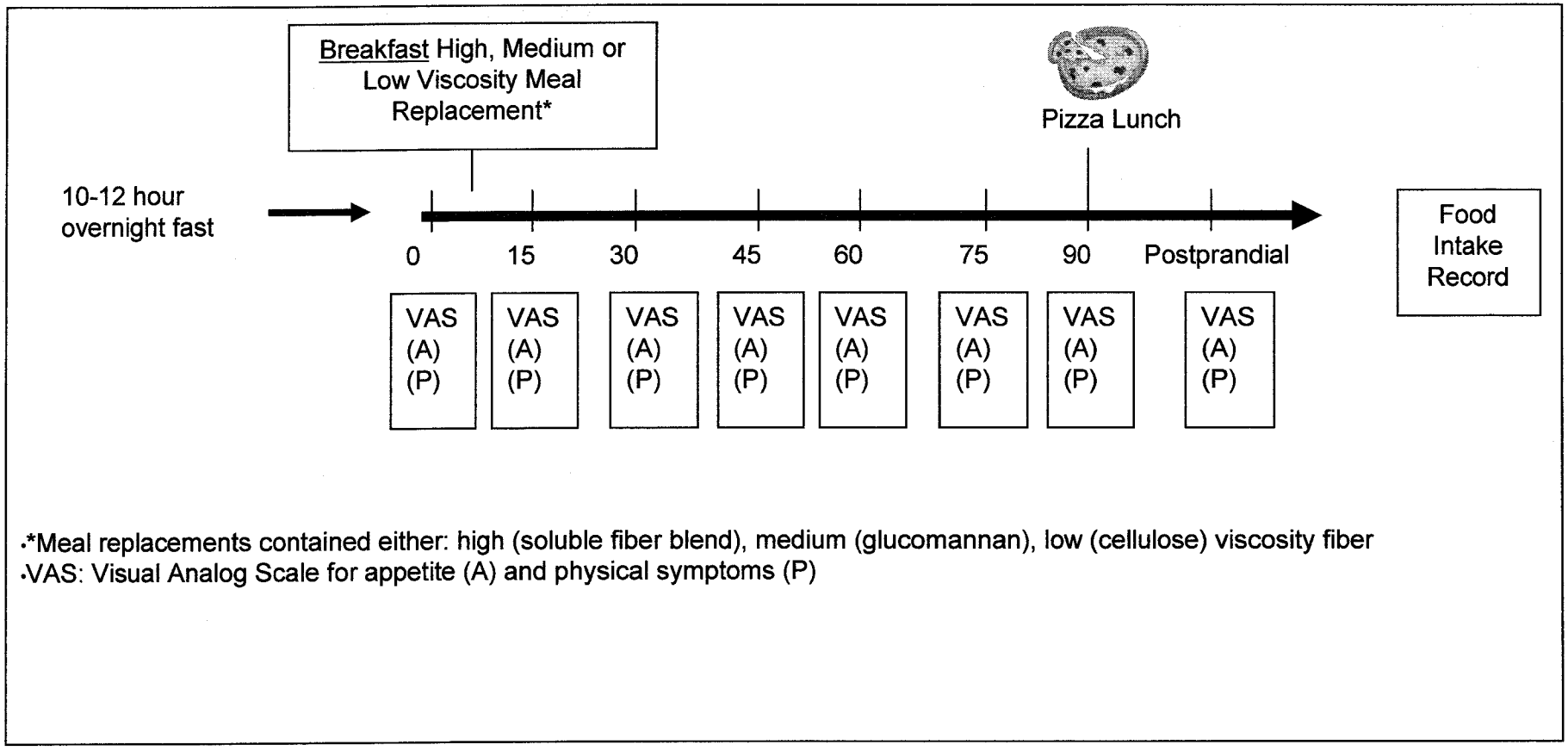



Figure 5.1. Study Day Protocol

The effects of preload breakfast drinks on appetite, symptoms and pizza intake were examined in an acute, randomized, crossover study design. Breakfasts were strawberry meal replacement drinks identical in taste and appearance but varied in type of fiber. Fibers were ether high (soluble fiber blend), medium (glucomannan) or low (cellulose) viscosity. Appetite and symptoms were assessed using visual analog scales at time points 0,15,30,45,60,90 and 120 minutes. Time "0" represents the fasting time point. After 90 minutes a pizza meal was presented to participants, who were instructed to eat until satisfied. Pizza was cut into small bite size pizzas, weighed and presented to participants. Left-over pizza was weighed and the amount was subtracted from the amount provided as a measure of the effects of breakfast treatments on energy intake. Food records were provided by participants from the time they left the clinic until they went to bed.

Average appetite scores were calculated as a summary measure using the following equation:

$$\text{Average appetite} = \frac{[Q1 + Q3 + Q4 + (10 - Q2)]}{4}$$

Since Question 2 assessed fullness, it has opposite anchors at each end of the 10 cm line compared to the other 3 questions. Therefore, Q2 is subtracted from 10 in the equation to adjust for this difference.

Subjective Physical Comfort: Physical comfort was assessed using a similar VAS as subjective appetite. For this assessment, however, participants marked either "yes" or "no" after each marker of physical comfort. If they marked "yes" they were instructed to rate the severity of the side-effect on a 60 mm VAS with opposite poles designated as 1 (low) to 7 (high) and to provide related comments. The physical comfort scale included bloating, belching, diarrhea, flatulence, excessive urination, nausea, headache, dizziness, disorientation, anxiety, impaired vision, heart flutters, joint pain, numbness and a category for "other". In the "other" category, participants were asked to specify what they meant by "other" and rate the severity using the 60 mm line.

Long-Term Food Intake: Following completion of the pizza meal, participants were provided with a food, activity and physical symptom diary template and were instructed to complete it over the next 24 hours and return it at the following visit. After receiving the diary instructions, participants were free to leave the clinic.

### 5.3.5 STATISTICAL ANALYSES

Satiety curves were plotted as the absolute and incremental change in levels over time. Incremental appetite values were used to control for baseline/fasting differences among the treatments. Statistical analyses were then performed using the Statistical Software for the Social Sciences (SPSS Inc, Version 15.0 for Windows, Chicago, Ill). A Linear Mixed Models design was used with treatment and time used as repeated measures to determine the interactive and independent effects of treatment and measurement time on parameters measured over time. If the interaction terms were significant, then pairwise comparisons between treatments were performed at each time point using the Sidak post hoc test. All results are expressed as mean ± SEM, unless stated otherwise. Differences between means were considered statistically significant if $p<0.05$.

## TABLE 5.1. NUTRIENT PROFILE OF PRELOAD MEALS

Preloads were strawberry flavour meal replacement drinks with either soluble fiber blend, glucomannan or cellulose (control) fiber. All three drinks were identical in taste and appearance. The meal replacement was mixed with water immediately prior to serving to prevent lump formation. Participants consumed preloads fasting and recorded motivation to eat every 15-30 minutes before and after consumption.

| Nutrient | Soluble Fiber Blend | Glucomannan | Cellulose |
|---|---|---|---|
| Calories (kcal) | 226.0 | 226.0 | 226.0 |
| Protein (grams) | 19.8 | 19.8 | 19.8 |
| Total carbohydrate (grams) | 15.0 | 15.0 | 15.0 |
| Usable carbohydrate (grams) | 9.9 | 9.9 | 9.9 |
| Fat (grams) | 6.9 | 6.9 | 6.9 |
| Fiber (grams) | 5.1 | 5.1 | 5.1 |
| Sugar (grams) | 8.3 | 8.3 | 8.3 |

## TABLE 5.2. NUTRIENT PROFILE OF PIZZA LUNCH

Preload meal replacement drinks with high(soluble fiber blend), medium(glucomannan) or low (cellulose) viscosity were provided fasting and 90 minutes later a pizza meal was presented to each participant. Vegetarian (5-inch diameter) pizzas purchased from local retailers were cooked and cut into quarters and randomly distributed on a tray so participants were not able to estimate the number of whole pizzas they consumed. Prior to serving and after participants reported being satisfied, pizzas were weighed. The amount left over was subtracted from the amount provided as a measure of the effect of preloads on energy consumption.

| Nutrient | Amount (for 96g serving or 1 pizza) |
|---|---|
| Energy | 214 kcal |
| Protein | 8.3g |
| Fat | 9.4g |
| Carbohydrate | 24g |

## 5.4 RESULTS

Thirty five participants (27 females) with a mean age of 16.2 ± 0.1 years and a mean BMI of 22.2 ± 3.6 kg/m$^2$ were included. There were no differences in consumption time of the preload among the three treatments (Table 5.3)

### 5.4.1 SYMPTOMS

Symptoms were reported to be low in magnitude. There were no differences among the three treatments in ratings of bloating, belching, diarrhea, flatulence, excessive urination, nausea, headache, dizziness, disorientation, anxiety, vision or heart problems, joint pain or numbness during the testing periods. Appendix 2 displays the means ± SEM of symptom ratings for the three treatments.

### 5.4.2 STUDY ANALYSES

#### 5.4.2.1 Appetite Ratings:

There were no differences in the subjective hunger ratings among the three treatments; however it is interesting to note that in each of the questions the SFB lead to numerically lower appetite and greater fullness than the other treatments (Figure 5.2).

#### 5.4.2.2 Short Term Food Intake:

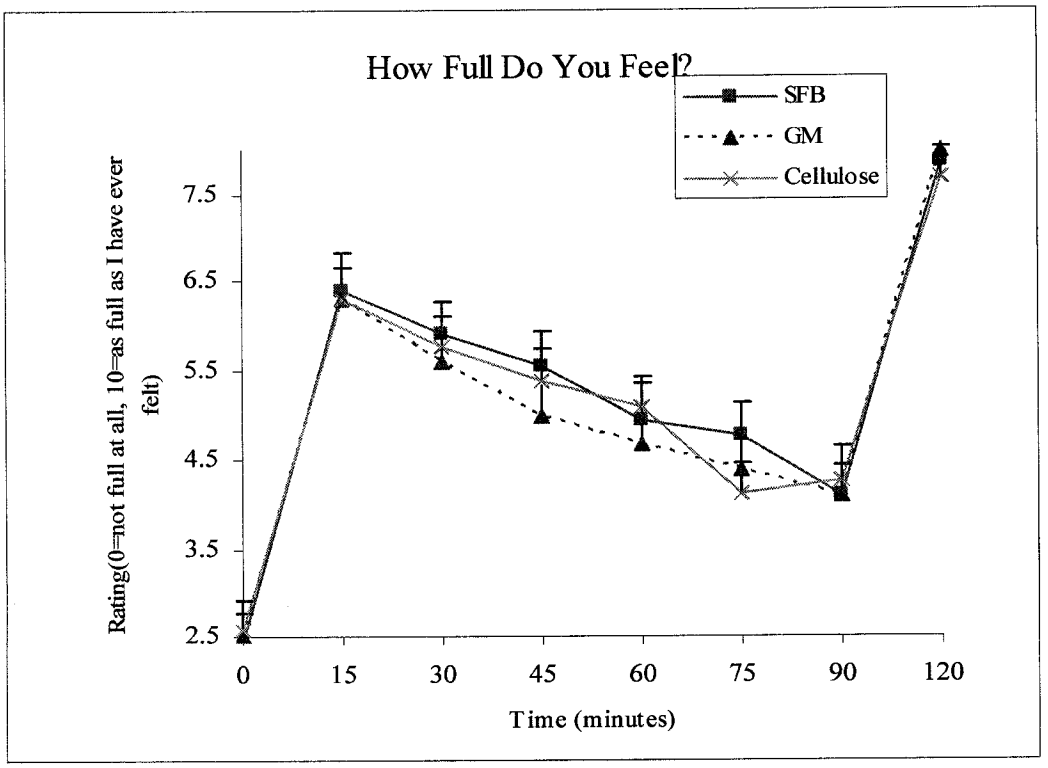
Pizza intake was significantly lower ($p=0.047$) after consumption of the highly viscous preload drink (mean pizza intake =264 ± 20g) compared to the glucomannan alone (317 ± 18g) (Figure 5.3). This 53-gram difference translated to a caloric difference of 118.2 kcal.

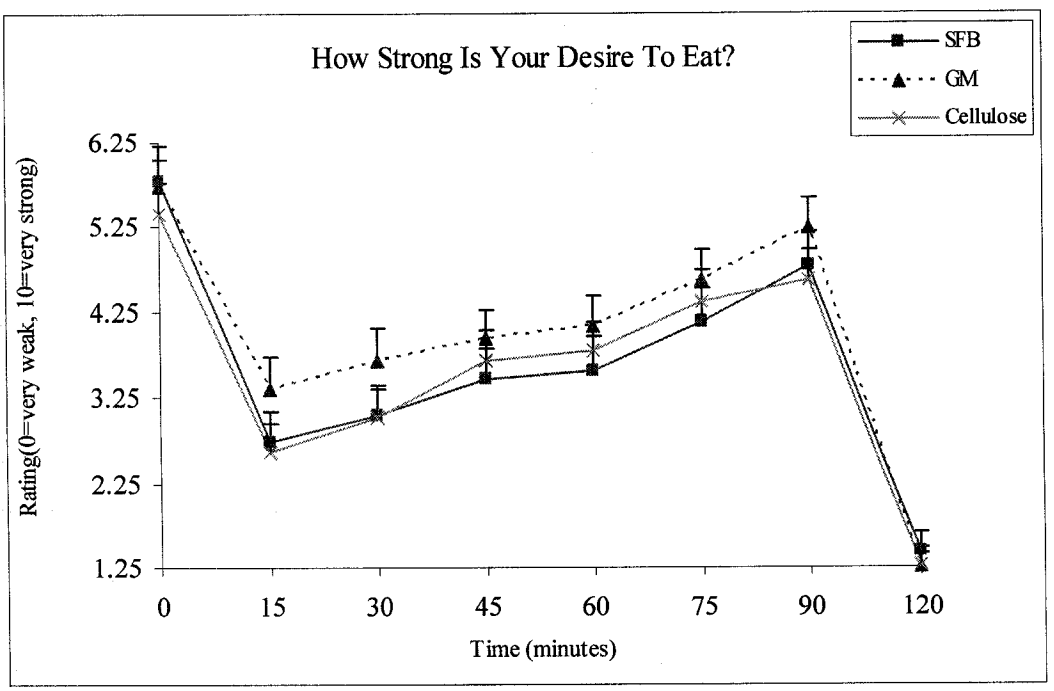
#### 5.4.2.3 Longer Term Food Intake:

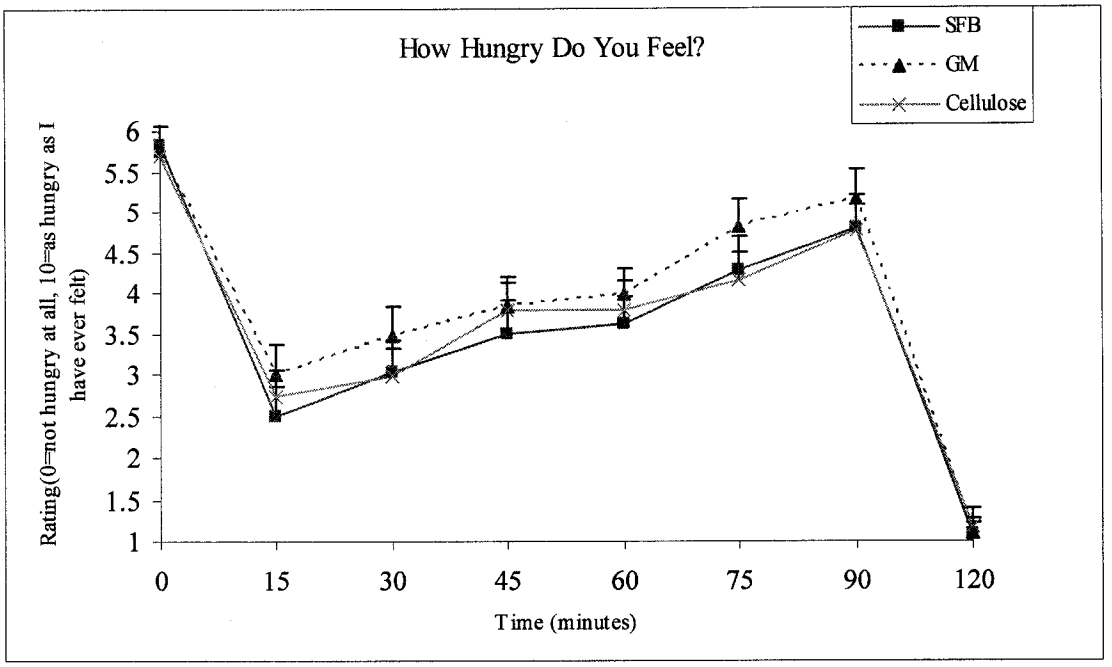
There were no differences in macronutrient intake among groups from the time they left the clinic until they went to sleep (Table 5.4).

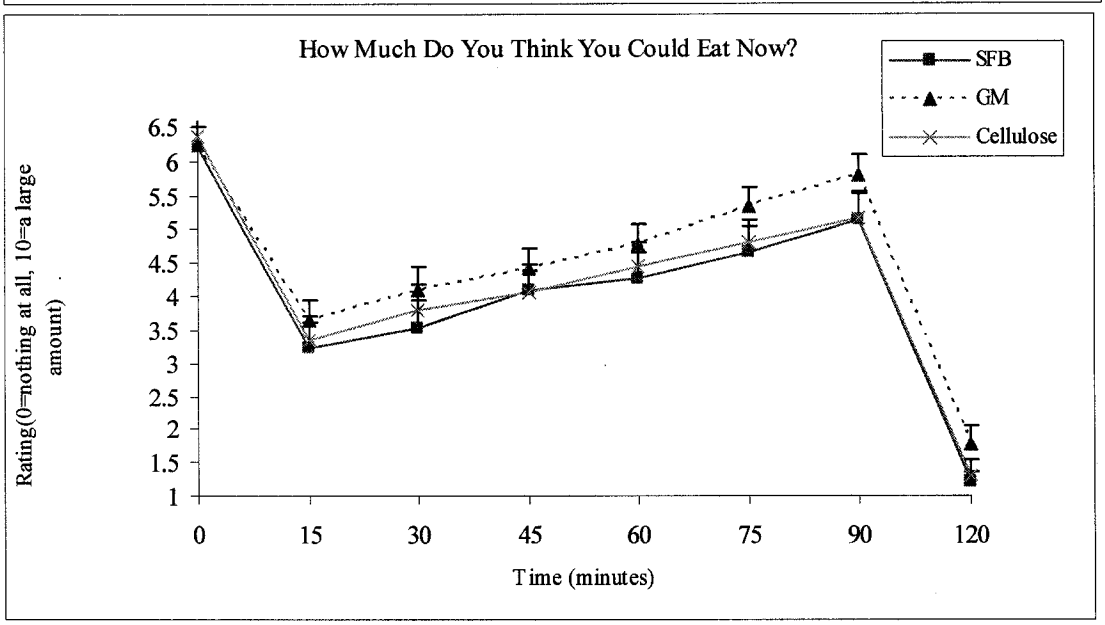
**TABLE 5.3. CONSUMPTION TIME OF THE THREE BREAKFAST PRELOADS.**
Breakfast preload drinks with high (soluble fiber blend), medium (glucomannan) or low (cellulose) viscosity fiber were provided to fasted participants. Participants were instructed to consume the drinks within 10 minutes and provided with electronic timers to record timing. For 90 minutes after preload consumption participants rated parameters of motivation to eat using a visual analog scale. After 90 minutes participants were provided with pizza to measure the effect of preload on energy intake.

| Treatment | Consumption Time (minutes) |
|---|---|
| Soluble Fiber Blend | 8.5 ± 0.7 |
| Glucomannan | 8.0 ± 0.7 |
| Cellulose | 7.5 ± 0.7 |


How Full Do You Feel?
SFB
GM
Cellulose
Rating(0=not full at all, 10=as full as I have ever felt)
7.5
6.5
5.5
4.5
3.5
2.5
0
15
30
45
60
75
90
120
Time (minutes)


How Strong Is Your Desire To Eat?
SFB
GM
Cellulose
Rating(0=very weak, 10=very strong)
6.25
5.25
4.25
3.25
2.25
1.25
0
15
30
45
60
75
90
120
Time (minutes)


How Hungry Do You Feel?
SFB
GM
Cellulose
Rating(0=not hungry at all, 10=as hungry as I have ever felt)
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0
15
30
45
60
75
90
120
Time (minutes)


How Much Do You Think You Could Eat Now?
SFB
GM
Cellulose
Rating(0=nothing at all, 10=a large amount)
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0
15
30
45
60
75
90
120
Time (minutes)

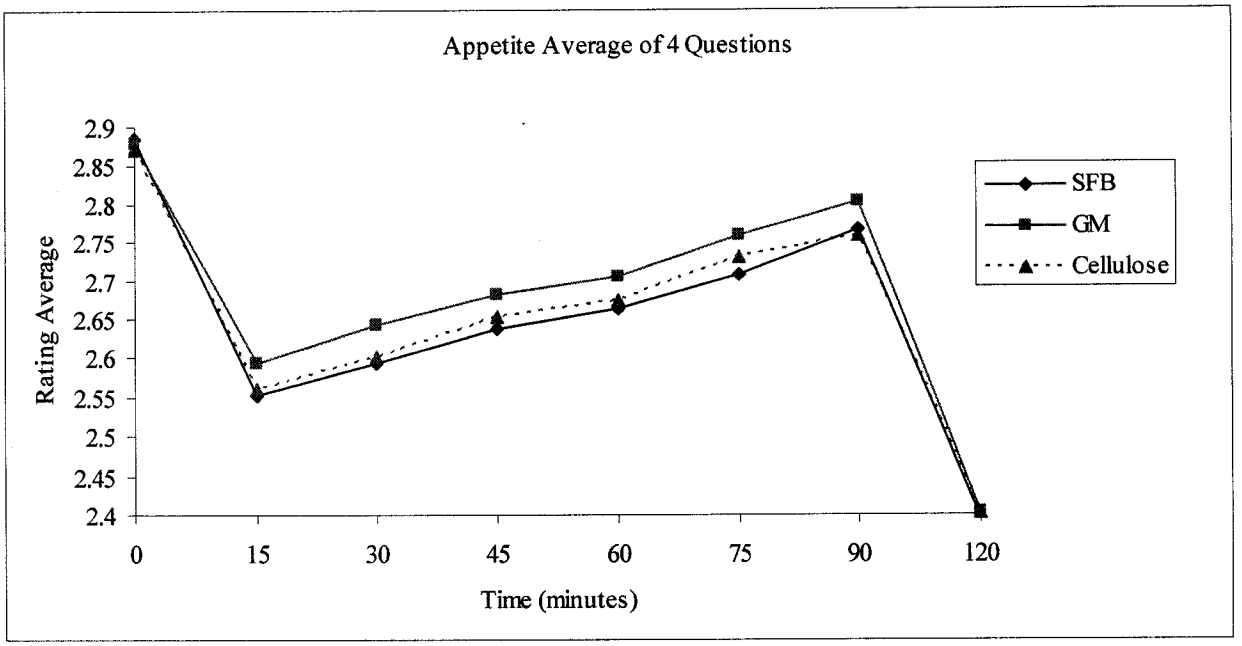



Figure 5.2. Appetite ratings during the study period.
In a randomized cross-over design, participants consumed a meal replacement breakfast drink with either high (soluble fiber blend), medium (glucomannan) or low (cellulose) viscosity fiber. Motivation to eat and symptom ratings were assessed using visual analog scales fasting (0 minutes) and every 15-30 minutes after the study treatment was consumed. Average rating of 4 questions was calculated using the equation [(Q1+Q3+Q4) +(10-Q2)]/4. SFB: soluble fiber blend, GM: glucomannan.

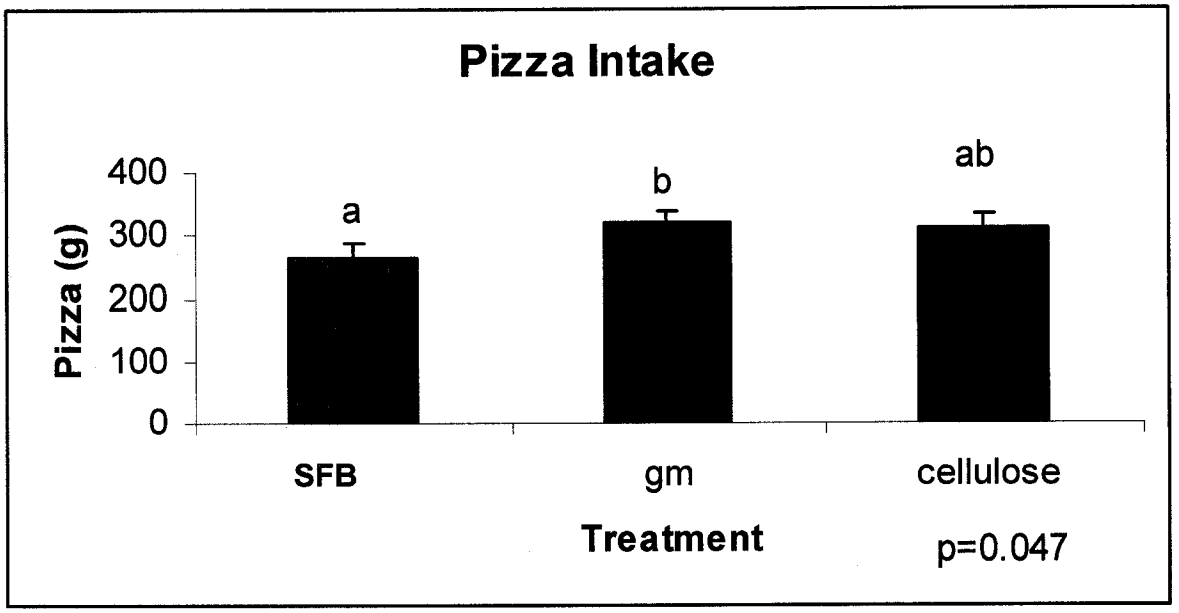



Figure 5.3. Pizza Intake

In a randomized cross-over design, participants consumed a meal replacement breakfast drink with either high (soluble fiber blend), medium (glucomannan) or low (cellulose) viscosity fiber. Motivation to eat and symptom ratings were assessed using visual analog scales fasting (0 minutes) and every 15-30 minutes after the study treatment was consumed. After 90 minutes had elapsed, participants were provided with pizza in bite size pieces. and instructed to consume the pizza until they were comfortably full. The amount of pizza intake was determined by subtracting the left over amount from the weighed amount provided as an indication of the effect of the breakfast treatments on energy intake.

Bars represent means ± SEM.

SFB: soluble fiber blend, gm: glucomannan.

**TABLE 5.4 LONG-TERM NUTRIENT INTAKE**

Participants were provided with preload meal replacement drinks consisting of either high (soluble fiber blend), medium (glucomannan) or low (cellulose) viscosity fiber. For 90 minutes after consumption of the meal replacement, participants recorded their ratings of motivation to eat and after 90 minutes pizza was provided as a measure of the effect of meal replacement fiber on energy intake. After 90 minutes participants completed another motivation to eat visual analog scale and left the clinic with instructions to record food intake long-term. This table represents macronutrient intake until bedtime.

| Treatment | Calories (kcal) | Protein (g) | Carbohydrate (g) | Fiber (g) | Fat (g) |
|---|---|---|---|---|---|
| Soluble Fiber Blend | 1138.79 ± 102.13 | 41.19 ± 3.92 | 160.98 ± 16.16 | 9.31 ± 1.03 | 34.92 ± 3.95 |
| Glucomannan | 1034.22 ± 110.33 | 42.28 ± 3.51 | 117.92 ± 12.68 | 7.95 ± 0.88 | 40.93 ± 6.77 |
| Cellulose | 1225.55 ± 122.76 | 52.79 ± 6.24 | 160.23 ± 15.36 | 8.87 ± 0.99 | 48.17 ± 7.24 |

## 5.5 DISCUSSION

The primary objectives of the previous two studies were to examine the influence of physico-chemical and gravimetric properties of the SFB on postprandial glucose, insulin and appetite response. The differences in satiety ratings suggested that further exploration may be warranted in a study design controlled for appetite and food intake parameters. Therefore, the current study was designed to examine the effects of SFB on appetite and food intake using previously established preload methods [63, 205].

The main finding of this study was that the highly viscous SFB resulted in greater inhibition of short-term food intake than a lower viscosity GM control. These results suggest that the combined principles of rheology and gravimetrics from the previous two studies may both be important in the effects of SFB on the glucostatic theory.

The previous study demonstrated that 4-6 g of SFB elicited a flattened glycemic response at various time points. In the current study, a similar amount of fiber (5g) lead to reduced food intake.

The practical implications of these results may relate to clinically significant weight loss. For instance, low dietary fiber intake is suggested to be related to increased risk of obesity through cross-sectional and epidemiologic studies[90-92]. Current clinical recommendations are that 1-2 lbs weight loss/week aid in effective, sustainable long-term weight maintenance. In this model, a deficit of 500kcal/day is required. A reduction of 118 kcal after 1 meal that was seen in the current study would not likely have a considerable impact on body weight. However, if this reduction is extrapolated to 3 meals and 2-3 snacks per day it could potentially result in a greater effect. For instance, the caloric intake of snacks is generally less than 200kcal and meals are, on average, approximately 500kcal. Therefore, in this study, since the test meal consumption averaged between 200-300kcal, it may be more reasonable to equate it to a snack and calculate that individuals could reduce intake by 118 kcal at snacks and closer to 197kcal (500*118/300) at meals. In this case, (197x3) + (118x2) = 591 + 236 = 827kcal. Thus, this calculation suggests that the SFB could lead to a deficit of 827kcal/day and may be helpful to individuals who struggle to follow restrictive weight loss diets. If, however, this is an over-interpretation of these results, the small reduction in caloric intake may still aid in weight maintenance after a successful weight

loss regimen. Further studies are required to test the reproducibility of these results with similar viscosity and to test the ability of the viscosity in the SFB to aid in weight loss and maintenance.

Despite the differences in food intake between SFB and GM, there were no differences in food intake between SFB and cellulose control, as hypothesized. The reason for this could be due to temporal differences in effect of soluble compared to insoluble fibers. For instance, Delargy et al (1997) found that different types of fiber (soluble and insoluble) may lead to time course changes in the patterns of eating. In this study soluble fiber breakfast did not lead to a greater suppression of intake compared to soluble fiber early in the day but lead to a reduced trend of food intake later in the day, whereas significantly less intake was consumed after the insoluble fiber than soluble fiber breakfast earlier in the day. It is possible that in the current study, the differences in intake may have been significant if the study had continued in the clinical laboratory later into the day, such as 9.5-13.5 hours after breakfast, as in the study by Delargy.[239]

Other studies that have examined the acute effects of glycemic index have generally demonstrated lower satiety, increased hunger and higher food intake after high glycemic index foods compared to lower glycemic index foods [240]. A study by Ludwig et al (1999) demonstrated that when equicaloric lunches that varied in glycemic index (low, medium, high) were provided to obese children, there was a 53% greater voluntary food intake after the high glycemic index lunch over the rest of the test day[241]. In the current study adolescents consumed approximately 15-17% less than the control treatments. Other studies have supported these findings, suggesting that satiety is prolonged after low glycemic index meals in obese adolescents [242]. Although the participants of these studies were overweight or obese, other studies that found greater lunch intake after high compared to low glycemic index breakfasts also found no effect of body weight status on lunch intake (Warren et al. 2003), suggesting these results may be generalizable [52]. Moreover, the results from this study were similar to the current study; between 18-81% less intake was seen after the low glycemic index breakfasts compared to the high glycemic index breakfast.

The mechanisms by which dietary fiber elicit reduction in intake and feeding patterns has been suggested to be due to increased exposure of coingested macronutrients, specifically fat, with

preabsorptive mechanisms of satiety in the small intestine [243]. Burton-Freeman et al (1996) demonstrated that infusing fat into the duodenum of rats at slow vs. faster rates lead to reduced average daily energy intake and reduced weight gain after the slow rate [244]. Therefore, if viscous dietary fibers are able to slow digestion and absorption of fat they may help reduce intake and potentially aid in adherence to low-fat weight loss diets[243].

Previous studies have demonstrated changes in appetite that correspond to levels of viscosity [152, 156-158, 165]; however the current study did not demonstrate significant differences in appetite between treatments. In the current study, visual analog scales (VAS) were used to investigate appetite-related cues to food intake. Although the VAS has been validated for use in research investigating appetite, the validation studies were performed on adults, not adolescents. It is possible that adolescents are less accurate at recording differences in appetite sensations than adults or that the mechanisms that induce satiety are not the same in adolescents as in adults due to differences in metabolic rates and temporary insulin resistance that has been noted to occur during puberty[245-249]. This population has the fastest growing rate of obesity and subsequent development of type 2 diabetes among any age category [226, 250-252]. Therefore, it is likely that a great deal of future research in the area of appetite and food intake will concentrate on adolescents. As such, it is important that future studies investigate the validity of these scales in this population.

In addition, although some studies in adults demonstrate that subjective appetite sensations are associated with measured energy intake[204, 253], while others[254] show they are not associated with energy intake in a free living context, making the clinical value of results from studies using the visual analog scale questionable. A recent study by Drapeau et al, examined the clinical meaningfulness of appetite sensations from visual analog scales to predict overall energy intake and body weight loss in 315 individuals involved in weight loss studies. The study found that one hour postprandial AUC for all appetite sensations represented the strongest predictors of ad libitum test lunch energy intake, and weaker predictors of 3-day self-reported energy intake. Moreover, they found that weight loss was associated with changes in appetite, and that the best predictors of body weight loss were fasting desire to eat,

hunger and predicted food consumption[255]. These studies were performed on an adult population; therefore, the clinical utility in adolescents is still questionable.

It is also possible, in previous studies of dietary fiber in the literature, that appetite scores may have differed due to side-effects caused by the fermentation of soluble fibers in the colon. The average intake of dietary fiber among teens in this age group is 15 g/day. The amount of fiber provided in the meal replacement preload was 5.1 grams. This adds approximately 33% more fiber than the amount that would be consumed, on average, in a day. It is unlikely that the participants would consume this much fiber in a concentrated form, especially viscous, fermentable fibers. Therefore, it is possible that other studies, which had even higher amounts of fiber may have lead to enough fermentation to cause bloating or other side effects that could have affected appetite ratings [150, 154, 164]. The present study was conducted over a 90 minute postprandial period. By 90 minutes it is unlikely that any of the fiber was present in the colon for fermentation. Therefore, it is possible that if the current study was conducted over a greater period of time, differences may have been found in the appetite ratings that may have been a result of side effects, such as bloating, caused by fermentation. Similarly, it could have been that there was not enough time between ingestion of the fiber and the pizza lunch to have allowed or for expression of appetite suppressing hormones, such as GLP-1 or PYY, from the ileum. Therefore, appetite differences may have been stronger if the study was conducted for a longer period of time.

Warren et al. (2003) compared the effects of low glycemic index, with and without 10% added sucrose with high glycemic index test breakfasts on ad libitum lunch intake, appetite, and satiety and found no difference in immediate satiation among treatments. At lunchtime, however hunger ratings were greater after the high glycemic index breakfast compared with other 2 test breakfasts. Pre-lunch satiety scales were inversely related to subsequent food intake. In the current study, although the appetite scores were not significantly different, there was a similar trend in pre-lunch rating of how much food participants thought they could eat and the pattern of the amount that was eaten. In other words, after participants consumed SFB they felt they could eat the least and ate the least and after consumption of glucomannan they felt they could eat the most and they ate the most and cellulose was in between the other groups in appetite rating and in intake. Therefore, these results may warrant further research to

elucidate whether there is a correlation between the amount participants think they can eat and actual intake at the lunch meal.

In conclusion, the prior two studies demonstrated a glycemic and insulinemic response that varied based on rheological and gravimetric properties of fiber and also suggested there may be a glucostatic relationship with appetite and/or food intake, as there was reduced pizza intake with the most viscous preload in the current study.

The current study however, demonstrated that the SFB has an augmented ability to reduce food intake in adolescents compared to glucomannan alone. Since this study was not designed to examine the physiological reasons for appetite and intake, future investigation must incorporate mechanistic markers that may explain differences in food intake seen in this study.

# **CHAPTER 6.** THE EFFECT OF A VISCOUS FIBER BLEND ON THE MECHANISMS OF APPETITE AND FOOD INTAKE

## 6.1 ABSTRACT

**Background**: Individual nutrients have the potential to affect several appetite mechanisms as they traverse through the gastrointestinal tract. The innate characteristics of food, such as macronutrient composition, physical characteristics and exposure time with the GI tract can interact with physiological mechanisms to add further complexity to the understanding of the appetite cascade. Results from the previous studies in this work found that glycemic and insulinemic response varied based on rheological and gravimetric properties of fiber and also suggested there may be a glucostatic relationship with appetite and/or food intake. **Objective**: To elucidate the mechanisms of action responsible for appetite and/or intake regulation, such as the metabolic parameters of appetite regulation, namely glucose and insulin and how they relate to gastric emptying time, subjective appetite ratings and the objective appetite indicator of food intake. **Design:** In a randomized, crossover design, participants consumed a standard breakfast with either cellulose control or soluble fiber blend (SFB) in a granulated form. Fasting and postprandial measures of plasma glucose, insulin, satiety ratings, physical comfort, food intake, gastric emptying time and growth hormone were assessed at 15 to 30 minute intervals for 240 minutes. Pizza intake and 24 hour food intake were also assessed. **Results**: In N=19 (39.0±2.6yrs; BMI:28.5±0.6kg/$m^2$) participants, 150min. satiety was greater ($p<0.05$) after SFB compared to control. Gastric emptying area under the curve (AUC) was slower ($p=0.004$) after control compared to SFB. Glucose was lower ($p<0.04$) after SFB compared to control at 60 and 240min. and glucose iAUC was lower ($p<0.0001$) after SFB compared to control. Insulin was lower ($p<0.02$) after SFB at 60, 90 and 240min. and insulin iAUC was lower ($p<0.0001$) after SFB compared to control. **Conclusion:** Despite lower glycemic and insulinemic responses that may have accounted for the differences seen in food intake the previous study, this study demonstrated no differences in appetite or food intake. SFB did, however, lead to faster gastric emptying rate markers compared to control. Due to methodological limitations, future research is necessary to further explore and determine other metabolic factors that may explain the findings of reduced intake and increase satiation that previous studies of highly viscous fibers have demonstrated.

## 6.2 INTRODUCTION

Food has the potential to affect several mechanisms of satiety and satiation as it traverses through the gastrointestinal tract. Oral (taste and texture), gastric (distension and emptying) and intestinal (neurohormonal) mechanisms can all be affected. Although previous theories focused on one of the related mechanisms, recent work has demonstrated that a variety of metabolic and mechanical mechanisms interact and influence satiety and food intake. In addition, the innate characteristics of food, such as macronutrient composition, physical characteristics and exposure time with the GI tract can interact with physiological mechanisms to add further complexity.

Results from the previous studies in this work found that glycemic and insulinemic response varied based on rheological and gravimetric properties of fiber and also suggested there may be a glucostatic relationship with appetite and/or food intake. The first two studies were, however, designed to examine the glycemic and insulinemic responses specifically. Although the third study demonstrated promising results with food intake and trends towards greater satiety with the highly viscous blend of soluble dietary fibers, it used the VAS, which has been validated in an adult population. In addition, it used a 90 minute postprandial period, which may have not allowed fiber to be present in the colon. It is conceivable that if the previous study was conducted over a greater period of time, differences may have been found in the appetite ratings that may have been a result of side effects, such as bloating, caused by fermentation. Similarly, it could have been that there was not enough time between ingestion of the fiber and the pizza lunch to have allowed or for expression of appetite suppressing hormones from the ileum. Therefore, it is possible that appetite differences may have been stronger if the study was conducted for a longer period of time.

Moreover, the previous study was not designed to examine any of the potential mechanisms associated with appetite and food intake. As such, besides the glucostatic theory that may be extracted from combining the results of the first 2 studies with the results of the third study, the reason for reduced food intake, from a physiological perspective, is unclear. Therefore, the aim of the current study was to further investigate mechanistic markers (i.e. gastric emptying using the acetaminophen technique) that

may explain differences in food intake seen in the previous study and to examine whether the glucose and insulin differences seen in the first two studies were related to appetite and intake differences.

## 6.3 SUBJECTS AND METHODS

### 6.3.1 STUDY SUBJECTS

Equal number of overweight men and premenopausal women, aged 19-55 with a BMI between 25 and 30 $kg \cdot m^{-2}$, were recruited in the Greater Toronto Area through postings in outpatient clinics. A total of 19 overweight but otherwise healthy participants (9 female, 10 male) completed the study. Participants were 39.0 ± 2.6 years old with a mean BMI of 28.5 ± 0.6 $kg/m^2$. Body fat percentage, measured with a bioelectrical impedance analyzer (Tanita Body Composition Analyzer BC-418, Arlington Heights, Illinois), was 30.2±1.4 (Female: 36.0±1.5, Male: 25.0±1.5) while abdominal fat percentage was 29.9±1.4 (Female: 33.0±1.8, Male: 27.0±1.7). Mean participant waist circumference was 91.9±9.14 inches. Potential study participants were screened using a telephone questionnaire (Appendix 1) and the study protocol was explained. Eligible subjects were invited to the clinic to be screened for general health, and had their blood pressure, body weight, height, waist circumference and body fat measured. Ratings of study food (pizza) enjoyment were measured using a 100 mm linear visual analog scale (Appendix 1). Only subjects who rate the pizza ≥ 50mm met the inclusion criteria of the study (Appendix 2). A royal college certified psychiatrist performed a standard psychiatric interview and completed elements of the structured Clinical Interview for DSM (Diagnostic and statistical Manual) Disorders (SCID) to standardize a diagnosis of depression, anxiety, substance and alcohol use, and eating disorders. He also reported on the five main axis diagnosis to the researchers and provided appropriate follow up care and also included concerns about suicide, homicide and psychotic disorders. The screen and assessment took approximately one hour. Written informed consent was obtained from all participants. The study was approved by the Research Ethics Board at St. Michael's Hospital.

Sample size calculation was based on results from a previous study on the effects of 3% guar gum on gastric emptying time. A sample size of 20 was calculated to be required to show a difference in gastric emptying half time of 20 minutes with 90% power and a significance of 0.05[74].

### 6.3.2 TEST MEALS

Preload meals consisted of a plain bagel, cream cheese, orange juice, water and 3 extra strength Tylenol™, which contains acetaminophen as a marker of gastric emptying. Before the breakfast was served to the participants, a 5-gram portion of granulated fiber was stirred into the cream cheese. The fiber consisted of either SFB or cellulose (Natural Factors, Coquitlam, British Columbia). Nutrient contents of experimental meals are presented in Table 6.1. Viscosity of the preload fibers was measured using a Brookfield (RVT) Viscometer (D.W. Brookfield Ltd., Cooksville, ON) at a concentration of 1% and a shear rate of 1/30sec at spindle type "F", $23^0$C.

Cheese pizzas (5-inch diameter) (Pizza Minis, Pillsbury, General Mills Inc., Minneapolis, Minnesota), purchased from local retailers were provided following the completion of the 120-minute motivation to eat and physical symptoms questionnaires. Pizzas were cooked on a baking pan in an oven for 10 minutes at 450 degrees Celsius. For each participant, 2 pizzas were cut into quarters and the bite-sized pieces were randomly distributed on the tray so that participants were not able to estimate the number of whole pizzas they consumed. Cooked pizzas were weighed on an electronic scale (Mettler PM 6000, Zurich, Switzerland) before serving and the amount of pizza left on the serving tray after the meal was complete was subtracted from the initial weight to provide a measure of total food intake. Nutrient contents of individual pizzas are presented in Table 6.2.

### 6.3.3 STUDY DESIGN

This study employed a randomized, double blinded crossover design in which participants acted as their own controls. Participants (N=19) attended the clinic on 2 separate visits with a minimum 1 week (or 1 month: menstrual phase) washout period between test days. Participants were asked to consume a usual dinner, prior to the first test day that could be reproduced the evening prior to the second test day. In addition, participants were asked to follow the same physical activity on the day prior to each testing day. After a 10-12 hour overnight fast and prior to receiving the test meal, body weights were re-evaluated and participants received a clinical questionnaire for previous day and study morning activities (Appendix 1). A cannula was inserted into the antecubital vein for blood sample collection. Participants

## TABLE 6.1. NUTRIENT CONTENT OF BREAKFAST MEAL

Participants arrived fasting and were provided with a breakfast meal, consisting of 1 plain bagel with cream cheese, orange juice, water and 3 extra strength Tylenol. Cream cheese was mixed with granulated fiber (soluble fiber blend) or control (cellulose) immediately prior to serving. Participants were given timers and instructed to consume the breakfast within 10 minutes. After the breakfast was complete, blood samples were taken for assessment of glucose, insulin, acetaminophen (Tylenol) and growth hormone and visual analog scales were completed by participants every 15-30 minutes. Following 210 minutes participants were provided with pizza lunches as a measure of the effect of soluble fiber blend and cellulose on energy intake.

| Nutrient | Bagel (100g) | Cream Cheese (60g) | Orange Juice (249ml) | Total |
|---|---|---|---|---|
| Energy (kcal) | 266.7 | 174.1 | 114.0 | 554.8 |
| Protein (g) | 8.9 | 3.9 | 2.1 | 14.9 |
| Fat (g) | 2.2 | 17.4 | 0.0 | 19.6 |
| Carbohydrate (g) | 52.2 | 3.9 | 27.0 | 83.1 |
| Sugar (g) | 4.4 | 3.9 | 22.8 | 31.1 |
| Fiber (g) | 2.2 | 0 | 0.0 | 2.2 |

## TABLE 6.2. NUTRIENT CONTENT OF PIZZA LUNCH

Participants consumed breakfasts with either granulated soluble fiber blend or cellulose. 210 minutes after completing the breakfast, participants were provided with cheese pizzas that were purchased at local retailers. Pizzas were cooked in an oven and cut into bite-size pieces and distributed on a tray to distract participants from the amount of whole pizzas they were consuming. Participants were instructed to eat until satisfied. Pizzas were measured before they were given to participants and left-overs were measured once participants reported being satisfied as a measure of the effects of soluble fiber blend or cellulose on energy intake.

| Nutrient | Amount (for 95g serving: 1 pizza) |
|---|---|
| Energy (kcal) | 210 |
| Protein (g) | 10 |
| Fat (g) | 8 |
| Carbohydrate (g) | 26 |
| Sugar (g) | 2 |
| Fiber (g) | 1 |

then consumed a breakfast meal (bagel, cream cheese, orange juice, water) containing either the granulated SFB (highly viscous fiber) or granulated cellulose (low viscosity fiber) control sprinkled and mixed into the cream cheese immediately prior to consumption. Participants were also provided with 3 extra strength Tylenol™ and instructed to systematically consume half a tablet with meal components so the meal would be as evenly distributed in the GI tract as possible. Prior to and every 15 minutes following the consumption of the meal, participants recorded subjective satiety scoring and physical comfort using a visual analog scale. Blood samples were drawn by a phlebotomist before the meal (fasting) and at 30, 60, 90, 120, 180 and 240 minutes after the meal. Blood was spun and plasma frozen for future analysis of glucose (whole blood), insulin and acetaminophen concentrations. A pizza lunch with bottled water was provided to participants at 210 minutes. Participants were instructed to consume as much lunch as they desired until they felt satisfied (not stuffed but not still hungry). Participants were also instructed that the amount of water consumed on the first study would be measured and served in the same quantity on the second study visit. The amount of pizza consumed at this lunch was measured to provide an objective indication of the effects of the SFB compared to cellulose on satiety (quantity of food chosen). In addition, 24-hour symptom diary, food intake and physical activity records began being collected by the participant immediately upon leaving the clinic on the study day. The purpose of the 24-hour records was to assess effects of the preloads on longer-term satiety. Each participant was asked to follow the same dietary, sleep and exercise routine they followed prior to the first study for the day prior to the next study visit (Figure 6.1).

Randomization and labeling of preload fiber containers was performed by a research assistant who was blinded to the study. Randomization of preload treatment order was done by alternating the first treatment between "A" or "B" by subject number.

#### 6.3.3.1 Study Environment

Participants spent both visits in a private office that was devoid of any visual or olfactory cues related to food. Magazines were provided for reading, however each was pre-screened by study personnel for pictures and articles related to food and drink. Participants were allowed to use the washroom; however remained in the study office for all blood collection procedures. Study foods were

served at a desk in the office and participants were provided with timers and instructed to consume the preload breakfast within 10 minutes. The door of the office remained closed throughout the study unless study personnel were entering.

### 6.3.4 EXPERIMENTAL ANALYSES

#### 6.3.4.1 Visual Analog Scales:

Subjective measurements of motivation to eat and physical comfort were assessed using visual analog scales (VAS)[238]. Each of the questions on the VAS was associated with a 100 mm line anchored at each end with opposing statements [238]. For instance, fullness was assessed with the following statement to the left side of the line: "not full at all" and the following statement to the right side of the line: "as full as I have ever felt". Participants marked an "X" on the line at a point that they felt reflected their feelings at the moment the test was taken. Scores were assessed by measuring the distance between the intersection of the "X" with the line and the left end of the line.

#### 6.3.4.2 Appetite scales:

Subjective appetite was assessed using the Motivation to Eat questionnaire, which included 4 questions:

Q1: How strong is your desire to eat? ("very weak" to "very strong")

Q2: How hungry do you feel? ("not hungry at all" to "as hungry as I have ever felt")

Q3: How full do you feel? ("not full at all" to "as full as I have ever felt")

Q4: How much do you think you could eat now? ("nothing at all" to "a large amount")

Average appetite scores were calculated as a summary measure using the following equation:

$$\text{Average appetite} = \frac{[Q1 + Q2 + Q4 + (100 - Q3)]}{4}$$

Since Question 3 assesses fullness, it has opposite anchors at each end of the 100 mm line compared to the other 3 questions. Therefore, Q3 is subtracted from 100 in the equation to adjust for this difference.

#### 6.3.4.3 Symptoms

Physical comfort was assessed using a similar VAS as subjective appetite. However, participants marked either "yes" or "no" after each marker of physical comfort. If they marked "yes" they were instructed to rate the severity of the side-effect on a 100 mm VAS and to provide any comments they felt

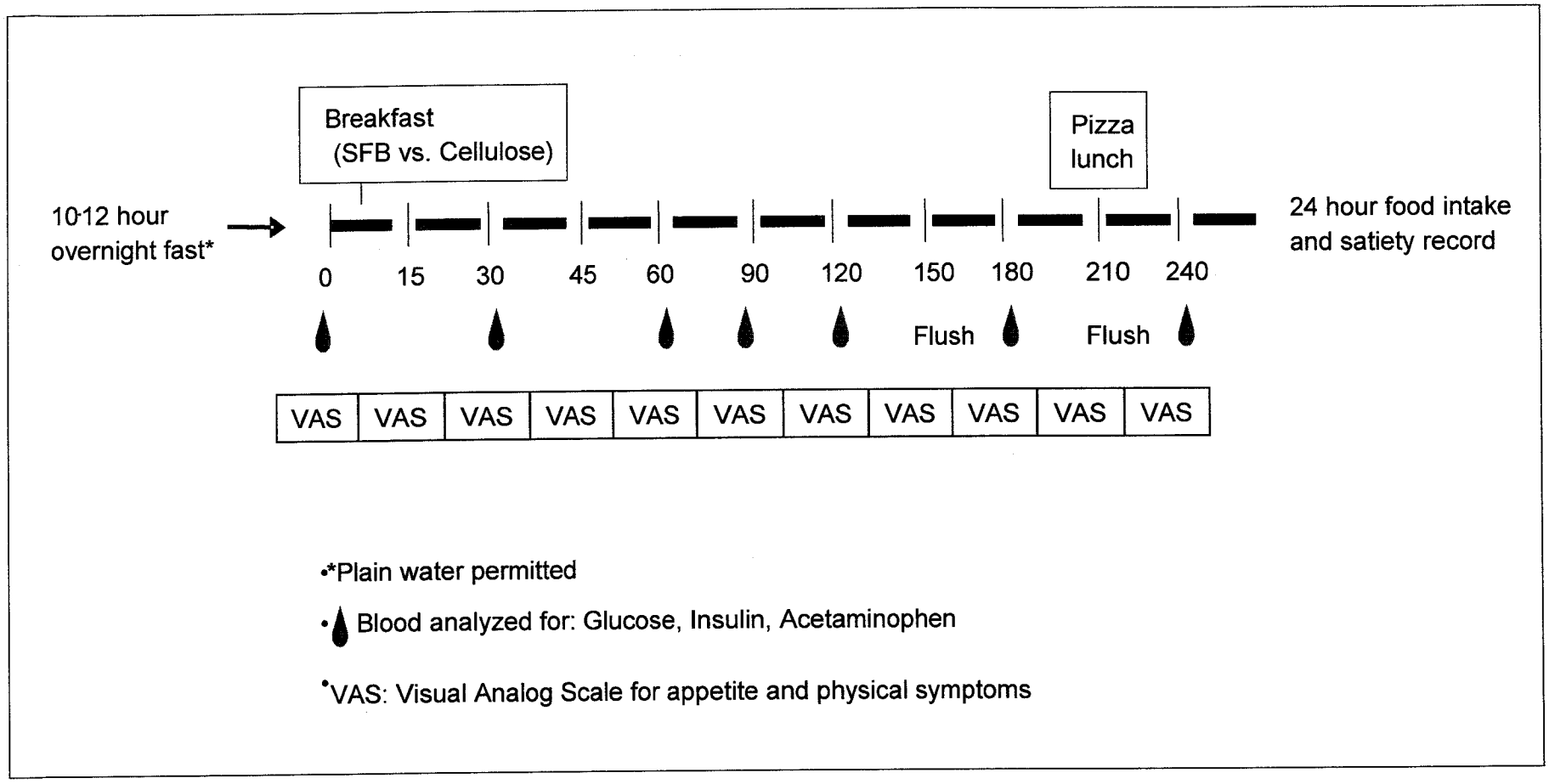



Figure 6.1. Study Day Protocol.
In an acute randomized cross-over study, participants arrived fasting and consumed a breakfast of a plain bagel, cream cheese, orange juice, 3 extra strength Tylenol (for measurement of gastric emptying time) and water. Cream cheese was mixed with either granulated soluble fiber blend (SFB) or cellulose control. After completion of the breakfast blood samples were collected for measurement of glucose, insulin, acetaminophen (Tylenol) and growth hormone and visual analog scales were completed for motivation to eat and symptoms. A pizza lunch was provided at 210 minutes. After completion of the study visit, participants were asked to record symptoms and food intake for 24-hours using a visual analog scale.

were necessary. The physical comfort scale included bloating, belching, diarrhea, flatulence, stomach pain, nausea, and a category for "other". In the "other" category, participants were asked to specify what they meant by "other" and rate the severity using the 100 mm line.

#### 6.3.4.4 Pizza Intake

Initially, 4 pizzas were served and subjects were informed that more hot pizza would be delivered to them after 10 minutes. After 10 minutes participants received the second batch of hot pizza. The second batch of pizza was provided in the same quantity, using the same cooking, weighing and presentation methods described. At the time the second batch was delivered, the first tray was removed from the participant's table and brought back to the kitchen to be weighed while the participant consumed the second batch. After approximately 15 minutes the researchers entered the participant's office and removed the water and second helping of pizza and both were weighed to provide an objective indication of the effects of the SFB vs. cellulose on satiety (i.e. quantity of food chosen).

#### 6.3.4.5 Long Term Symptom and Appetite Records

The 24-hour symptom and appetite visual analog scale questionnaires were identical to the questionnaires completed during the study visit. Questionnaires were provided for before and after each meal (breakfast, lunch, dinner) for the next 24 hours. Questionnaires were also provided for before and after any snacks that participants may have consumed in the 24 hours following leaving the clinic and were instructed to copy the questionnaires if they decided to have more meals or snacks than the number of questionnaires that were provided.

#### 6.3.4.6 Gastric Emptying

The paracetamol (acetaminophen) test was used to assess gastric emptying rate[256]. Participants consumed 1.5 grams of acetaminophen in the form of 3 extra strength Tylenol™ caplets. The Tylenol™ caplets were provided with the preload breakfast and participants were instructed to consume ½ a tablet at regular intervals during the meal in order to evenly distribute the acetaminophen within the meal. The validity of the paracetamol absorption test in comparison with scintigraphy for gastric emptying assessment was evaluated previously[257]. In this review, authors found that the paracetamol absorption technique correlated well with scintigraphic assessment of liquid phase gastric emptying. Blood was

collected in BD Vacutainer® SST™ tubes containing spray-coated silica and a polymer gel for serum separation. Tubes filled with blood were immediately inverted several times and placed in a rack at room temperature to allow for clotting. After clotting, samples were separated using a refrigerated GS-6KR centrifuge (Beckman, Palo Alto, CA, USA) at 3000G for 15 minutes at 4°Celsius and serum was transferred to 1.5ml Eppendorf flex tubes (Eppendorf AG, Hamburg, Germany) and frozen at -70 $^{0}$ Celsius until analysis. Analysis of acetaminophen levels was performed by HPLC (high performance liquid chromatography) with UV detection. To 100uL of sample, 50 uL of internal standard (7-B-hydroxy-ethyl theophylline) and 250uL of ethyl acetate. This was vortex mixed for 1 minute then centrifuged for 5 minutes at 9000 rpm. The top organic layer was removed and dried by evaporation with room air. The dried residue was reconstituted in 150uL of methanol deionized water (ratio: 25%:75%) and 10-20uL of sample was injected into the chromatograph [258]. These levels were used as an indirect assessment of gastric emptying time since the acetaminophen is only absorbed once it has emptied out of the stomach and entered the proximal small intestine, where it is absorbed into the blood.

**6.3.4.7 Glucose**

Whole blood was transferred from a BD Vacutainer® SST™ tubes containing spray-coated silica and a polymer gel for serum separation immediately after blood collection to specially prepared tubes. The tubes were prepared with anti-clot solution. To prepare the solution, 7 ml of distilled water was mixed with the contents of three potassium oxalate, sodium fluoride Vacutainer® tubes and 50µl of this solution was then pipetted into 7ml tubes (Sarstedt, St. Leonard, Quebec). Seven ml of water were used together with 3 potassium oxalate tubes as it corresponds to the volume of blood intended for the glucose measurement tubes, i.e. assuming 1 drop of blood is 50 µl, addition of 3-4 drops of blood to the 50µl of solution pipetted into the Sarsted tube will be at the same concentration of 7ml of blood in the 7ml Vacutainer® tube. The Sarstedt tubes were left to air dry for 24 hours before capping.

These samples were analyzed for glucose using the YSI 2300 STAT PLUS (Yellow Springs, Ohio, USA). This machine uses a glucose oxidase method to analyze plasma glucose levels. The probe of the machine is fitted with a three layer membrane containing immobilized enzyme in the middle layer. When a blood sample is aspirated into the buffer-filled chamber, glucose diffuses through the membrane.

On contact with the immobilized oxidase enzyme, it is rapidly oxidized, producing hydrogen peroxide. They hydrogen peroxide is then oxidized at the platinum anode, producing electrons. A dynamic equilibrium is achieved when the rate of H2O2 leaving the immobilized enzyme layer is constant, which is indicated by a steady state response. The electron flow is linearly proportional to the steady state H2O2 production and the rate at which H2O2 leaves the immobilized enzyme layer are constant. The instrument was calibrated with a standard glucose solution prior to analysis of the samples using a solution of 10mmol/L glucose.

**6.3.4.8 Insulin and Growth Hormone**

Blood samples were collected in BD Vacutainer® SST™ tubes containing spray-coated silica and a polymer gel for serum separation. Tubes filled with blood were immediately inverted several times and placed in a rack at room temperature to allow for clotting. After clotting, samples were separated using a refrigerated GS-6KR centrifuge (Beckman, Palo Alto, CA, USA) tubes were spun in a at 3000G for 15 minutes at 4°Celcius and serum was transferred to 1.5ml Eppendorf flex tubes (Eppendorf AG, Hamburg, Germany) and frozen at -70 °Celsius until analysis. Serum samples were analyzed for insulin and growth hormone.

Insulin

The Beckman Access Ultrasensitive Insulin Assay is a simultaneous one-step immunoenzymatic ("sandwich") assay. A sample is added to a reaction vessel along with mouse monoclonal anti-insulin alkaline phosphatase conjugate and paramagnetic particles coated with mouse monoclonal anti-insulin antibody. The serum insulin binds to the antibody on the solid phase, while the conjugate reacts with a different antigenetic site on the insulin molecule. After incubation in the reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of insulin in the sample. The amount of analyte in the sample is determined from a stored, multipoint calibration curve. The laboratory coefficients of variation (CVs) for insulin were: for 66.0 pmol/L, mean CV was 5.12, 439 pmol/L, mean CV was 3.55 and for 1060 pmol/L mean CV was 3.45.

Human Growth Hormone

Growth Hormone was measured as an adjunct to an original protocol that included the collection of blood samples for the measurement of plasma ghrelin responses. It has been documented that ghrelin is a ligand for the growth hormone secretagogue receptor in the anterior pituitary, which can stimulate the secretion of growth hormone[259]. Although funding restrictions did not permit completion of the ghrelin assays, the growth hormone assays were still completed so that future research on the samples may be interpreted physiologically in the context of appetite suppression.

The Beckman Access Ultrasensitive hGH Assay is a simultaneous one-step immunoenzymatic ("sandwich") assay. A sample is added to a reaction vessel along with polyclonal goat anti-hGH alkaline phosphatase conjugate and paramagnetic particles coated with mouse monoclonal anti-hGH antibody. The serum hGH binds to the monoclonal anti-hGH on the solid phase, while the goat anti-hGH-alkaline phosphatase conjugate reacts with a different antigenetic site on the serum hGH. After incubation in the reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of hGH in the sample. The amount of analyte in the sample is determined from a stored, multipoint calibration curve. The laboratory coefficients of variation (CVs) for growth hormone were: for 2.90 ug/L, mean CV was 4.24, 5.50 ug/L, mean CV was 4.16 and for 10.65 ug/L mean CV was 5.40.

### 6.3.5 STATISTICAL ANALYSES

Data were analyzed using SPSS software version 15.0 for Windows (Chicago, Ill). A Linear Mixed Models design was used with treatment and time used as repeated measures to determine the interactive and independent effects of treatment and measurement-time on parameters measured over time. If the interaction terms were significant, then pairwise comparisons between treatments were performed at each time point using the Sidak post hoc test. Body weights and consumption time between treatments were compared using a paired t-test. Results are expressed as mean ± SEM, unless otherwise stated. $P<0.05$ was taken as the criterion for significance.

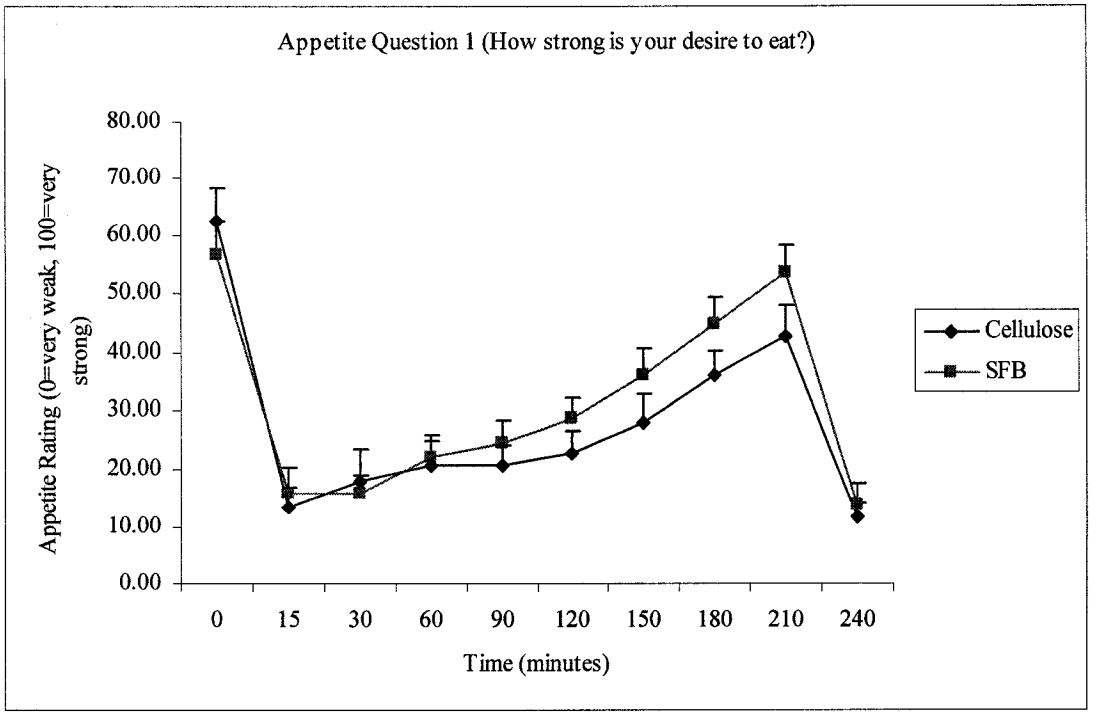
## 6.4 RESULTS

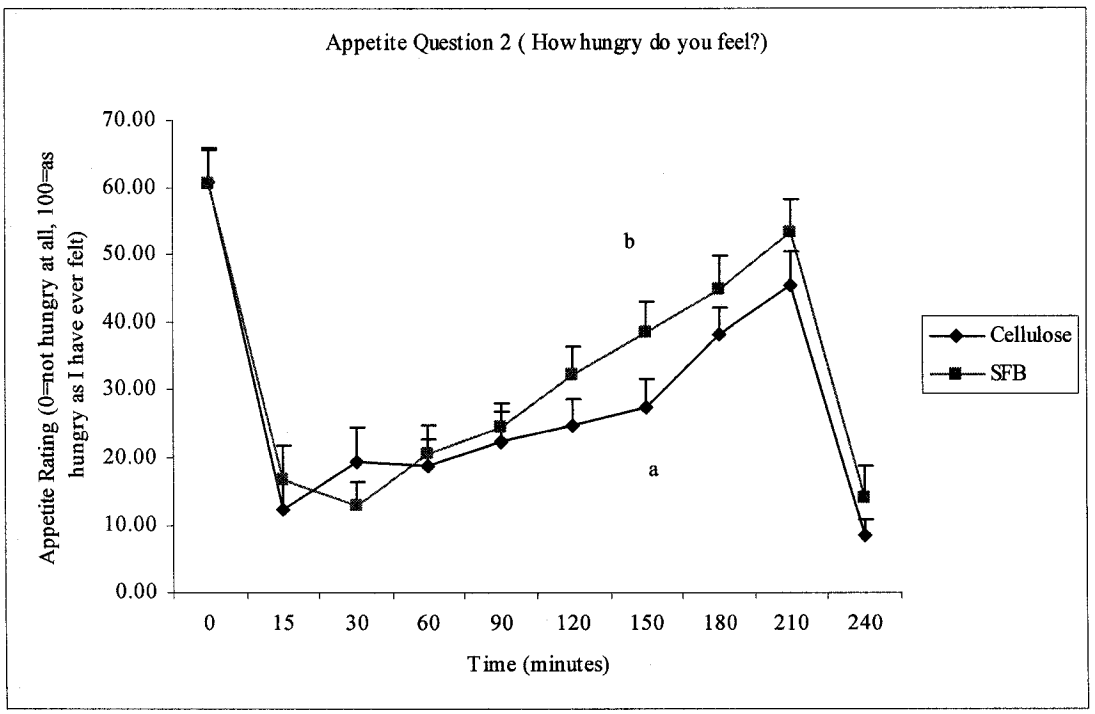
Body weight did not differ between treatment dates and screening (data not shown). All participants completed both study visits. Two of the 19 participants did not consume the acetaminophen used to determine gastric emptying time due to a protocol change following their enrolment in the study. One participant accidentally did not complete the 24 hour appetite and symptom record. All participants consumed the experimental breakfast within the designated 10 minute time frame. Consumption time did not differ between visits. The mean consumption time for cellulose was 9.8±0.8min and for SFB was 9.4±0.7min. All female participants completed the test within the first 10 days of the menstrual cycle. Number of hours of sleep per night on the evening prior to the tests did not differ between treatments.

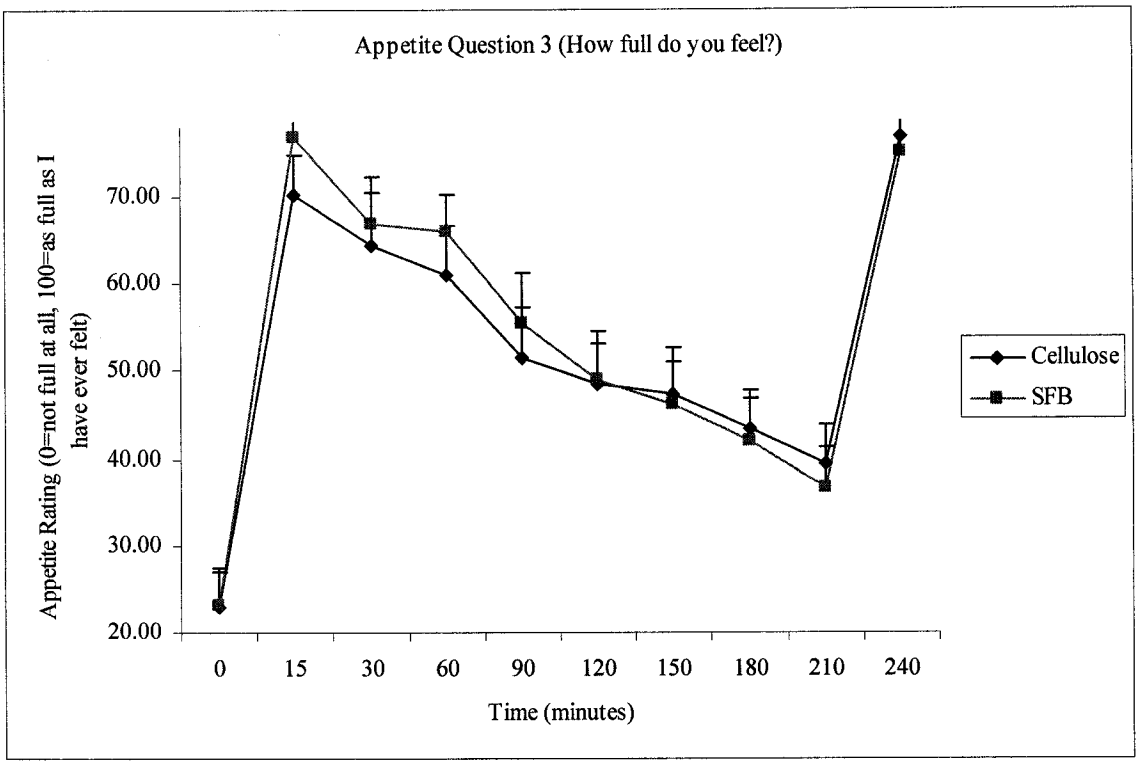
### 6.4.1 EXPERIMENTAL ANALYSES

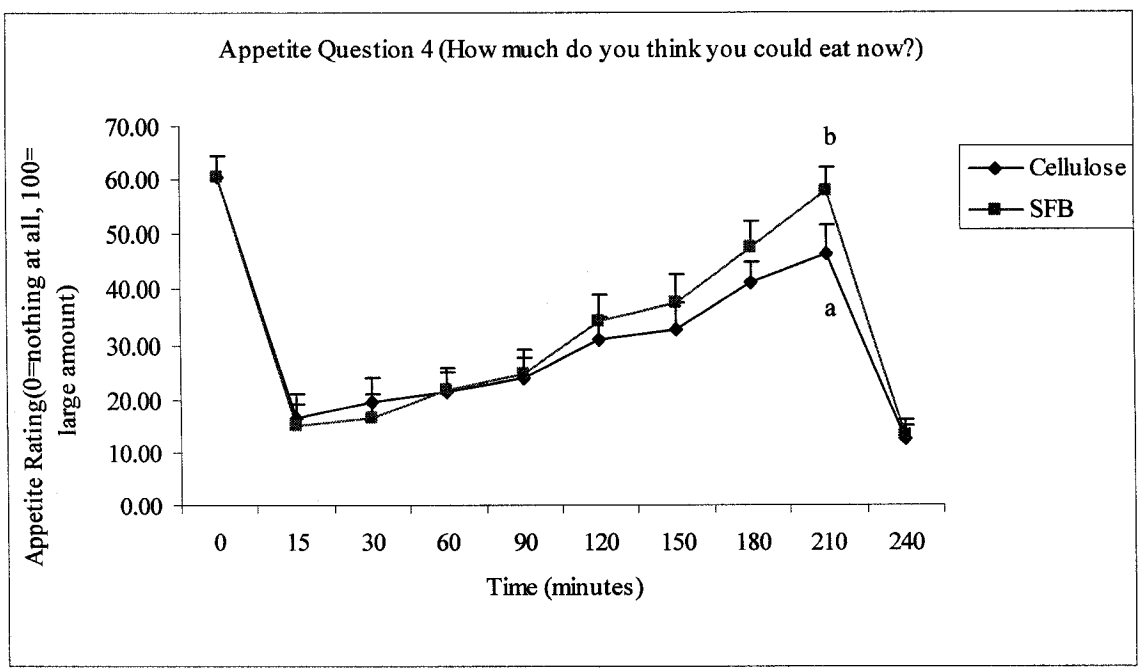
#### 6.4.1.1 Appetite

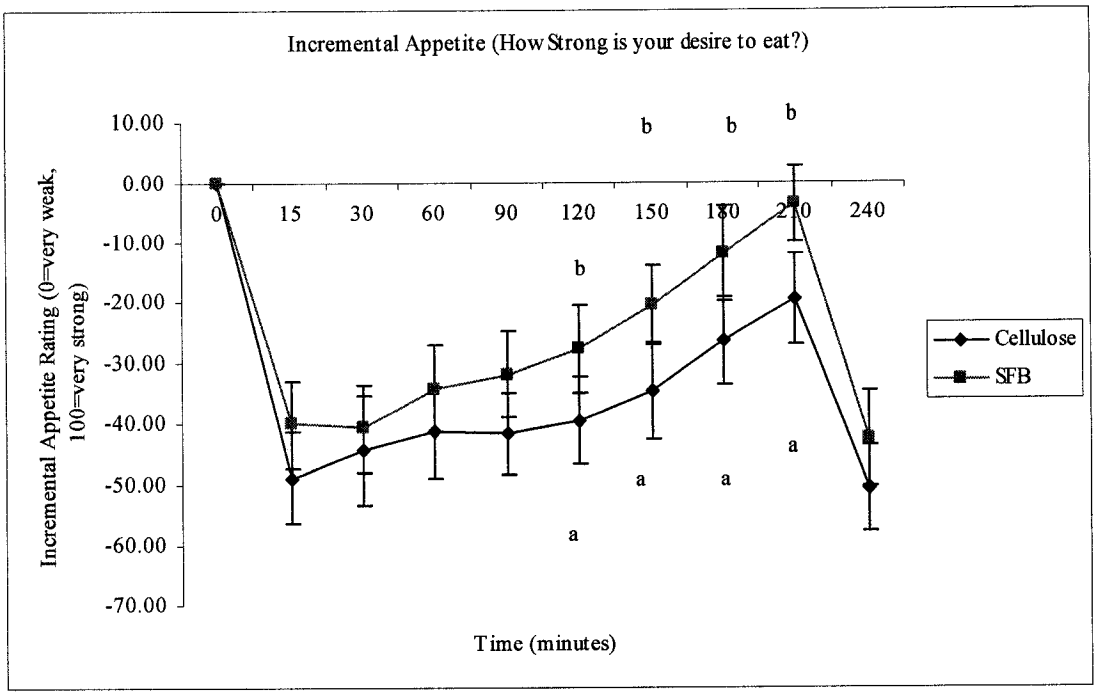
After 150 minutes, those consuming the SFB had greater hunger ratings ($p<0.05$) compared to cellulose control (SFB (38.32±4.49); control (27.54±4.05)). After 210 minutes, individuals consuming the SFB felt they could eat more ($p=0.026$) than after consuming the cellulose control (SFB (56.9±4.2mm); control (46.3±4.2mm)) (Figure 6.2). In addition, after 210 minutes, the average of the 4 appetite questions tended to be greater ($p=0.06$) in treatment compared to control (Figure 6.3). There was also a significantly different ($p=0.03$) effect of SFB (-12.0±7.0mm) on incremental appetite for question 1 (How strong is your desire to eat?) at 180 minutes compared to cellulose control (-25.8±7.0mm) and at 210 minutes (control:-19.4±7.0mm, SFB:-3.6±7.0m; $p=0.011$) (Figure 6.2). Incremental average of the 4 Appetite questions was significantly higher ($p=0.05$) after SFB (18.1±5.4mm) compared to cellulose control (8.4±5.4mm). (Figure 6.3)

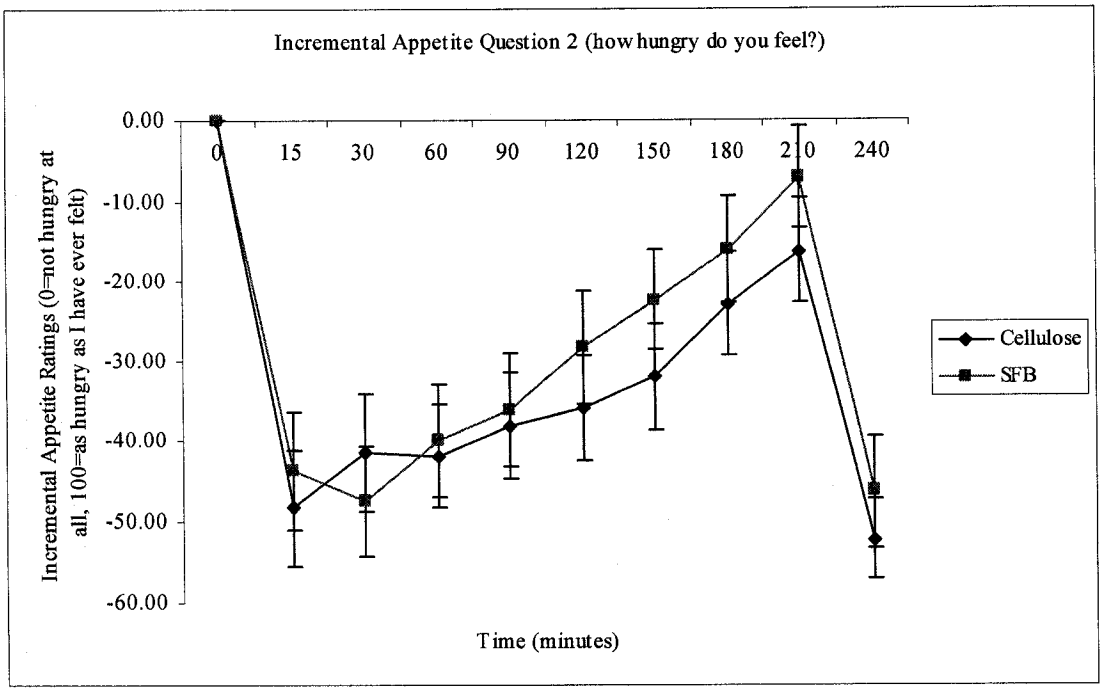

Appetite Question 1 (How strong is your desire to eat?)
Appetite Rating (0=very weak, 100=very strong)
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
0
15
30
60
90
120
150
180
210
240
Time (minutes)
Cellulose
SFB

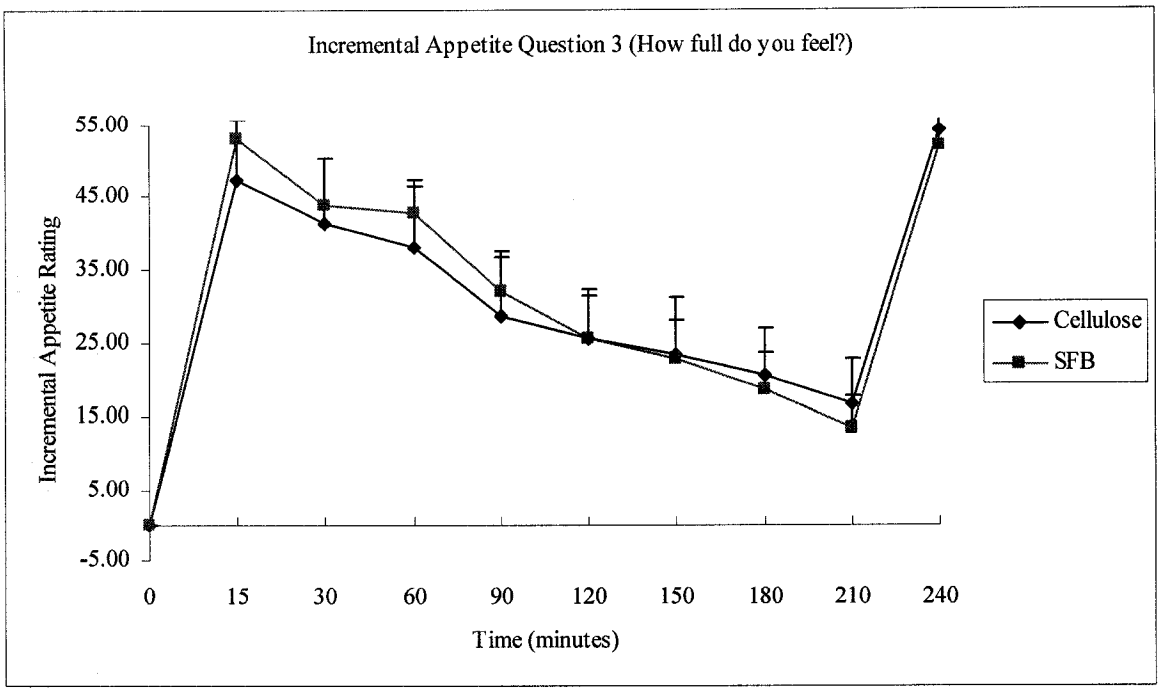

Appetite Question 2 ( How hungry do you feel?)
Appetite Rating (0=not hungry at all, 100=as hungry as I have ever felt)
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
b
a
0
15
30
60
90
120
150
180
210
240
Time (minutes)
Cellulose
SFB


Appetite Question 3 (How full do you feel?)
Appetite Rating (0=not full at all, 100=as full as I have ever felt)
70.00
60.00
50.00
40.00
30.00
20.00
0
15
30
60
90
120
150
180
210
240
Time (minutes)
Cellulose
SFB


Appetite Question 4 (How much do you think you could eat now?)
Appetite Rating(0=nothing at all, 100= large amount)
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
b
a
0
15
30
60
90
120
150
180
210
240
Time (minutes)
Cellulose
SFB


Incremental Appetite (How Strong is your desire to eat?)
Incremental Appetite Rating (0=very weak, 100=very strong)
10.00
0.00
-10.00
-20.00
-30.00
-40.00
-50.00
-60.00
-70.00
0
15
30
60
90
120
150
180
210
240
b
b
b
b
a
a
a
Time (minutes)
Cellulose
SFB


Incremental Appetite Question 2 (how hungry do you feel?)
Incremental Appetite Ratings (0=not hungry at all, 100=as hungry as I have ever felt)
0.00
-10.00
-20.00
-30.00
-40.00
-50.00
-60.00
0
15
30
60
90
120
150
180
210
240
Time (minutes)
Cellulose
SFB



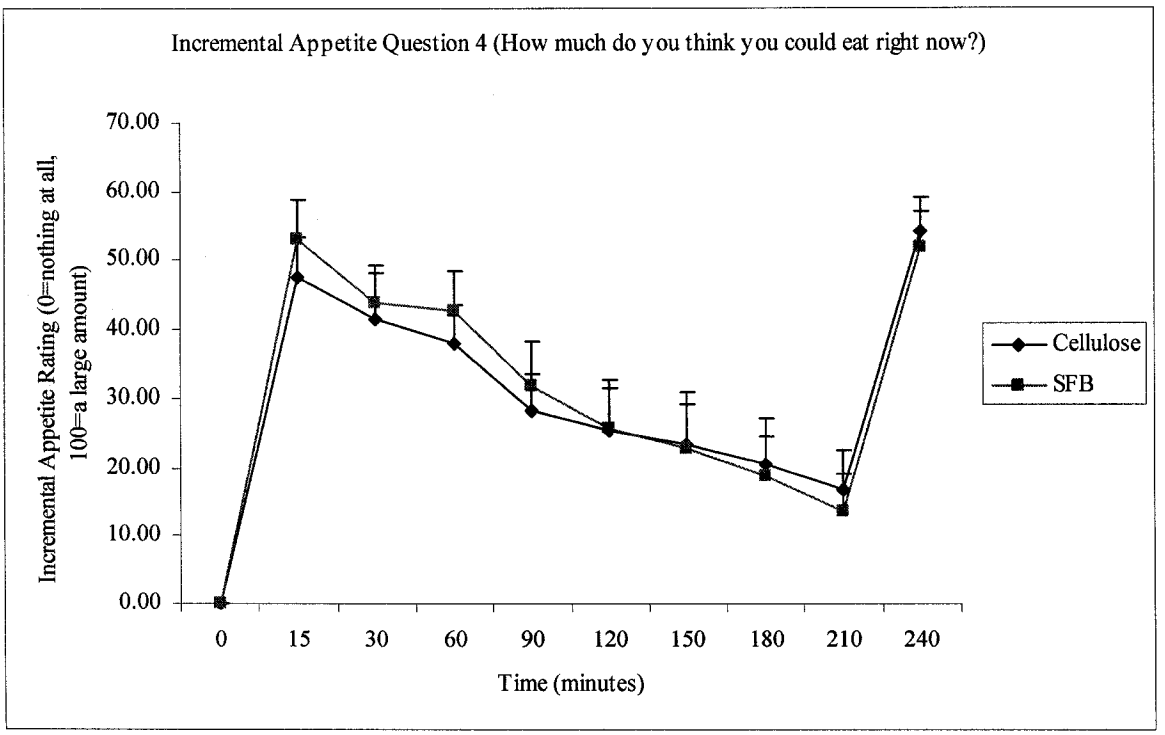




Figure 6.2. Absolute and Incremental Appetite

In a randomized crossover design, participants consumed a breakfast, which included a breakfast (plain bagel with cream cheese, orange juice, water and 3 acetaminophen as a marker of gastric emptying time). Granulated fiber (soluble fiber blend or cellulose control) was sprinkled into the cream cheese immediately prior to consumption. Appetite and symptom ratings were assessed fasting (0 minute time point) and every 15-30 minutes after the study treatment was consumed for 240 minutes using visual analog scales. After 210 minutes a pizza lunch was provided as a measure of the effect of fibers on food intake. Points and bars represent means ± SEM, respectively. Control fiber was cellulose and SFB was soluble fiber blend.

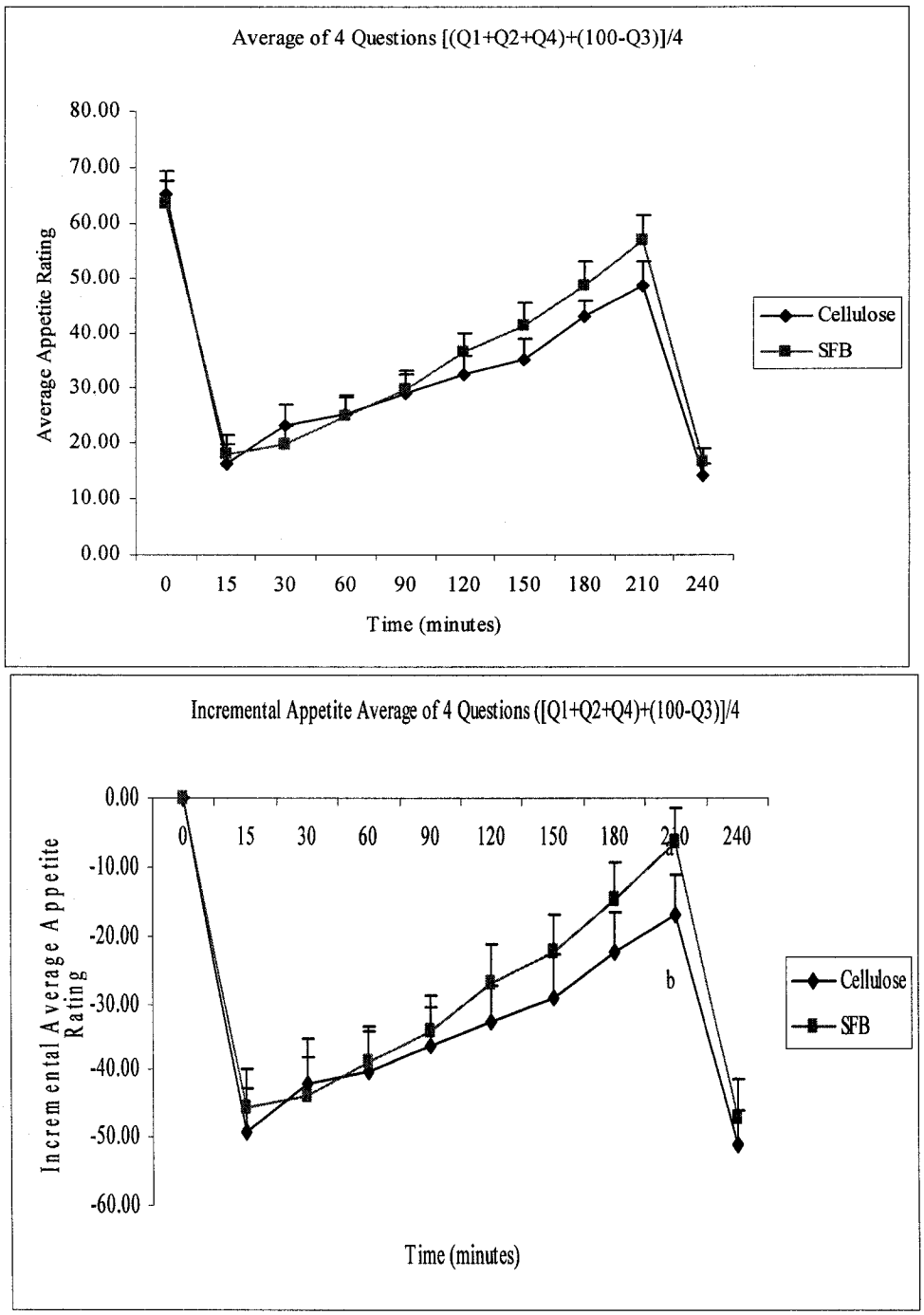



Figure 6.3 Average Appetite Scores
In a randomized crossover design, participants consumed a breakfast, which included a breakfast (plain bagel with cream cheese, orange juice, water and 3 acetaminophen as a marker of gastric emptying time). Granulated fiber (soluble fiber blend or cellulose control) was sprinkled into the cream cheese immediately prior to consumption. Appetite and symptom ratings were assessed fasting (0 minute time point) and every 15-30 minutes after the study treatment was consumed for 240 minutes using visual analog scales. After 210 minutes a pizza lunch was provided as a measure of the effect of fibers on food intake. Average scores were calculated by adding the three appetite questions related to hunger and subtracting the question related to fullness from 100. The sum was divided by the number of questions (4 questions). Points and bars represent means ± SEM, respectively.

#### 6.4.1.2 Symptoms:

Mean symptom ratings were reported to be low in magnitude. There were no differences in symptoms between SFB and control treatments (Appendix 2).

#### 6.4.1.3 Food Intake:

There was no difference between treatments in pizza intake at the test meal (Figure 6.4).

#### 6.4.1.4 Twenty Four Hour Symptoms, Appetite and Intake

There was a significantly greater amount of belching after snack with SFB (11.7 ± 8.4 mm) compared to control (3.7 ± 3.3mm) ($p=0.024$) but were no other differences in symptoms between SFB and control (Table 6.3). There was a significantly lower ($p=0.042$) rating for the 24-hour record of question 2 (How hungry do you feel?) after control (14.4 ± 4.9mm) compared to SFB (31.5 ± 5.2mm) after lunch (Figure 6.5). No differences existed in 24-hour food intake between SFB and control (Table 6.4)

#### 6.4.1.5 Gastric Emptying

There was a significantly lower ($p=0.006$) level of serum acetaminophen after control (65.5±7.3 umol/l) compared to SFB (89.1±7.8 umol/l) at 30 minutes. Similarly, at 60 minutes, there was a significantly lower ($p=0.004$) serum level of acetaminophen for control (94.2±7.3 umol/l) compared to SFB (119.1±7.2 umol/l). There was a significantly lower ($p=0.004$) serum acetaminophen area under the curve (AUC) after control (18330.13 ± 1570.02 umol/l.min) compared to SFB (19201.41±1470.54umol/l.min) (Figure 6.6). These results suggest that control had a slower gastric emptying rate than SFB.

#### 6.4.1.6 Glucose

Plasma glucose was significantly lower ($p=0.039$) after SFB (5.2±0.2mmol/l) compared to control (5.7±0.2mmol/l) at 60 minutes. It was also lower ($p=0.007$) at 240 minutes after SFB (4.5±0.2mmol/l) compared to control (4.4±0.2mmol/l). Incremental glucose response was also significantly lower ($p=0.02$) after SFB (0.7±0.2min.mmol/l) compared to control (1.2±0.2min.mmol/l) at 60 minutes and was significantly lower ($p=0.003$) after SFB (0.3±0.2min.mmol/l) at 240 minutes compared to control (0.9 ±

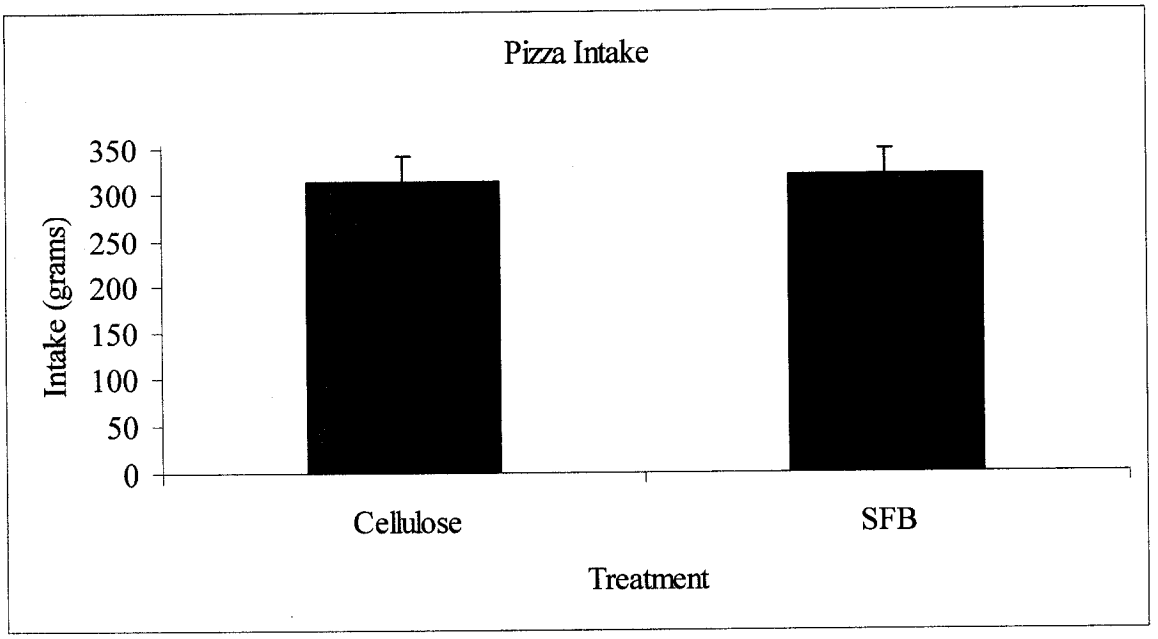


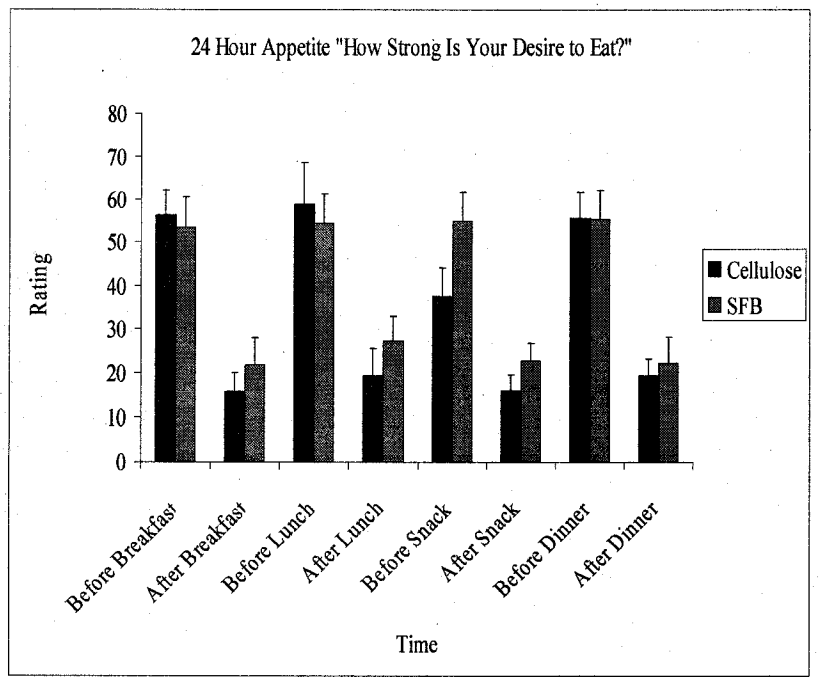

Figure 6.4. Pizza Intake
In a randomized crossover design, participants consumed a breakfast, which included a breakfast (plain bagel with cream cheese, orange juice, water and 3 acetaminophen as a marker of gastric emptying time). Granulated fiber (soluble fiber blend or cellulose control) was sprinkled into the cream cheese immediately prior to consumption. Appetite and symptom ratings were assessed fasting (0 minute time point) and every 15-30 minutes after the study treatment was consumed for 240 minutes using visual analog scales and blood samples were taken for assessment of glucose, insulin, acetaminophen and growth hormone. After 210 minutes a pizza lunch was provided as a measure of the effect of fibers on food intake. Participants were provided with unlimited amounts of pizza and were told to consume the pizza until they were comfortably full. The amount of pizza intake was determine by subtracting the left over amount from the weighed amount provided. Bars represent means ± SEM, respectively. SFB: soluble fiber blend.

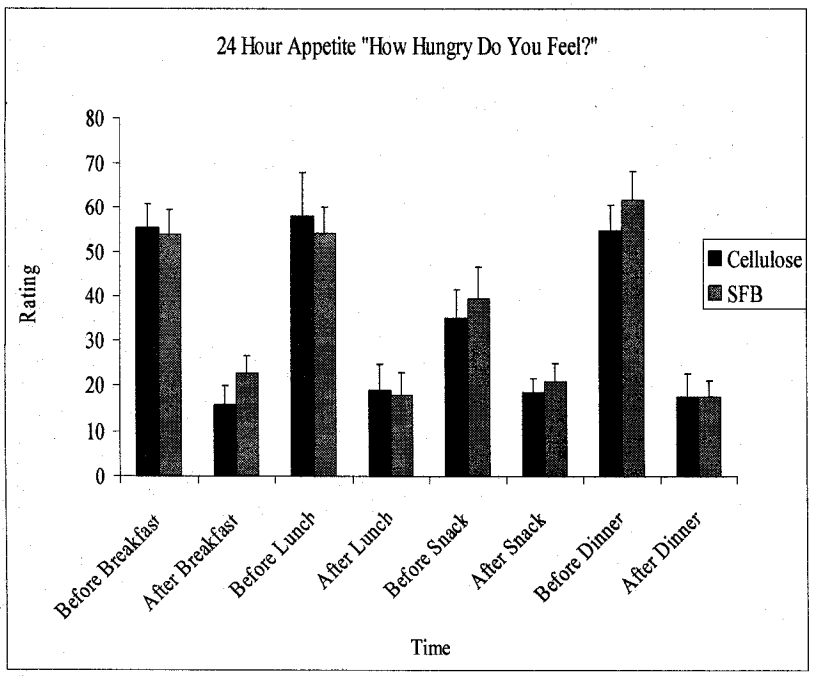
## TABLE 6.3. 24-HOUR SYMPTOMS

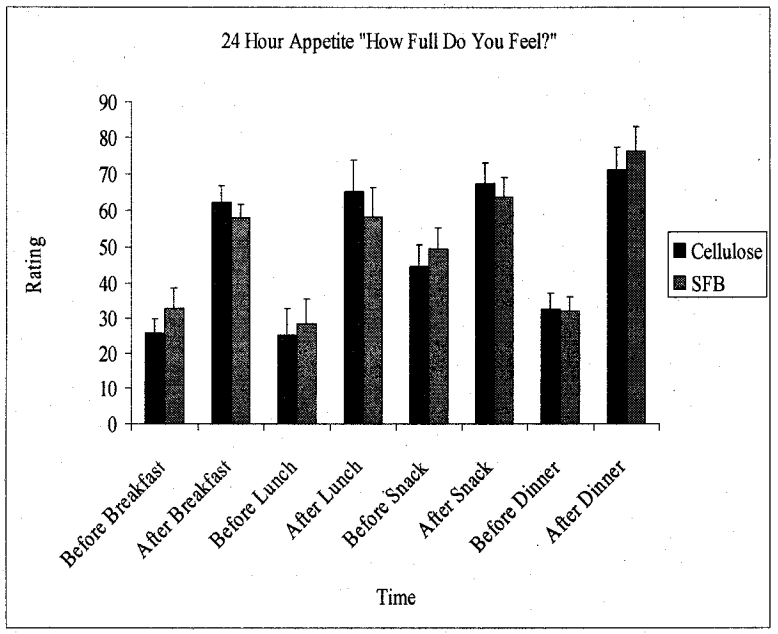
Participants consumed a breakfast with a bagel, cream cheese, orange juice, 3 extra strength Tylenol and water. Cream cheese was mixed with either granulated soluble fiber blend (SFB) or cellulose control. After completion of the breakfast blood samples were collected for measurement of glucose, insulin, acetaminophen (Tylenol) and growth hormone and visual analog scales were completed for motivation to eat and symptoms. A pizza lunch was provided at 210 minutes. After completion of the study visit, participants were asked to record symptoms for 24-hours using a visual analog scale.

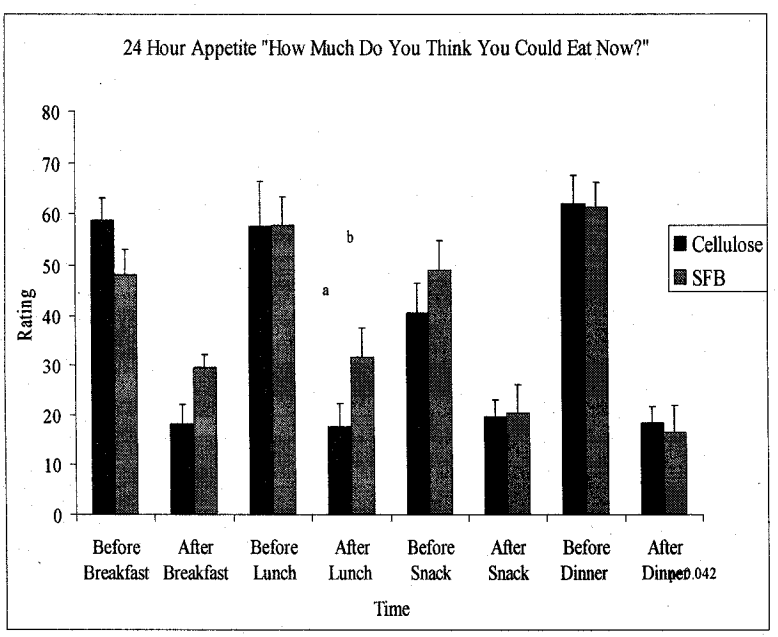
| | Before Dinner | After Dinner | Before Snack | After Snack | Before Breakfast | After Breakfast | Before Lunch | After Lunch |
|---|---|---|---|---|---|---|---|---|
| **Bloating** | | | | | | | | |
| Cellulose | 4.5±2.7 | 8.8±4.0 | 6.7±5.4 | 11±7.2 | 6.8±3.8 | 5.6±3.0 | 3.4±2.5 | 4.3±2.2 |
| SFB | 5.2±3.3 | 13.1±5.4 | 11.1±7.7 | 12.3±8.4 | 6.5±3.2 | 6.4±3.3 | 3±2.3 | 3.9±1.9 |
| **Belching** | | | | | | | | |
| Cellulose | 4.5±2.9 | 6.8±3.9 | 5.0±5.1 | 3.5±3.3[a] | 5.6±2.9 | 3.2±1.9 | 2.3±1.1 | 5.0±2.6 |
| SFB | 4.7±2.7 | 10.0±5.0 | 10.9±7.6 | 11.7±8.3[b] | 7.0±3.4 | 5.1±2.2 | 3.7±2.4 | 3.6±1.9 |
| **Nausea** | | | | | | | | |
| Cellulose | 5.1±2.2 | 2.5±1.2 | 1.3±0.7 | 7.0±4.5 | 3.4±1.9 | 0.9±0.2 | 1.6±0.8 | 0.9±0.4 |
| SFB | 4.9±2.7 | 3.6±1.5 | 2.2±0.3 | 4.0±1.9 | 5.6±2.6 | 3.8±1.9 | 4.5±2.9 | 4.0±2.3 |
| **Diarrhea** | | | | | | | | |
| Cellulose | 1.1±0.3 | 1.3±0.4 | 1.4±0.5 | 1.9±0.8 | 1.0±0.3 | 1.1±0.3 | 1.3±0.3 | 1.8±0.7 |
| SFB | 1.1±0.4 | 1.2±0.4 | 1.3±0.3 | 1.6±0.4 | 1.4±0.6 | 1.2±0.6 | 1.2±0.6 | 3.0±1.9 |
| **Stomach Pain** | | | | | | | | |
| Cellulose | 4.6±2.6 | 2.6±1.6 | 10.7±5.7 | 4.3±3.2 | 2.8±1.7 | 1.2±0.3 | 1.8±0.8 | 0.9±0.3 |
| SFB | 4.3±3.4 | 3.2±2.1 | 5.2±3.0 | 5.9±3.7 | 6.7±2.8 | 4.8±2.1 | 5.6±3.4 | 2.1±0.8 |
| **Flatulence** | | | | | | | | |
| Cellulose | 4.1±2.9 | 7.8±3.8 | 14.3±9.2 | 11.4±8.0 | 6.8±3.2 | 6.8±4.0 | 2.7±2.3 | 6.4±3.7 |
| SFB | 6.1±3.7 | 7.1±4.1 | 10.3±6.2 | 12.5±7.9 | 7.8±3.9 | 5.6±3.6 | 3.4±2.0 | 3.7±1.9 |

Values represent means ± SEM. Means from the 100 mm scale were used. Values within a row with unlike superscript letters are considered significantly different. *p=0.024


24 Hour Appetite "How Strong Is Your Desire to Eat?"
Rating
80
70
60
50
40
30
20
10
0
Cellulose
SFB
Before Breakfast
After Breakfast
Before Lunch
After Lunch
Before Snack
After Snack
Before Dinner
After Dinner
Time


24 Hour Appetite "How Hungry Do You Feel?"
Rating
80
70
60
50
40
30
20
10
0
Cellulose
SFB
Before Breakfast
After Breakfast
Before Lunch
After Lunch
Before Snack
After Snack
Before Dinner
After Dinner
Time


24 Hour Appetite "How Full Do You Feel?"
Rating
90
80
70
60
50
40
30
20
10
0
Before Breakfast
After Breakfast
Before Lunch
After Lunch
Before Snack
After Snack
Before Dinner
After Dinner
Time
Cellulose
SFB


24 Hour Appetite "How Much Do You Think You Could Eat Now?"
Rating
80
70
60
50
40
30
20
10
0
a
b
Before Breakfast
After Breakfast
Before Lunch
After Lunch
Before Snack
After Snack
Before Dinner
After Dinner
Time
Cellulose
SFB

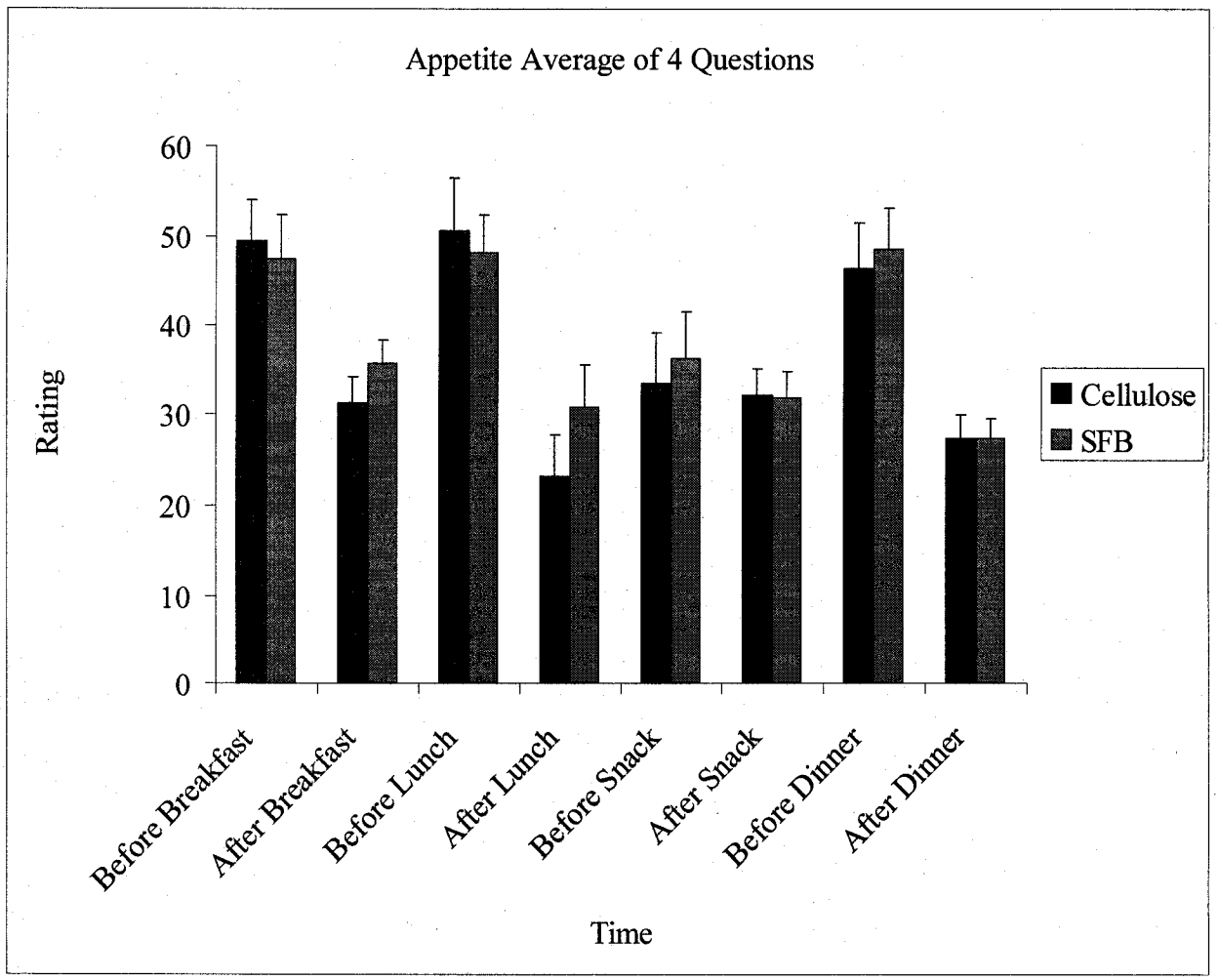



Figure 6.5. Long-Term Appetite
In a randomized crossover design, participants consumed a breakfast, which included a breakfast (plain bagel with cream cheese, orange juice, water and 3 acetaminophen as a marker of gastric emptying time). Granulated fiber (soluble fiber blend or cellulose control) was sprinkled into the cream cheese immediately prior to consumption. Appetite and symptom ratings were assessed fasting (0 minute time point) and every 15-30 minutes after the study treatment was consumed for 240 minutes using visual analog scales. After 210 minutes a pizza lunch was provided as a measure of the effect of fibers on food intake. Appetite ratings and food intake were recorded by participants for 24 hours after the end of the study period. Participants were given a package of visual analog scales, which they were asked to complete before and after any meals and snacks they consumed. Q1: How strong is your desire to eat? ("very weak" to "very strong"), Q2: How hungry do you feel? ("not hungry at all" to "as hungry as I have ever felt"), Q3: How full do you feel? ("not full at all" to "as full as I have ever felt"), Q4: How much do you think you could eat now? ("nothing at all" to "a large amount").
Bars and lines represent means and SEM, respectively.

**TABLE 6.4. 24 HOUR FOOD INTAKE**

Participants consumed a breakfast with a bagel, cream cheese, orange juice, 3 extra strength Tylenol and water. Cream cheese was mixed with either granulated soluble fiber blend (SFB) or cellulose control. After completion of the breakfast blood samples were collected for measurement of glucose, insulin, acetaminophen (Tylenol) and growth hormone and visual analog scales were completed for motivation to eat and symptoms. A pizza lunch was provided at 210 minutes. After completion of the study visit, participants were asked to record symptoms and food intake for 24-hours after they left the clinic.

| 24 hour intake | Calories | Protein | Carbohydrate | Fiber | Sugar | Fat | Water | Caffeine |
|---|---|---|---|---|---|---|---|---|
| **Cellulose** | 1902 ± 160 | 84 ± 8 | 264 ± 26 | 21 ± 2 | 94 ± 15 | 65 ± 7 | 1434 ± 162 | 110 ± 18 |
| **SFB** | 1799 ± 153 | 83 ± 7 | 242 ± 27 | 20 ± 2 | 97 ± 14 | 57 ± 5 | 1461 ± 146 | 110 ± 20 |

Values represent means ± SEM. Values within a column with unlike superscript letters are significantly different ($p<0.05$).

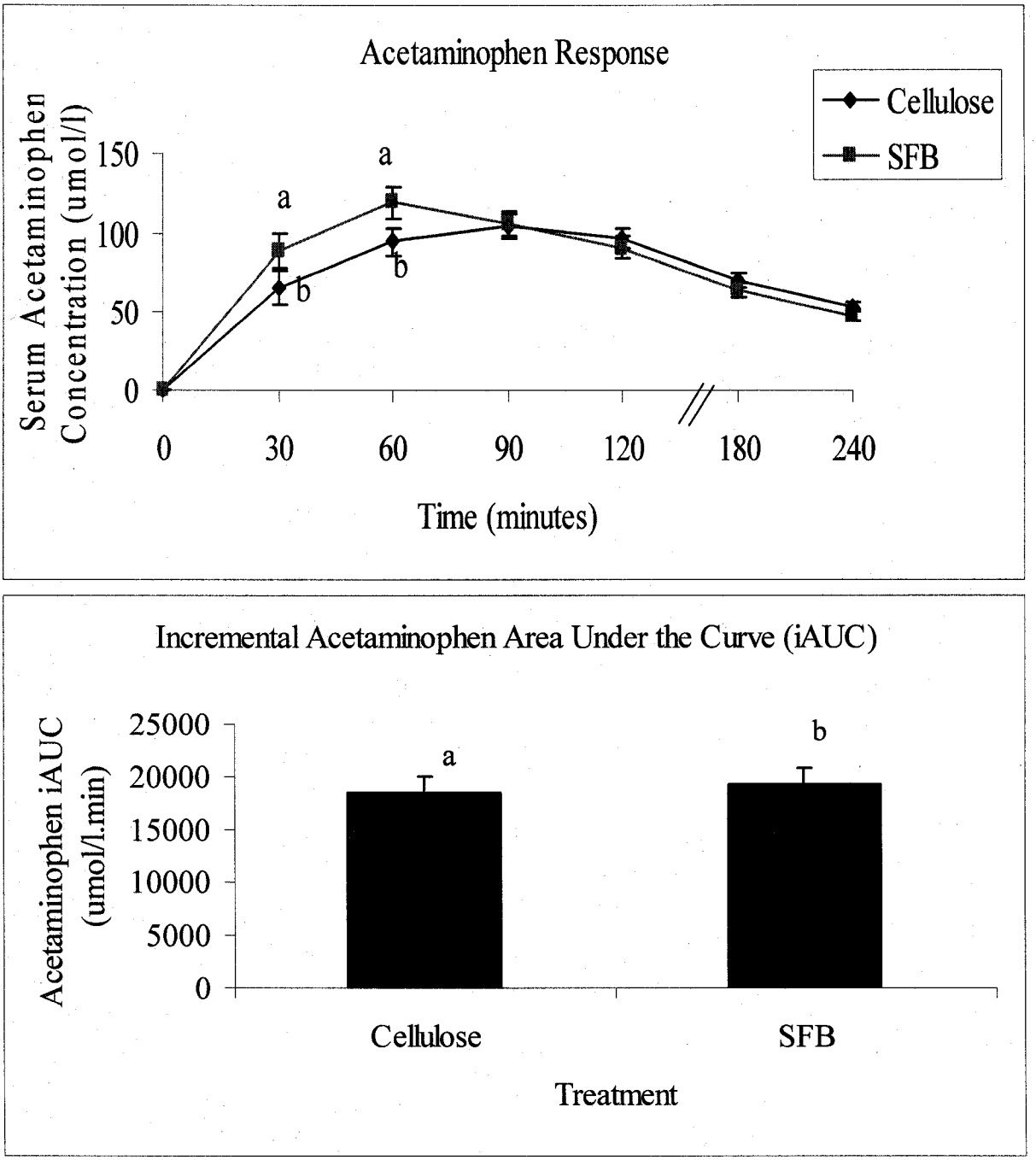



Figure 6.6. Serum Acetaminophen Response

In a randomized crossover design, participants consumed a breakfast, which included a breakfast (plain bagel with cream cheese, orange juice, water and 3 extra strength Tylenol (acetaminophen as a marker of gastric emptying time). Granulated fiber (soluble fiber blend or cellulose control) was sprinkled into the cream cheese immediately prior to consumption. Appetite and symptom ratings were assessed fasting (0 minute time point) and every 15-30 minutes after the study treatment was consumed for 240 minutes using visual analog scales. Blood samples were collected for assessment of glucose, insulin, serum acetaminophen and growth hormone fasting and at 30,60,90,120,180 and 240 minutes. After 210 minutes a pizza lunch was provided as a measure of the effect of fibers on food intake. Bars and points represent means and lines represent SEM. SFB: soluble fiber blend.

0.2 min.mmol/l). Plasma glucose iAUC was significantly lower ($p<0.0001$) after SFB (125.6±7.9 mmol/L.min) compared to control (181.2±7.8 mmol/L.min) (Figure 6.7)

#### 6.4.1.7 Insulin

Serum insulin was significantly lower ($p=0.001$) after SFB (317.7±46.5 pmol/l) compared to control (469.4±47.2 pmol/l) at 60 minutes and was also significantly lower ($p=0.012$) after SFB (208.9±46.5pmol/l) compared to control (324.7±47.2pmol/l) at 90 minutes. After 240 minutes, there was a significantly lower ($p=0.01$) insulin response for SFB (257.1±46.5pmol/l) compared to control (376.4±47.2pmol/l). Incremental insulin followed the same pattern. At 60 minutes there was a significantly lower ($p=0.001$) incremental insulin response for SFB (264.1±42.1pmol.min/l) compared to control (423.2±42.8pmol.min/l) and after 90 minutes SFB was significantly lower ($p=0.007$) than control (SFB: 155.2±42.1 vs. control: 278.5±42.8 pmol.min/l). SFB was also significantly lower ($p=0.006$) at 240 minutes (203.4±42.1pmol.min/l) compared to control (330.2±42.8pmol.min/l). Incremental area under the curve was also significantly lower ($p<0.0001$) after SFB (38751.3±3256.4pmol/l.min) compared to control (57661.6±3321.4pmol/l.min) (Figure 6.8).

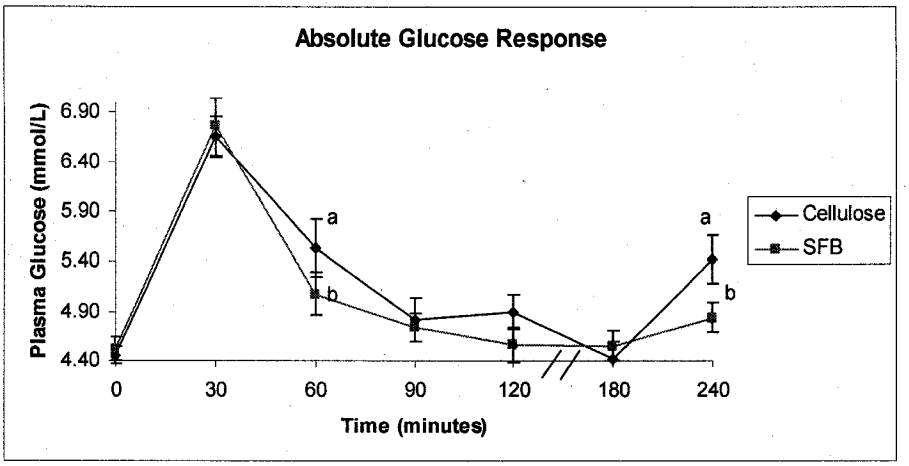
#### 6.4.1.8 Growth Hormone

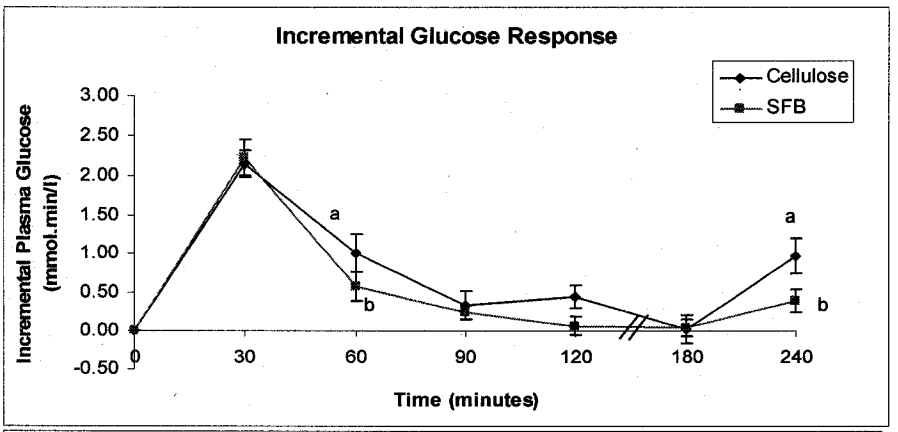
There were no differences in growth hormone level between treatment and control at any time points over the study period. Similarly, there were no differences in growth hormone net incremental area under the curve (AUC) between groups over the time period measured (Figure 6.9).

## 6.5 DISCUSSION

In the previous study, SFB lead to statistically lower intake compared to control and there was also a numeric trend towards reports of less hunger. The objectives of the current study were to determine whether the effect of the SFB on appetite and intake is correlated with glycemic, insulinemic effects and whether it can be explained by differences in gastric emptying compared to control.

The results of this study demonstrated lower glucose and insulin responses and AUC after SFB compared to control. However, despite these differences the gastric empting time was shorter (faster) after SFB than control; contrary to the hypothesis. In addition, there were no differences in appetite or food intake acutely or in the 24 hour period following the study.



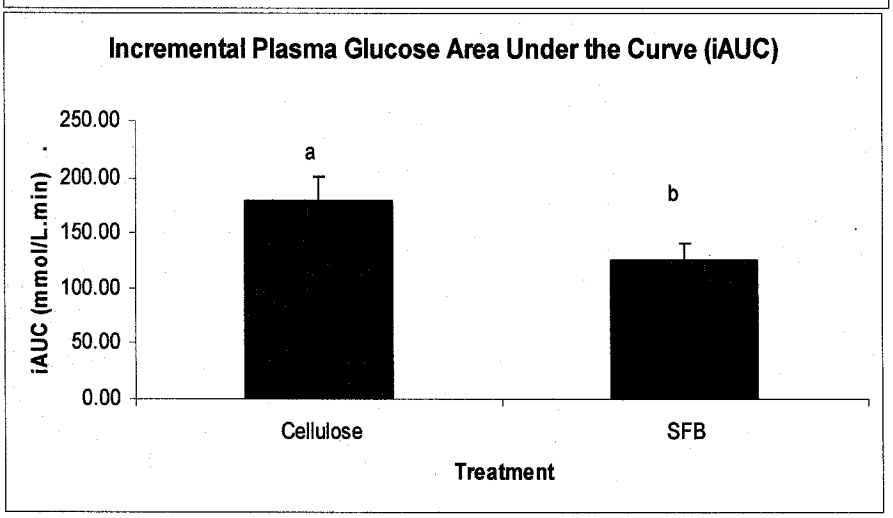
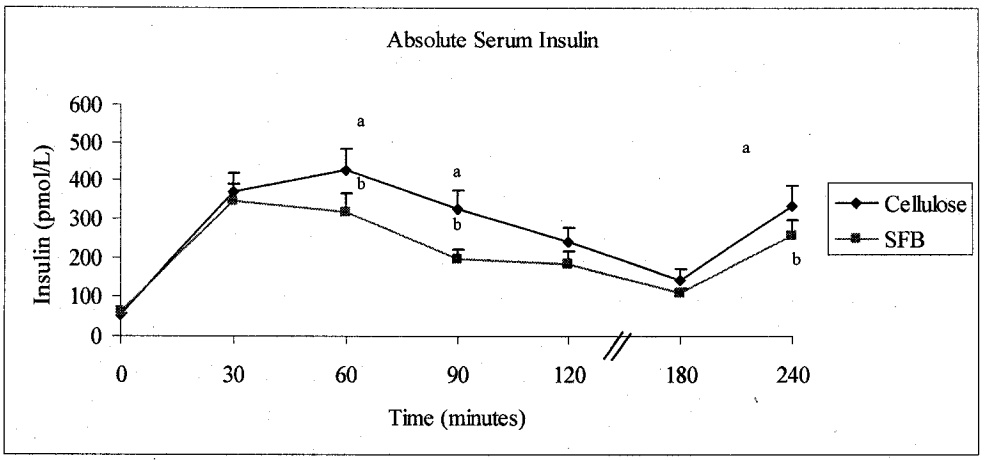
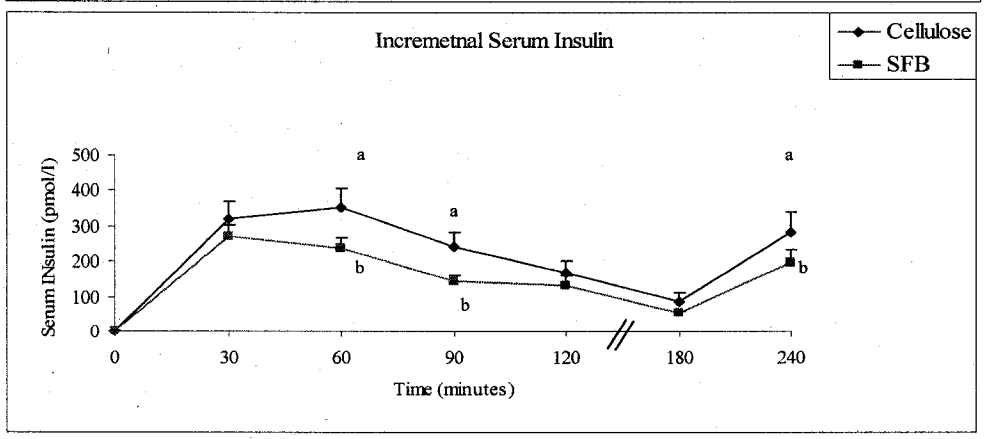




Figure 6.7. Plasma Glucose

In a randomized crossover design, participants consumed a breakfast, which included a breakfast (plain bagel with cream cheese, orange juice, water and 3 extra strength Tylenol (acetaminophen as a marker of gastric emptying time). Granulated fiber (soluble fiber blend or cellulose control) was sprinkled into the cream cheese immediately prior to consumption. Appetite and symptom ratings were assessed fasting (0 minute time point) and every 15-30 minutes after the study treatment was consumed for 240 minutes using visual analog scales. Blood samples were collected from the antecubital vein for assessment of glucose, insulin, serum acetaminophen and growth hormone fasting and at 30,60,90,120,180 and 240 minutes. After 210 minutes a pizza lunch was provided as a measure of the effect of fibers on food intake. Bars and points represent means and lines represent SEM. SFB: soluble fiber blend.



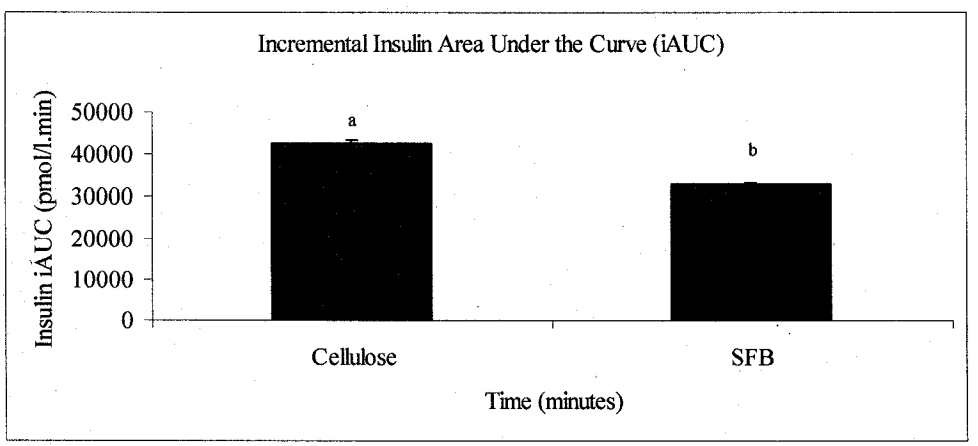




Figure 6.8. Serum Insulin

In a randomized crossover design, participants consumed a breakfast, which included a breakfast (plain bagel with cream cheese, orange juice, water and 3 extra strength Tylenol (acetaminophen as a marker of gastric emptying time). Granulated fiber (soluble fiber blend or cellulose control) was sprinkled into the cream cheese immediately prior to consumption. Appetite and symptom ratings were assessed fasting (0 minute time point) and every 15-30 minutes after the study treatment was consumed for 240 minutes using visual analog scales. Blood samples were collected from the antecubital vein for assessment of glucose, insulin, serum acetaminophen and growth hormone fasting and at 30,60,90,120,180 and 240 minutes. After 210 minutes a pizza lunch was provided as a measure of the effect of fibers on food intake. Bars and points represent means and lines represent SEM. SFB: soluble fiber blend.

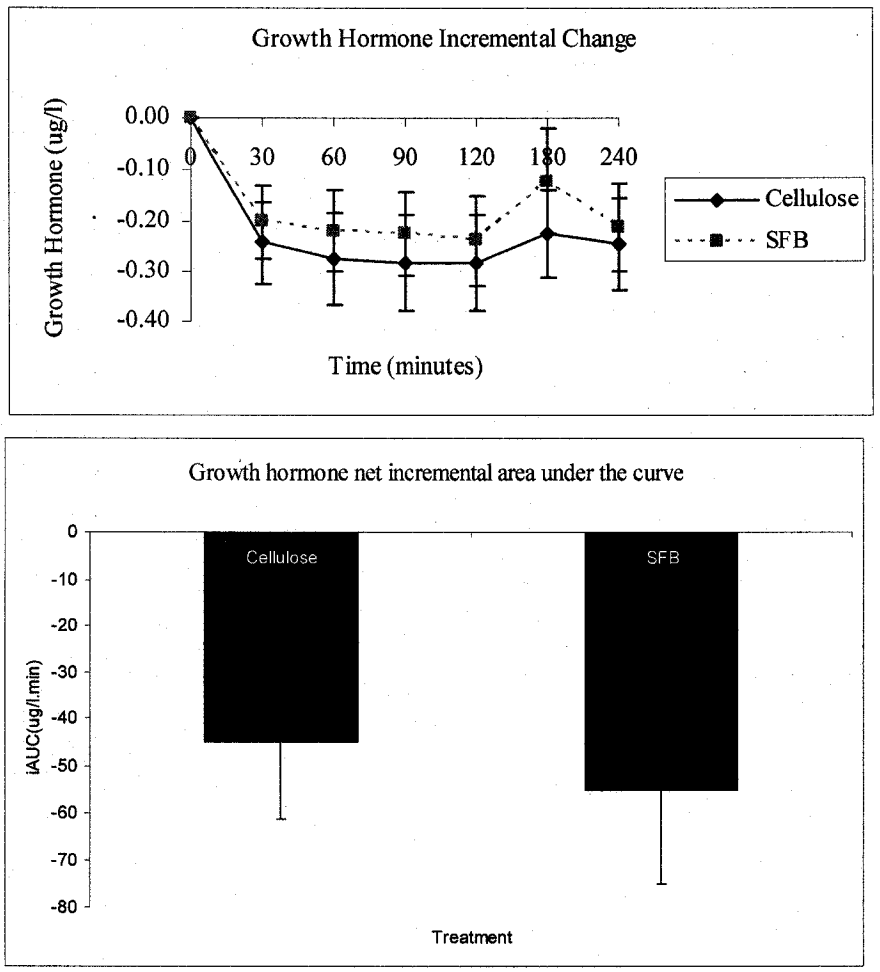



Figure 6.9. Growth Hormone

In a randomized crossover design, participants consumed a breakfast, which included a breakfast (plain bagel with cream cheese, orange juice, water and 3 extra strength Tylenol (acetaminophen as a marker of gastric emptying time). Granulated fiber (soluble fiber blend or cellulose control) was sprinkled into the cream cheese immediately prior to consumption. Appetite and symptom ratings were assessed fasting (0 minute time point) and every 15-30 minutes after the study treatment was consumed for 240 minutes using visual analog scales. Blood samples were collected from the antecubital vein for assessment of glucose, insulin, serum acetaminophen and growth hormone fasting and at 30,60,90,120,180 and 240 minutes. After 210 minutes a pizza lunch was provided as a measure of the effect of fibers on food intake. Bars and points represent means and lines represent SEM. SFB: soluble fiber blend.

The glucose and insulin results of this study support the previous dose-response and particle size studies, which demonstrated that both the dose of viscous fiber and the particle size used in the current study lead to lower glucose and insulin responses compared to controls. Recently, the glycemic index of SFB was performed using a standard glycemic index protocol and SFB was found to have a significantly lower glycemic index than white bread control [260].

The glucostatic theory postulates that the postprandial augmentation in plasma glucose is detected in the hypothalamic neurons and initiates a physiological signal for meal termination[83]. Despite the lower glucose responses in the current study there were no differences in appetite or food intake after SFB compared to control. Although the relationship between plasma glucose concentrations and appetite/intake have been supported by the glucostatic theory, somewhat controversial results of the theory exist in the literature. For instance, in a summary of studies measuring hunger and/or satiety in response to glycemic index, low glycemic index foods were associated with greater satiety/reduced hunger in 15 studies, but showed no difference in 16 studies[261]. Two of the studies that found no differences demonstrated that a high glycemic index meal increased satiety more than low glycemic index meal [262, 263] and one study found a positive correlation between postprandial glucose response and satiety [264]. Similarly only half of the studies found changes in intake that would support the glucostatic theory, suggesting that other factors may be contributing to the appetite besides glucose.

Despite debate surrounding the glucostatic theory, strong support of the theory still exists. In addition, recent research has revealed numerous additional factors beyond the glucostatic theory that may contribute to the regulation of energy intake, such as neuro-humeral signals. One factor that contributes to these signals is gastric emptying (GE) rate; the rate at which contents empty from the stomach into the proximal duodenum. The GE rate is highly variable and accounts for approximately 34% of the variability in the peak postprandial blood glucose response to a 75g glucose solution[265]. Studies of viscous dietary fibers show great inconsistency in the GE rate, compounding the variability in glucose response and potential glucostatic relationship [74, 94, 151, 153, 155, 159-162, 167, 168, 266-270]. Discrepancies could be due to methodology used for assessment of gastric emptying or from differences in test meal form (i.e. solid vs. liquid). For instance, liquids and solids show different gastric emptying kinetics;

liquids empty exponentially whereas solids and fats empty according to a linear function[166]. In the current study the paracetamol (acetaminophen) test of GE time, which has been found to be highly correlated with the gold standard MRI,[257, 271] demonstrated that the SFB had a faster gastric emptying rate compared to control. Although these results are contrary to the study hypothesis, an explanation derived from liquid and solid phase kinetics may provide a better understanding of the results. Following solid/liquid kinetics, it is possible that the liquid phase of the test breakfast emptied at an exponential rate in both SFB and control, however the mixing of the liquid and solid phases of the test meal did not occur in the presence SFB, due to the formation of a viscous gel formed with the solid phase. In this case, the liquid phase may have bypassed the gel and emptied at an exponential rate, carrying with it the acetaminophen (paracetamol) as it emptied and thereby leading to rapid increases in acetaminophen and fluid in the proximal duodenum. Conversely, in control, since no gel formation occurred, the liquid may have been free to mix with the solid portion of the meal in the stomach and emptied together in a more linear fashion. Support for this explanation comes from several research studies involving solid-liquid meal ingestion, which demonstrate that the solid food is retained in the proximal stomach until approximately 80% of the liquid has emptied [272-274]. In addition, the glucose and insulin results suggest that there was still a factor that lead to slowed digestion and absorption of glucose in the meal; possibly due to the formation of a gel, which temporarily bound the carbohydrate in the preload meal and prevented its absorption. Therefore, the current results of the gastric emptying test must be interpreted carefully and further exploration into the liquid and solid-phase differences in GE rate between SFB and control may lead to a better understanding of the relationship between the viscosity and the gastrointestinal mechanisms associated with a viscous fiber blend. One way this could be examined is by mixing the acetaminophen with the meal.

Besides differences in GE rates of liquid and solid phases of the meal, it is possible that the GE results were inconsistent with the hypothesis due to an interaction between viscosity and the amount of fiber present in the test breakfasts, as opposed to just the effect of viscosity on GE as well as timing. The dose of fiber required to suppress GE rate remains uncertain; some studies have found that larger doses (e.g. 10-15g) of fibers, such as pectin, suppress the GE of a solid-liquid meal [163, 275], whereas lower doses

(e.g. 2g) begin to suppress GE rate only in the late postprandial phase [276]. In the current study, although the viscosity of the SFB was higher than most 10-15g portions of other, less viscous fibers, perhaps both the quantity and rheological properties are important in GE rate. It is possible that a longer study period, in which dinner was controlled, may have demonstrated difference due to negative feedback inhibition once the gel emptied out of the stomach and responses throughout the gastrointestinal tract may have been compared.

In addition, there may have been methodological reasons that there were no differences between hunger and food intake in highly viscous SFB and control. For instance, the preloading paradigm is the most frequently used methodology and involves consumption of a food in which a food/nutrient attribute is modified for investigation. The effects of the modification are then measured shortly after in a test meal. Although this is an established and highly used methodology, variations exist within the methodology that may affect measurement of satiation. The time between ingestion of the preload and test meal is one source of variability that may have lead to different results in the current study, which did not demonstrate intake differences, compared to the previous study, which showed intake differences. In the current study, a 3.5 hour period elapsed between preload and test meal ingestion, whereas in the previous study a 90 minute time period elapsed. The 3.5 hour period was chosen to mimic the amount of time that would typically elapse between breakfast and lunch in an *ad libitum* setting. Studies reporting energy compensation after liquid foods have typically used short (0-20 minute time intervals between preload and test meal [63, 277-279], whereas energy compensation after solid foods typically have 2-4h time intervals [280-282]. A study by Rolls et al. (1991) found that as the time interval between preload and test meal increased, the accuracy of the compensation decreased [205]. Therefore, the results of the current study must be reassessed using a variety of intervals between preload and test meal while assessing the effect of SFB viscosity on the mechanisms of intake, since the mechanisms may be time-dependent.

Like the other studies, this study did not demonstrate differences in symptoms between treatments. This finding is an important clinical finding, as symptoms, such as bloating and gas that can occur with the addition of copious amounts of viscous fiber to a previously low fiber diet limit the practicality of adding fiber to the diet to reach current dietary guidelines. SFB reaches a high viscosity

with a small amount of fiber compared to other, less viscous, dietary fibers. Therefore, it is important to find that no differences existed between symptoms of the amount used in this study and a relatively low amount of non-viscous fiber control. If a smaller amount of fiber can be used in the diet to achieve the health benefits that the current dietary fiber guidelines are based on, it may increase the acceptability of adding viscous fiber to the diet. In addition, results in studies of appetite and intake, may be confounded by the presence of symptoms such as bloating and gas; where individuals may terminate food intake or feel more satiated due to the symptoms of not adapting to the level of fiber intake, rather than the mechanistic effects of the treatments. These results provide promising support for future studies that differences found in appetite and intake with SFB are likely not due to symptoms.

Future studies of SFB in relation to appetite and intake should, therefore, consider the time interval between preload and test meal, crushing the acetaminophen into the solid phase of the study meal and keeping the methodology standardized so that the amount of carbohydrate in the test meal is proportional to the amount of fiber used.

In conclusion, this study examined the effect of SFB compared to an insoluble fiber control on appetite, food intake and the mechanisms responsible, such as glucose, insulin and gastric emptying rate. Despite lower glycemic and insulinemic responses, there were no differences in appetite and food intake and SFB lead to faster gastric emptying rate compared to control. Future research is necessary to determine the methodological implications of these findings and continue to determine other metabolic factors, in addition to glucose and insulin that may explain the findings of reduced intake and increase satiation that previous studies of highly viscous fibers have demonstrated.

# **CHAPTER 7**. MAIN FINDINGS, GENERAL SUMMARY, LIMITATIONS AND FUTURE DIRECTIONS

# MAIN FINDINGS, GENERAL SUMMARY, LIMITATIONS AND FUTURE DIRECTIONS

## 7.1 MAIN FINDINGS

**Study 1:** The objective of study 1 was to determine the most efficacious particle size in a constituent of SFB to affect postprandial glycemic, insulinemic and appetite regulation. The results from this study found that glucose iAUC was lower ($p<0.01$) with large compared to medium and control particles and insulin iAUC was higher ($p<0.01$) in control compared to all particles and that satiety was greater ($p=0.04$) after large compared to other particles. Therefore, this study demonstrated that the most effective particle size in reducing glucose iAUC in the SFB was the largest particle size, illustrating the importance of identifying the particle size and other physical properties of soluble dietary fibers before examining their physiological responses.

**Study 2**: The objectives of study 2 were, using the most effective particle size from study 1, to determine the most effective dose of SFB in glucose and appetite regulation. This study demonstrated that glucose was lower ($p<0.05$) with 4 and 6g compared to control at certain postprandial time points and that glucose iAUC was higher ($p=0.0001$) in control compared to all doses. The results from this study suggest that an amount of SFB equal to or greater than 4.0 g may be appropriate for aiding in glycemic control of a meal, however since no differences existed among doses for glucose iAUC, there may be no additional benefit of ingestion of amounts equal to or greater than 4-6 grams compared to 2 grams.

**Study 3**: The objective of study 3 was to explore the effects of various viscosities of SFB on subjective and objective appetite and food intake using pre-established preload methodology in healthy participants. This study found that the SFB lead to lower ($p=0.047$) pizza intake compared to glucomannan (by 53g). Although no differences existed in subjective appetite ratings among different viscosities, the study demonstrated that SFB has an augmented ability to reduce food intake compared to glucomannan alone but not cellulose, the fiber with the lowest viscosity. Therefore, given that there were no differences between the highest and lowest viscosities, these results are of interest but must not be over-interpreted, however, since this study was not designed to examine the physiological reasons for appetite and intake, future investigation must incorporate mechanistic markers that may explain differences in food intake seen in this study.

**Study 4:** The objectives of the fourth study were to elucidate the mechanisms of action responsible for appetite and/or intake regulation, such as the metabolic parameters of appetite regulation, namely glucose and insulin and how they relate to gastric emptying time, subjective appetite ratings and the objective appetite indicator of food intake. The main findings of this study were that hunger was lower ($p<0.05$) after SFB, gastric emptying AUC was slower ($p=0.004$) after control and that glucose and insulin iAUC were lower ($p<0.0001$) after SFB. Despite lower glycemic and insulinemic responses that may have accounted for the differences seen in food intake the previous study, this study demonstrated no differences in appetite or food intake. SFB did, however, lead to faster gastric emptying rate markers compared to control. Due to methodological limitations, future research is necessary to further explore and determine other metabolic factors that may explain the findings of reduced intake and increase satiation that previous studies of highly viscous fibers have demonstrated.

## 7.2 GENERAL SUMMARY

The main findings of this research were that in soluble fiber blend, 4-6grams of larger particle size with highest viscosity lead to the greatest reductions in glucose, insulin, appetite and food intake. Future studies are required to examine the most appropriate methodology to confirm these and mechanistic findings.

Hypocaloric diets aid in body weight reduction but rely on strong willpower and typically result in discontinuation and weight regain. A dietary modality that aids in hypocaloric diet maintenance is required given the current obesity problem. Dietary fiber can reduce hunger through a combination of mechanisms, possibly by augmenting the abilities of co-ingested nutrients to control hunger. However, the population currently consumes half of the national fiber recommendations for adequate intake[1, 3]. Abdominal discomfort from increasing fiber intake quickly may hinder achievement optimal levels and result in research in this area having limited practical significance.

In addition, the literature provides inconsistent findings on the effects of soluble dietary fibers on hunger, food intake and their controlling mechanisms. For instance, some studies demonstrate reductions in hunger and slowed gastric emptying time, while others do not show any differences. One possible explanation for these inconsistencies is that the soluble fibers studied differ in variety, batch and therefore

physico-chemical properties. These small differences may have a large impact on the outcomes being measured. When the chemical properties are considered, the amount of dietary fiber required to achieve recommendations and health benefits may be reduced to a more acceptable amount. For instance, a combination of dietary fibers could be used that act synergistically to develop into a highly viscous gel and the potential to have a greater impact on health than its constituents alone. Until now, no studies have examined the effects of various gravimetric and physicochemical properties of viscous soluble dietary fibers on glucose, insulin and appetite regulation.

This work is the first to begin to examine the effects of a blend of viscous dietary fibers, as a model for a standardized soluble fiber that may be ingested in smaller quantities than other fibers to help individuals reach the same health benefits achievable with the current national recommendations. The findings of the four studies presented provide evidence of the role of both rheological and gravimetric factors as well as methodological approaches that must be considered in future studies for standardization of fibers and for standardization of methodologies in the literature that may make results more comparable.

Future advice may include the addition of 5 grams of granulated soluble fiber blend to a meal as an acceptable alternative to the population to achieve the recommended daily intake of dietary fiber for maximum health benefits.

Future studies are, however, required to further define fiber properties, appetite mechanisms and methodology used to elucidate the mechanisms that affect appetite and food intake, which are currently inconsistent in the literature used.

Controlling for variability in studies of fibers is of great importance given that research involving appetite and food intake includes so many extraneous sources of variability, such as psychological factors, cues and belief that may confound findings. A more thorough knowledge of these characteristics may allow previous findings in the literature to be better interpreted and future findings to be more comparable and may aid in the clinical advice used with hypocaloric diets for long-term weight loss and weight maintenance.

## 7.3 LIMITATIONS

Despite the results found in these studies, there were several methodological limitations that, if addressed, may lead to stronger future studies.

In the first study, which examined the effect of various particle sizes on glucose response and satiety, the results did not demonstrate a graded glycemic response. In other words, given that the large particle size was the only treatment to show differences in glucose compared to other particle sizes, it could be hypothesized that the medium particle size should have showed a lower glycemic response compared to control but a greater glycemic response compared to large particle size and that small particle size also should have demonstrated a lower glycemic response compared to control but a greater glycemic response compared to medium and large particle sizes. Two potential limitations of the study may be proposed for this lack of graded glycemic response. First, perhaps the differences in particle size were not great enough to demonstrate physiological differences. Larger differences in particle size than the ones in the current study may be required. The differences in mesh size between the medium and large particle sizes or the small and large particle sizes may have been too small to lead to differences in hydration rates and therefore speed at which a viscous gel is developed in vivo. In addition, in vitro investigations of rate of gel formation and strength were not performed at each particle size. By examining the performance of the samples under conditions of distilled water as well as in vivo modeling of physiological gastric conditions, a better understanding of the rheological characteristics that may impact rate of digestion and absorption and glycemic response may be established.

The second possible limitation to the study design is that the dose of the fiber may not have been great enough to show differences between medium and small particle sizes. In this study a dose of 4 grams of the various particle sizes of fiber blend were consumed as the test treatments. Previous studies in the literature that have examined the dose-response of dietary fibers have found that there is a critical level of viscous fibers, such as β-glucan, past which an inverse, linear relationship between dose and glucose response no longer occurred [4]. Therefore, it is possible that there is also a critical level of viscous fibers where difference that are attributable to rheological effects may occur.

Future studies that examine particle size effect on physiological and appetite parameters must examine the differences in particle size at a variety of doses within the same study to determine whether there is an interaction between gravimetric (dose), rheological properties and physiological responses.

In studies 1 and 2 the methodology used to assess satiety during the study periods had several limitations. The primary aim of these studies was to assess glycemic response, not satiety. As such, the visual analog scale used for the study did not incorporate the multiple parameters of motivation to eat (e.g. desire to eat and perceived consumption amounts etc.) that validated visual analog scales use. The importance of assessing these parameters was demonstrated in a recent study, where fullness was shown to be the strongest predictor of food intake[204]. Because the studies did not assess these parameters, the results of these two studies are only indicative of satiety, which is defined as the state of inhibition over future eating which follows the end of an eating episode.

Moreover, the conditions under which satiety was assessed did not control for several confounding external variables. First, external cues of desire to eat and hunger can arise from olfactory stimulation. In both the particle size and dose-response investigations, study participants were seated in a large clinic room at tables with other study participants. Although this study environment would not be expected to affect glucose response to a test meal, it could affect motivation to eat. For instance, if one participant started their study period earlier in the morning than other participants then the other participants may smell and see the food being served once the first study participant completes the study protocol. These cues may lead to greater ratings of hunger than if the participants were in isolation from each other. Similarly, visual cues, such as posters, magazine articles or auditory cues, such as discussions about food or the sound of utensils may affect the participants' ratings of motivation to eat. Therefore, the findings from these studies, both trends and significant differences, must not be over-interpreted due to the potential of confounding factors.

In addition to satiety methodology, another limitation to these studies is that the fiber was added to a drink containing a low volume of meal (less than 300kcal) and no other breakfast was provided. Although the amount of carbohydrate in the test meals was equivalent to previous studies investigating the glycemic effect of foods, an average North American breakfast has approximately 500kcal.

Therefore, although the results of the 4 treatments were appropriate to assess glycemic response and results of each treatment are comparable to each other, the satiety responses may not be generalizable or clinically relevant as separate studies.

Future investigations using preestablished, validated preload and satiety methodology that also incorporates an assessment of the effect of study treatments and satiety markers on food intake would have provided stronger evidence of the effects of particle size and dose on the parameters of satiety and food intake [63, 205].

In the third study, although validated visual analog scales were used to investigate appetite-related cues to food intake, no differences were seen in any of the parameters on the scales. Although the VAS has been validated for use in research investigating appetite, the validation studies were performed on adults, not adolescents. It is possible that adolescents are less accurate at recording differences in appetite sensations than adults or that the mechanisms that induce satiety are not the same in adolescents as in adults due to differences in metabolic rates and temporary insulin resistance that has been noted to occur during puberty[245-249].

Moreover, the third study was conducted over a 90 minute postprandial period. By 90 minutes it is unlikely that any of the fiber was present in the colon for fermentation in the colon. Therefore, it is possible that if the current study was conducted over a greater period of time, differences may have been found in the appetite ratings that may have been a result of symptoms, such as bloating, caused by fermentation.

Similarly, it is possible that enough time elapsed between ingestion of the fiber and the pizza lunch to have allowed for expression of appetite suppressing hormones, such as GLP-1 or PYY, from the ileum. Therefore, appetite differences may have been stronger if the study was conducted for a longer period of time.

In the 4$^{th}$ study, several methodological limitations existed. Firstly, in this study the paracetamol (acetaminophen) test was used as an indirect measure of gastric emptying. Although this procedure has been found to have high correlation with the "gold standard" MRI [257, 271], the use of acetaminophen in a test meal may be more effective at assessing gastric emptying if given in the liquid phase of the meal. In

this study acetaminophen was consumed with liquid intermittently with a standard breakfast of bagel/cream cheese. Therefore, it was unknown whether the acetaminophen was incorporated in the solid phase of the meal or whether it emptied out of the stomach with the liquid phase. Since liquids empty exponentially whereas solids and fats empty according to a linear function[166], the results of gastric emptying from this study may be opposite to the hypothesis due to the liquid phase of the test breakfast emptying at an exponential rate in both SFB and control without mixture with the solid, viscous fiber-containing phase of the meal. Therefore, the liquid phase may have bypassed the gel and emptied at an exponential rate, carrying with it the acetaminophen as it emptied and thereby leading to rapid increases in acetaminophen and fluid in the proximal duodenum. Future studies must separate the meal phases of the test meal by incorporating the acetaminophen into either a liquid or solid preload meal. This would make the results of test and control more comparable.

Another methodological limitation with the fourth study was the ratio of fiber to carbohydrate present in the test breakfasts. In standard glycemic index methodology and in the previous studies test foods contained 50g of available carbohydrates[200]. Although this study was not designed as an assessment of glycemic index, perhaps the amount of carbohydrate present in the test meal (83.1g) could be lower in relation to the amount of fiber (5g) present. According to a review by Wolever et al (1991), in which glycemic index methodology is discussed, the amount of carbohydrate load in a test meal can affect the glycemic index value of a food[44, 283]. The dose-response for a food is linear up to 50g of available carbohydrate and the response flattens between 50 and 100g [200]. Therefore, perhaps a stronger response would have been present if the carbohydrate load was lower.

Another limitation of the fourth study was that the dose of fiber used in this study may have been too low to suppress gastric emptying rate to a level where differences would have existed due to viscosity. The dose of fiber required to suppress GE rate remains uncertain; some studies have found that larger doses (e.g. 10-15g) of fibers, such as pectin, suppress the GE of a solid-liquid meal[163, 275], whereas lower doses (e.g. 2g) begin to suppress GE rate only in the late postprandial phase.[276] In the current study, although the viscosity of the SFB was higher than most 10-15g portions of other, less viscous fibers, perhaps both the quantity and rheological properties are important in GE rate.

Although this study was planned to specifically assess satiety and food intake in relation to mechanisms, there may have been methodological reasons that there were no differences between hunger and food intake in highly viscous SFB and control. For instance, the preloading paradigm is the most frequently used methodology and involves consumption of a food in which a food/nutrient attribute is modified for investigation. The effects of the modification are then measured shortly after in a test meal. One of the variations within this methodology is the time period between preload ingestion and test meal. The study used a time period of 3.5 hours to mimic a typical time period between breakfast and lunch meals. Although this time period has been used in past investigations, other studies report energy compensation after a short period of time (0-20 minutes)[63, 277-279]. Although a 3.5 hour time period would allow for digestion and absorption to occur through a longer portion of the gastrointestinal tract, where various neuro-hormonal signals of appetite and food intake may be stimulated, it may have been too long to demonstrate energy compensation. Therefore, it is difficult to determine whether the time period used in this study was insufficient, perhaps too long, to identify differences in food intake.

**7.4 FUTURE DIRECTIONS**

The four studies performed have provided rationale for future studies involving the effects of both gravimetrics and rheological characteristics of both a soluble fiber blend and of soluble fibers alone on the parameters of food intake and appetite. Limitations in these studies suggest that future studies are required to examine the magnitude of differences in particle size required for maximal reduction in glucose and insulin. Future studies should examine the effect of larger particle sizes than the largest one used and smaller than the smallest used here.

In addition, future investigations of the most appropriate dose of soluble fiber at each particle size are needed for planning examination of viscous dietary fibers on appetite, satiety and food intake. In previous investigations, SFB provided in quantities of 6g/day lead to significant improvements in cardiovascular disease risk factors (blood pressure, lipid profile) and diabetes markers (acute and long-term glucose and insulin regulation) [113, 114, 198] Therefore, the amounts used in the current study seemed to be reasonable amounts to begin investigating for SFB. Other studies in the literature that have examined the acute effects of dietary fiber on appetite, food intake and metabolic parameters (e.g. glucose, insulin)

used fiber doses ranging from 4-50g/d [194, 195], whereas the current study used a tighter range (2-6g). Previous studies have found that greater doses of dietary fiber lead to greater effects, such as glycemic response, however some researchers have demonstrated a threshold, beyond which greater doses do not elicit greater effects. For instance, Makelainen et al (2007) found that there is a critical level of viscous fiber β-glucan, past which an inverse, linear relationship between dose and glucose response no longer occurred [4].

Since the results of the current study demonstrated no differences between 4g and 6g in glycemic AUC response, the conclusions were that there may be no additional benefit of ingestion of amounts equal to or greater than this amount, however greater doses are required from those used in this study to determine if there is additional benefit beyond 6g compared to the lower doses used.

Although clinically the goal of using SFB is to minimize the dose of additional fiber intake for individuals who already seem reluctant to meet national dietary fiber guidelines, it is necessary to demonstrate the dose where a threshold may exist. If this is done a better understanding of the physiological response of SFB may be achieved for future research on its physical properties.

Future studies are also required to determine the effect of these amounts of SFB on postprandial glucose, insulin and satiety after a meal with 50 grams of available carbohydrate. Since this was the first set of studies to investigate the effects of SFB on parameters of appetite and food intake, which are highly subjective indicators of potential weight loss, further studies must test the reproducibility of these results with similar viscosity and to continue the line of research to assess the ability of the viscosity in the SFB to aid in weight loss and maintenance.

Besides future studies examining the effects of SFB on physiological responses, methodological questions have arisen from this work that warrant more research. For instance, it is likely that a great deal of future research in the area of appetite and food intake will concentrate on adolescents, given the current obesity epidemic and rate of obesity development in this population. As such, it is important that future studies investigate the validity of visual analog scales in this population.

In addition, there has been great deal of variation in the literature with respect to the amount of time which elapses between the preload meal and the test meal. In the current series of studies, a 90

minute and a 3.5 hour period elapsed between preload and test meal ingestion. The 3.5 hour period was chosen to mimic the amount of time that would typically elapse between breakfast and lunch in an *ad libitum* setting. Studies reporting energy compensation after liquid foods have typically used short (0-20 minute) time intervals between preload and test meal[63, 277-279], whereas energy compensation after solid foods typically have 2-4h time intervals[280-282]. A study by Rolls et al. (1991) found that as the time interval between preload and test meal increased, the accuracy of the compensation decreased[205]. Over a greater period of time, digesta have a greater opportunity to trigger gastrointestinal responses throughout a greater portion of the GI tract. In addition, a greater period of time would allow for feedback mechanisms that slow gastric emptying and secretion of hormones in the distal ileum and colon as well as allowing for the potential for fermentation and gas to cause side effects that would reduce food intake and appetite. If a variety of intervals between preload and test meal was used while assessing the effect of SFB viscosity on the mechanisms of intake, time-dependent mechanisms may be established.

Further research is also warranted based on these results to elucidate whether there is a correlation between the amount participants think they can eat and actual intake at the lunch meal. Previous investigations have found correlations, however due to the lack of significant results in this study, it was not appropriate to assess whether correlations existed. If future studies find differences in appetite before the test meal and differences in the test meal this may be warranted.

With respect to the gastric transit time of SFB, further exploration into gastric emptying must be conducted. The current results of the gastric emptying test must be interpreted carefully and further exploration into the liquid and solid-phase differences in GE rate between SFB and control may lead to a better understanding of the relationship between the viscosity and the gastrointestinal mechanisms associated with the ingestion of a highly viscous fiber blend. In this research, the acetaminophen should be crushed into either the solid phase of the study meal or the liquid phase and both should be compared to each other in the same investigation. Although the use of the acetaminophen test has been found to have high correlation with results from the "gold standard" MRI [257, 271], it still has some limitations, such as an inability to assess differences in liquid and solid kinetics. An alternative to the acetaminophen test to consider for future studies includes the use of either MRI, scintigraphy or ultrasound. These tests are

more invasive, which may lead to differences in appetite, for instance, from being surrounded by an MRI/scintigraphy machine or from lying in the supine position after consumption of the preload meal, rather than differences due exclusively to variations in preload fiber properties.

In addition, there have been criticisms of these methods. For instance, scintigraphy studies have reported problems with the resolution of the image and the exposure of the participant to radiation. They also do not present information about the total gastric volume, only the amount of radio-labeled meal remaining in the stomach at various time points. Given the role of gastric secretions on viscosity development, scintigraphy may have limited value[156]. Ultrasound limitations include problems with the air/fluid interfaces in some parts of the stomach, which can interrupt the ultrasound beam and lead to inaccurate reports of the amount of volume remaining in the stomach at a given time[156]. Moreover, participants must remain in the supine position for an extended period of time, which may lead to abdominal discomfort. Echo-planar MRI, which uses ultra-high speed MRI that can freeze gastric motility with 130ms image acquisition, and can assess in vivo viscosity of gastric contents[284]. This technique is the most sophisticated method to assess gastric empting, however is limited due to the high cost of assessments and due to potentially limited schedules of the MRI machine for research purposes.

If, however, funding and timing of future studies permits, research could focus exclusively on the gastric empting and viscosity parameters of the SFB using various procedures.

A lack of symptoms was a positive finding of all 4 studies; no differences were found in symptoms between control and test treatments. This is a clinically significant finding, since one complaint of increasing fiber intake quickly is the unpleasant bloating and gas associated with the ingestion of fermentable fibers. However, since these studies were conducted over a short period of time, it is possible that the fiber did not have enough time to ferment. Therefore, it is important to find that no differences existed between symptoms of the amount used in this study and a relatively low amount of non-viscous fiber control over a longer period of time. Although the 4$^{th}$ study assessed symptoms over a 24 hour period following the study, perhaps a longer period would be required to capture the responses of individuals who have longer gastrointestinal transit time and would not experience these symptoms until 48 hours had elapsed.

Finally, although in the 4th study blood samples were taken for glucose, insulin, growth hormone and acetaminophen levels, other hormone related to the appetite cascade would also be warranted, considering the controversy around the glucostatic theory and the more recent research that has established the multifactorial nature of the appetite cascade. Future work in this area must include more markers of the appetite cascade to make the results more comprehensive. For instance, the literature has had much interest in the effects of dietary fiber on acute orexigenic (e.g. ghrelin) and anorexigenic (e.g. $PYY_{3-36}$, CCK, GLP-1) hormones.

$PYY_{3-36}$ is secreted by the L-cells of the distal ileum and colon and peaks 1-2 hours after food consumption. It has been shown to suppress appetite and reduce food intake[285]. Research in rodents[120, 123, 286] and humans[129, 287, 288] has suggested that soluble fiber is associated with increases in plasma PYY concentration. However, results have been mixed, as other studies in humans have shown no effect on PYY[289]. Given the knowledge of the role of soluble fiber on PYY, it is likely that the current studies PYY may be increased after consumption of highly viscous fibers compared to controls due to a greater portion of caloric content reaching the distal segments of the GI tract, providing a greater opportunity for colonic stimulation of PYY secretion.

CCK is secreted from the pyloric region of the stomach, the I-cells of the duodenum and jejunum and from the brain. It peaks within 15 minutes postprandially and returns to baseline in approximately 1 hour. It has been shown to stimulate pancreatic enzymes, induce satiety, inhibit gastric emptying and inhibit food intake postprandially. Evidence has demonstrated a heightened postprandial CCK response after consumption of soluble fiber[290, 291], however contrary results have shown little or no effect on CCK secretion with fiber[150, 292]. It would be hypothesized that in future studies of SFB, there would be a delay in nutrient release due to entrapped coingested nutrients (protein and fat) in the viscous gel. This delay may increase the opportunity for these nutrients to stimulate release of CCK in a more sustained manner.

GLP-1 is expressed from the L-cells of the ileum and colon in response to carbohydrate, protein and lipid. The rise in GLP-1 occurs within minutes after food intake and stimulates insulin secretion, glucose uptake, slows gastric emptying, suppresses appetite and reduces food intake. Studies in the literature of the effects of dietary fiber on postprandial serum GLP-1 levels have also been mixed.

Results show that GLP-1 is increased[120, 129, 293], decreased[263, 294] or not changed[128, 295, 296] after consumption of dietary fiber. Therefore, it is unknown whether SFB would elicit a greater postprandial GLP-1 response, however it can be hypothesized that since GLP-1 is stimulated by all macronutrients that the results may be more sustained, not necessarily higher, than after a non-viscous fiber, where these macronutrients are digested and absorbed more quickly.

Ghrelin, an orexigenic hormone secreted by the Gr-cells in the oxyntic glands of the stomach, acts on the hypothalamus to stimulate growth hormone secretion and also stimulate feeding. This hormone is thought to stimulate appetite in habitual eaters. Research has shown that the effects of fiber on postprandial ghrelin are not fully elucidated due to limited research. There is evidence that fiber decreases postprandial ghrelin[297, 298], however another study demonstrated no change in ghrelin after 23g of psyllium[299]. Therefore, if ghrelin were to be investigated in future research with adolescents using SFB, it may decrease when hunger increases but not corresponds with appetite, as shown in a study by Lomenick (2008)[287]. In addition, given the lack of difference in growth hormone response in the fourth study in this work, it is unlikely differences in ghrelin would occur. Moreover, inclusion criteria would have to stratify participants into habitual breakfast and lunch eaters so that habitual effect of ghrelin secretion may be better controlled.

It is known that many factors, including beliefs, past experiences, physiological markers and cues contribute to an individual's decision to eat. A comprehensive study that includes as many of these parameters as possible could help researchers gain a better understanding of the interplay among these factors, however knowledge of the intricacies surrounding each individual factor is necessary before an understanding of the whole cascade is possible.

# **CHAPTER 8.** REFERENCES

# REFERENCES


1. Alaimo K, McDowell MA, Briefel RR, et al. Dietary intake of vitamins, minerals, and fiber of persons ages 2 months and over in the United States: Third National Health and Nutrition Examination Survey, Phase 1, 1988-91. Adv Data 1994(258):1-28.
2. Medicine Io. Dietary reference intakes: energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC: ; 2005.
3. Statistics C. Canadian Community Health Survey Cycle 2.2, Nutrition. Ottawa, Ontario; 2004.
4. Makelainen H, Anttila H, Sihvonen J, et al. The effect of beta-glucan on the glycemic and insulin index. Eur J Clin Nutr 2007;61(6):779-85.
5. WHO TWHO. Global Strategy on Diet, Physical Activity and Health. From Global strategy on Diet, Physical Activity and Health. . 2006.
6. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. JAMA 2002;288(14):1723-7.
7. Statistics C. Adult Body Mass Index (BMI): Community Health Survey CCHS 3.1. 2006.
8. Cassano PA RB, Vokonas, PS, Weiss ST. Obesity and body fat distribution in relation to the incidence of non-insulin-dependent diabetes mellitus. A prospective cohort sutyd of men in the normative aging study. Am J Epidemiol 1992;136(12):1474-86.
9. Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Bjorntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. Br Med J (Clin Res Ed) 1984;288(6428):1401-4.
10. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA 1999;282(16):1523-9.
11. Resnick HE, Valsania P, Halter JB, Lin X. Relation of weight gain and weight loss on subsequent diabetes risk in overweight adults. J Epidemiol Community Health 2000;54(8):596-602.
12. Carey VJ, Walters EE, Colditz GA, et al. Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study. Am J Epidemiol 1997;145(7):614-9.
13. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 1994;17(9):961-9.
14. Lundgren H, Bengtsson C, Blohme G, Lapidus L, Sjostrom L. Adiposity and adipose tissue distribution in relation to incidence of diabetes in women: results from a prospective population study in Gothenburg, Sweden. Int J Obes 1989;13(4):413-23.
15. Ohlson LO, Larsson B, Svardsudd K, et al. The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. Diabetes 1985;34(10):1055-8.
16. Wei M, Gaskill SP, Haffner SM, Stern MP. Waist circumference as the best predictor of noninsulin dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other anthropometric measurements in Mexican Americans--a 7-year prospective study. Obes Res 1997;5(1):16-23.
17. Mokdad AH, Ford ES, Bowman BA, et al. Diabetes trends in the U.S.: 1990-1998. Diabetes Care 2000;23(9):1278-83.
18. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339(4):229-34.
19. Haffner SM, Stern MP, Hazuda HP, Rosenthal M, Knapp JA, Malina RM. Role of obesity and fat distribution in non-insulin-dependent diabetes mellitus in Mexican Americans and non-Hispanic whites. Diabetes Care 1986;9(2):153-61.
20. Hartz AJ, Rupley DC, Jr., Kalkhoff RD, Rimm AA. Relationship of obesity to diabetes: influence of obesity level and body fat distribution. Prev Med 1983;12(2):351-7.
21. Kissebah AH, Vydelingum N, Murray R, et al. Relation of body fat distribution to metabolic complications of obesity. J Clin Endocrinol Metab 1982;54(2):254-60.
22. Caro JF, Dohm LG, Pories WJ, Sinha MK. Cellular alterations in liver, skeletal muscle, and adipose tissue responsible for insulin resistance in obesity and type II diabetes. Diabetes Metab Rev 1989;5(8):665-89.

23. DeFronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 1988;37(6):667-87.
24. Krauss RM, Eckel RH, Howard B, et al. AHA Dietary Guidelines: revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. Stroke 2000;31(11):2751-66.
25. Williamson DF, Pamuk E, Thun M, Flanders D, Byers T, Heath C. Prospective study of intentional weight loss and mortality in never-smoking overweight US white women aged 40-64 years. Am J Epidemiol 1995;141(12):1128-41.
26. Padwal R, Li SK, Lau DC. Long-term pharmacotherapy for overweight and obesity: a systematic review and meta-analysis of randomized controlled trials. Int J Obes Relat Metab Disord 2003;27(12):1437-46.
27. Padwal R, Li SK, Lau DC. Long-term pharmacotherapy for obesity and overweight. Cochrane Database Syst Rev 2003(4):CD004094.
28. Di Marzo V, Matias I. Endocannabinoid control of food intake and energy balance. Nat Neurosci 2005;8(5):585-9.
29. Horvath TL. Endocannabinoids and the regulation of body fat: the smoke is clearing. J Clin Invest 2003;112(3):323-6.
30. Osei-Hyiaman D, Depetrillo M, Harvey-White J, et al. Cocaine- and amphetamine-related transcript is involved in the orexigenic effect of endogenous anandamide. Neuroendocrinology 2005;81(4):273-82.
31. Pagotto U, Vicennati V, Pasquali R. The endocannabinoid system and the treatment of obesity. Ann Med 2005;37(4):270-5.
32. Liu YL, Connoley IP, Wilson CA, Stock MJ. Effects of the cannabinoid CB1 receptor antagonist SR141716 on oxygen consumption and soleus muscle glucose uptake in Lep(ob)/Lep(ob) mice. Int J Obes (Lond) 2005;29(2):183-7.
33. Cota D MG, Tschop M, et al. . The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. J Clin Invest 2003;112(423-31).
34. Despres JP, Golay A, Sjostrom L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N Engl J Med 2005;353(20):2121-34.
35. Gomez R, Navarro M, Ferrer B, et al. A peripheral mechanism for CB1 cannabinoid receptor-dependent modulation of feeding. J Neurosci 2002;22(21):9612-7.
36. Gary-Bobo M, Elachouri G, Scatton B, Le Fur G, Oury-Donat F, Bensaid M. The cannabinoid CB1 receptor antagonist rimonabant (SR141716) inhibits cell proliferation and increases markers of adipocyte maturation in cultured mouse 3T3 F442A preadipocytes. Mol Pharmacol 2006;69(2):471-8.
37. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA 2006;295(7):761-75.
38. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet 2005;365(9468):1389-97.
39. Cleland R, Graybill D, Hubbard V, et al. . Commercial Weight Loss Products and Programs: What Consumers Stand to Gain and Lose. In: Washington DC: Federal Trade Commission BoCP, 1998, ed.; 1998.
40. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. JAMA 2005;293(1):43-53.
41. Gardner CD, Kiazand A, Alhassan S, et al. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. JAMA 2007;297(9):969-77.
42. Shai I, Schwarzfuchs D, Henkin Y, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med 2008;359(3):229-41.
43. Halton TL, Willett WC, Liu S, et al. Low-carbohydrate-diet score and the risk of coronary heart disease in women. N Engl J Med 2006;355(19):1991-2002.

44. Jenkins DJ, Wolever TM, Taylor RH, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr 1981;34(3):362-6.
45. Lau DC, Douketis JD, Morrison KM, Hramiak IM, Sharma AM, Ur E. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [summary]. CMAJ 2007;176(8):S1-13.
46. Anderson JW, Konz EC, Frederich RC, Wood CL. Long-term weight-loss maintenance: a meta-analysis of US studies. Am J Clin Nutr 2001;74(5):579-84.
47. Wadden TA, Sternberg JA, Letizia KA, Stunkard AJ, Foster GD. Treatment of obesity by very low calorie diet, behavior therapy, and their combination: a five-year perspective. Int J Obes 1989;13 Suppl 2:39-46.
48. Eisenstein J, Roberts SB, Dallal G, Saltzman E. High-protein weight-loss diets: are they safe and do they work? A review of the experimental and epidemiologic data. Nutr Rev 2002;60(7 Pt 1):189-200.
49. Skov AR, Toubro S, Ronn B, Holm L, Astrup A. Randomized trial on protein vs carbohydrate in ad libitum fat reduced diet for the treatment of obesity. Int J Obes Relat Metab Disord 1999;23(5):528-36.
50. Ludwig DS. Dietary glycemic index and obesity. J Nutr 2000;130(2S Suppl):280S-3S.
51. Roberts SB. Glycemic index and satiety. Nutr Clin Care 2003;6(1):20-6.
52. Warren JM, Henry CJ, Simonite V. Low glycemic index breakfasts and reduced food intake in preadolescent children. Pediatrics 2003;112(5):e414.
53. Howarth NC, Saltzman E, Roberts SB. Dietary fiber and weight regulation. Nutr Rev 2001;59(5):129-39.
54. Koh-Banerjee P, Rimm EB. Whole grain consumption and weight gain: a review of the epidemiological evidence, potential mechanisms and opportunities for future research. Proc Nutr Soc 2003;62(1):25-9.
55. Pereira MA, Ludwig DS. Dietary fiber and body-weight regulation. Observations and mechanisms. Pediatr Clin North Am 2001;48(4):969-80.
56. Rolls BJ, Bell EA, Castellanos VH, Chow M, Pelkman CL, Thorwart ML. Energy density but not fat content of foods affected energy intake in lean and obese women. Am J Clin Nutr 1999;69(5):863-71.
57. Rolls BJ, Bell EA, Thorwart ML. Water incorporated into a food but not served with a food decreases energy intake in lean women. Am J Clin Nutr 1999;70(4):448-55.
58. Zemel MB. The role of dairy foods in weight management. J Am Coll Nutr 2005;24(6 Suppl):537S-46S.
59. Blundell JE, Burley VJ. Satiation, satiety and the action of fibre on food intake. Int J Obes 1987;11 Suppl 1:9-25.
60. Blundell JE. Pharmacology of appetite control. Trends in Pharmacological Sciences 1991;12:147-57.
61. Blundell JE, & Rogers, P.J. Satiating power of food 1991.
62. Blundell JE, Halford JC. Regulation of nutrient supply: the brain and appetite control. Proc Nutr Soc 1994;53(2):407-18.
63. Kissileff HR. Satiating efficiency and a strategy for conducting food loading experiments. Neurosci Biobehav Rev 1984;8(1):129-35.
64. Havel PJ. Peripheral signals conveying metabolic information to the brain: short-term and long-term regulation of food intake and energy homeostasis. Exp Biol Med (Maywood) 2001;226(11):963-77.
65. Bonfield C. Dietary Fibre and body weight management. Dietary Fibre in Health and Disease ed. St. Paul, MN: Eagan Press; 1995.
66. Krotkiewski MS. Dietary Fibre in Obesity. Dietary Fibre Perspectives Reviews and Bibliography ed. London; 1985.
67. Iggo A. Tension receptors in the stomach and the urinary bladder. J Physiol 1955;24:1007-10.
68. Paintal AS. A study of gastric stretch receptors; their role in the peripheral mechanism of satiation of hunger and thirst. J Physiol 1954;126(2):255-70.
69. Hellstrom PM, Naslund E. Interactions between gastric emptying and satiety, with special reference to glucagon-like peptide-1. Physiol Behav 2001;74(4-5):735-41.
70. Bergmann JF, Chassany O, Petit A, Triki R, Caulin C, Segrestaa JM. Correlation between echographic gastric emptying and appetite: influence of psyllium. Gut 1992;33(8):1042-3.

71. Carney BI, Jones KL, Horowitz M, Sun WM, Penagini R, Meyer JH. Gastric emptying of oil and aqueous meal components in pancreatic insufficiency: effects of posture and on appetite. Am J Physiol 1995;268(6 Pt 1):G925-32.
72. Horowitz M, Jones K, Edelbroek MA, Smout AJ, Read NW. The effect of posture on gastric emptying and intragastric distribution of oil and aqueous meal components and appetite. Gastroenterology 1993;105(2):382-90.
73. Rolls BJ, Bell EA, Waugh BA. Increasing the volume of a food by incorporating air affects satiety in men. Am J Clin Nutr 2000;72(2):361-8.
74. French SJ, Read NW. Effect of guar gum on hunger and satiety after meals of differing fat content: relationship with gastric emptying. Am J Clin Nutr 1994;59(1):87-91.
75. Shafer RB, Levine AS, Marlette JM, Morley JE. Effects of xylitol on gastric emptying and food intake. Am J Clin Nutr 1987;45(4):744-7.
76. Poppitt SD, Prentice AM. Energy density and its role in the control of food intake: evidence from metabolic and community studies. Appetite 1996;26(2):153-74.
77. Rolls BJ, Drewnowski A, Ledikwe JH. Changing the energy density of the diet as a strategy for weight management. J Am Diet Assoc 2005;105(5 Suppl 1):S98-103.
78. Yao M, Roberts SB. Dietary energy density and weight regulation. Nutr Rev 2001;59(8 Pt 1):247-58.
79. Malagelada J. Gastric, pancreatic and biliary responses to a meal. Johnson L ed. New York; 1981.
80. Muurahainen N, Kissileff HR, Derogatis AJ, Pi-Sunyer FX. Effects of cholecystokinin-octapeptide (CCK-8) on food intake and gastric emptying in man. Physiol Behav 1988;44(4-5):645-9.
81. Sepple CP, Read NW. Gastrointestinal correlates of the development of hunger in man. Appetite 1989;13(3):183-91.
82. Kraly FS, Gibbs J. Vagotomy fails to block the satiating effect of food in the stomach. Physiol Behav 1980;24(5):1007-10.
83. Meyer J. Regulation of energy intake and the body weight, the glucostatic theory and the lipostatic hypothesis. Ann NY Acad Sci 1955;63:15-43.
84. Penicaud L, Leloup C, Lorsignol A, Alquier T, Guillod E. Brain glucose sensing mechanism and glucose homeostasis. Curr Opin Clin Nutr Metab Care 2002;5(5):539-43.
85. Campfield LA, Smith FJ. Transient declines in blood glucose signal meal initiation. Int J Obes 1990;14 Suppl 3:15-31; discussion -4.
86. Wolever TM. The glycemic index. World Rev Nutr Diet 1990;62:120-85.
87. Campfield LA, Smith FJ, Rosenbaum M, Hirsch J. Human eating: evidence for a physiological basis using a modified paradigm. Neurosci Biobehav Rev 1996;20(1):133-7.
88. Brand-Miller J. Importance of Glycemic Index in Diabetes. Am J Clin Nutr 1994;59:747S-52S.
89. Holt SH, Brand Miller JC, Petocz P. Interrelationships among postprandial satiety, glucose and insulin responses and changes in subsequent food intake. Eur J Clin Nutr 1996;50(12):788-97.
90. Alfieri MA, Pomerleau J, Grace DM, Anderson L. Fiber intake of normal weight, moderately obese and severely obese subjects. Obes Res 1995;3(6):541-7.
91. Burkitt DPT, H.C. Refined Carbohydrate Food and Disease. London, UK: Academic Press; 1975.
92. Van Itallie TB. Dietary Fiber and Obesity. Am J Clin Nutr 1978;31 (Suppl):S43-S52.
93. Wolever TM, Hamad S, Gittelsohn J, et al. Low dietary fiber and high protein intakes associated with newly diagnosed diabetes in a remote aboriginal community. Am J Clin Nutr 1997;66(6):1470-4.
94. Jenkins DJ, Wolever TM, Leeds AR, et al. Dietary fibres, fibre analogues, and glucose tolerance: importance of viscosity. Br Med J 1978;1(6124):1392-4.
95. Jarjis HA, Blackburn NA, Redfern JS, Read NW. The effect of ispaghula (Fybogel and Metamucil) and guar gum on glucose tolerance in man. Br J Nutr 1984;51(3):371-8.
96. Schneeman BO. Dietary fiber and gastrointestinal function. Nutrition Research 1998;18(4):605-765.
97. Rigaud D, Royer, I. Dietary Fibre: Facts and Fiction. Gastroenterol Clin Biol 1988;12(133-1748).
98. Rigaud D PF, Meulemans A, Merrouche M, Mignon M. Effect of psyllium on gastric emptying , hunger feeling and food intake in normal volunteers: A double blind study. Eur J Clin Nutr 1998;52(239-245).

99. Battilana P, Ornstein K, Minehira K, et al. Mechanisms of action of beta-glucan in postprandial glucose metabolism in healthy men. Eur J Clin Nutr 2001;55(5):327-33.
100. Jenkins DJA WT, Leeds AR, Gassull MA, Dilawari JB, Goff DV, Metz GL, Alberti KGMM. Dietary Fibres, fibre analgogures and glucose tolerance: importance of viscosity. Brit Med J 1978;1:1392-94.
101. Jenkins DJ. Lente carbohydrate: a newer approach to the dietary management of diabetes. Diabetes Care 1982;5(6):634-41.
102. Jenkins DJ, Thorne MJ, Camelon K, et al. Effect of processing on digestibility and the blood glucose response: a study of lentils. Am J Clin Nutr 1982;36(6):1093-101.
103. Jenkins DJ, Jenkins AL. The clinical implications of dietary fiber. Adv Nutr Res 1984;6:169-202.
104. Jenkins DJA JA, Wolever TMS, et al. Lente carbohydrate or slowly absorbed starch: physiological and therapuetic implications. In: Kritchevsky D Bonfield C AJe, ed. Dietary Fiber: Chemistry, Physiology and Health effects. New York: Plenum Press; 1988:247-59.
105. Braaten JT, Scott FW, Wood PJ, et al. High beta-glucan oat bran and oat gum reduce postprandial blood glucose and insulin in subjects with and without type 2 diabetes. Diabet Med 1994;11(3):312-8.
106. Ludwig D. Dietary glycemic index and obesity. J Nutr 2000;130(280s-83s).
107. Read NW, Sepple CP, Brown NJ. The ileal break: is it relevant to the action of viscous polysaccharides? In: Kritchevsky D Bonfield C AJe, ed. Dietary fiber: chemistry, physiology and health effects. NY, NY: Plemnum Press; 1988.
108. Brand JC, Colagiuri S, Crossman S, Allen A, Roberts DC, Truswell AS. Low-glycemic index foods improve long-term glycemic control in NIDDM. Diabetes Care 1991;14(2):95-101.
109. Wolever TM, Jenkins DJ, Vuksan V, et al. Beneficial effect of a low glycaemic index diet in type 2 diabetes. Diabet Med 1992;9(5):451-8.
110. Wolever TM, Jenkins DJ, Vuksan V, Jenkins AL, Wong GS, Josse RG. Beneficial effect of low-glycemic index diet in overweight NIDDM subjects. Diabetes Care 1992;15(4):562-4.
111. Aro A, Uusitupa M, Voutilainen E, Hersio K, Korhonen T, Siitonen O. Improved diabetic control and hypocholesterolaemic effect induced by long-term dietary supplementation with guar gum in type 2 (insulin-independent) diabetes. Diabetologia 1981;21(1):29-33.
112. Jenkins DJ, Wolever TM, Hockaday TD, et al. Treatment of diabetes with guar gum. Reduction of urinary glucose loss in diabetics. Lancet 1977;2(8042):779-80.
113. Vuksan V, Jenkins DJ, Spadafora P, et al. Konjac-mannan (glucomannan) improves glycemia and other associated risk factors for coronary heart disease in type 2 diabetes. A randomized controlled metabolic trial. Diabetes Care 1999;22(6):913-9.
114. Vuksan V, Sievenpiper JL, Owen R, et al. Beneficial effects of viscous dietary fiber from Konjac-mannan in subjects with the insulin resistance syndrome: results of a controlled metabolic trial. Diabetes Care 2000;23(1):9-14.
115. Kovacs EM, Westerterp-Plantenga MS, Saris WH, et al. The effect of guar gum addition to a semisolid meal on appetite related to blood glucose, in dieting men. Eur J Clin Nutr 2002;56(8):771-8.
116. Evans E, Miller DS. Bulking agents in the treatment of obesity. Nutr Metab 1975;18(4):199-203.
117. Pasman WJ, Saris WH, Wauters MA, Westerterp-Plantenga MS. Effect of one week of fibre supplementation on hunger and satiety ratings and energy intake. Appetite 1997;29(1):77-87.
118. Layer P HJ. GLP-1: a humoral mediator o f the ileal break in humans? Digestion 1993;54(385-86).
119. Read N, French, S, Cunningham K. The role of the gut in regulating food intake in man. Nutr Rev 1994;52(1-10).
120. Keenan MJ, Zhou J, McCutcheon KL, et al. Effects of resistant starch, a non-digestible fermentable fiber, on reducing body fat. Obesity (Silver Spring) 2006;14(9):1523-34.
121. Reimer RA, Russell JC. Glucose tolerance, lipids, and GLP-1 secretion in JCR:LA-cp rats fed a high protein fiber diet. Obesity (Silver Spring) 2008;16(1):40-6.
122. Wang ZQ, Zuberi AR, Zhang XH, et al. Effects of dietary fibers on weight gain, carbohydrate metabolism, and gastric ghrelin gene expression in mice fed a high-fat diet. Metabolism 2007;56(12):1635-42.
123. Delzenne NM, Cani PD, Daubioul C, Neyrinck AM. Impact of inulin and oligofructose on gastrointestinal peptides. Br J Nutr 2005;93 Suppl 1:S157-61.

124. Delzenne NM, Kok NN. Biochemical basis of oligofructose-induced hypolipidemia in animal models. J Nutr 1999;129(7 Suppl):1467S-70S.
125. Massimino SP, McBurney MI, Field CJ, et al. Fermentable dietary fiber increases GLP-1 secretion and improves glucose homeostasis despite increased intestinal glucose transport capacity in healthy dogs. J Nutr 1998;128(10):1786-93.
126. Kok NN, Morgan LM, Williams CM, Roberfroid MB, Thissen JP, Delzenne NM. Insulin, glucagon-like peptide 1, glucose-dependent insulinotropic polypeptide and insulin-like growth factor I as putative mediators of the hypolipidemic effect of oligofructose in rats. J Nutr 1998;128(7):1099-103.
127. Reimer RA, McBurney MI. Dietary fiber modulates intestinal proglucagon messenger ribonucleic acid and postprandial secretion of glucagon-like peptide-1 and insulin in rats. Endocrinology 1996;137(9):3948-56.
128. Frost GS, Brynes AE, Dhillo WS, Bloom SR, McBurney MI. The effects of fiber enrichment of pasta and fat content on gastric emptying, GLP-1, glucose, and insulin responses to a meal. Eur J Clin Nutr 2003;57(2):293-8.
129. Greenway F, O'Neil CE, Stewart L, Rood J, Keenan M, Martin R. Fourteen weeks of treatment with Viscofiber increased fasting levels of glucagon-like peptide-1 and peptide-YY. J Med Food 2007;10(4):720-4.
130. Nilsson AC, Ostman EM, Holst JJ, Bjorck IM. Including indigestible carbohydrates in the evening meal of healthy subjects improves glucose tolerance, lowers inflammatory markers, and increases satiety after a subsequent standardized breakfast. J Nutr 2008;138(4):732-9.
131. Adam TC, Westerterp-Plantenga MS. Glucagon-like peptide-1 release and satiety after a nutrient challenge in normal-weight and obese subjects. Br J Nutr 2005;93(6):845-51.
132. Adam TC, Westerterp-Plantenga MS. Nutrient-stimulated GLP-1 release in normal-weight men and women. Horm Metab Res 2005;37(2):111-7.
133. Blundell JE, Naslund E. Glucagon-like peptide-1, satiety and appetite control. Br J Nutr 1999;81(4):259-60.
134. Gutzwiller JP, Drewe J, Goke B, et al. Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. Am J Physiol 1999;276(5 Pt 2):R1541-4.
135. Gutzwiller JP, Goke B, Drewe J, et al. Glucagon-like peptide-1: a potent regulator of food intake in humans. Gut 1999;44(1):81-6.
136. Naslund E G, M , Skogar S, Rossner S, Hellstrom PM,. Glucagon-like peptide 1 increases the period of postprandial satieyt ans slows gastric emptying in obese men. Am J Clin Nutr 1998;68(525-530).
137. Ranganath LR BJMLea. Attenuated GLP-1 secretion in obesity: cause or consequence? Gut 1996;38(916-9).
138. Wang Z, Yang L, Liu H, Tan X. [Effects of refined konjac meal on lipid metabolism and blood viscosity of rats fed by high fat forage]. Wei Sheng Yan Jiu 2002;31(2):120-1.
139. He G, Aoyama Y. Effects of adding some dietary fibers to a cystine diet on the activities of liver antioxidant enzymes and serum enzymes in rats. Biosci Biotechnol Biochem 2003;67(3):617-21.
140. Yoshida M, Sawa J, Hozumi T, et al. Effects of long-term high-fiber diet on macrovascular changes and lipid and glucose levels in STZ-induced diabetic SD rats. Diabetes Res Clin Pract 1991;13(3):147-52.
141. Ebihara K, Schneeman BO. Interaction of bile acids, phospholipids, cholesterol and triglyceride with dietary fibers in the small intestine of rats. J Nutr 1989;119(8):1100-6.
142. Vido L, Facchin P, Antonello I, Gobber D, Rigon F. Childhood obesity treatment: double blinded trial on dietary fibres (glucomannan) versus placebo. Padiatr Padol 1993;28(5):133-6.
143. Signorelli P, Croce P, Dede A. [A clinical study of the use of a combination of glucomannan with lactulose in the constipation of pregnancy]. Minerva Ginecol 1996;48(12):577-82.
144. Cairella M, Marchini G. [Evaluation of the action of glucomannan on metabolic parameters and on the sensation of satiation in overweight and obese patients]. Clin Ter 1995;146(4):269-74.
145. Livieri C, Novazi F, Lorini R. [The use of highly purified glucomannan-based fibers in childhood obesity]. Pediatr Med Chir 1992;14(2):195-8.
146. Vita PM, Restelli A, Caspani P, Klinger R. [Chronic use of glucomannan in the dietary treatment of severe obesity]. Minerva Med 1992;83(3):135-9.

147. Oku T, Konishi F, Hosoya N. Mechanism of inhibitory effect of unavailable carbohydrate on intestinal calcium absorption. J Nutr 1982;112(3):410-5.
148. Walsh DE, Yaghoubian V, Behforooz A. Effect of glucomannan on obese patients: a clinical study. Int J Obes 1984;8(4):289-93.
149. Biancardi G, Palmiero, L. , Ghirardi P.E.,. Glucomannan in the Treatment of Overweight Patients with Osteoarthrosis. Current Therapeutic Research 1989;46(5):908-12.
150. Di Lorenzo C, Williams CM, Hajnal F, Valenzuela JE. Pectin delays gastric emptying and increases satiety in obese subjects. Gastroenterology 1988;95(5):1211-5.
151. Harju E. Increases in meal viscosity caused by addition of guar gum decrease postprandiale acidity and rate of emptying of gastric contents in healthy subjects. Panminerva Med 1985;27(3):125-8.
152. Hoad CL, Rayment P, Spiller RC, et al. In vivo imaging of intragastric gelation and its effect on satiety in humans. J Nutr 2004;134(9):2293-300.
153. Kasper H, Eilles C, Reiners C, Schrezenmeir J. The influence of dietary fiber on gastric transit time. Hepatogastroenterology 1985;32(2):69-71.
154. Krotkiewski M. Effect of guar gum on body-weight, hunger ratings and metabolism in obese subjects. Br J Nutr 1984;52(1):97-105.
155. Lavin JH, Read NW. The effect on hunger and satiety of slowing the absorption of glucose: relationship with gastric emptying and postprandial blood glucose and insulin responses. Appetite 1995;25(1):89-96.
156. Marciani L, Gowland PA, Spiller RC, et al. Gastric response to increased meal viscosity assessed by echo-planar magnetic resonance imaging in humans. J Nutr 2000;130(1):122-7.
157. Marciani L, Gowland PA, Spiller RC, et al. Effect of meal viscosity and nutrients on satiety, intragastric dilution, and emptying assessed by MRI. Am J Physiol Gastrointest Liver Physiol 2001;280(6):G1227-33.
158. Mattes RD, Rothacker D. Beverage viscosity is inversely related to postprandial hunger in humans. Physiol Behav 2001;74(4-5):551-7.
159. Morgan LM, Tredger JA, Madden A, Kwasowski P, Marks V. The effect of guar gum on carbohydrate-, fat- and protein-stimulated gut hormone secretion: modification of postprandial gastric inhibitory polypeptide and gastrin responses. Br J Nutr 1985;53(3):467-75.
160. Penagini R, Velio P, Vigorelli R, et al. The effect of dietary guar on serum cholesterol, intestinal transit, and fecal output in man. Am J Gastroenterol 1986;81(2):123-5.
161. Ray TK, Mansell KM, Knight LC, Malmud LS, Owen OE, Boden G. Long-term effects of dietary fiber on glucose tolerance and gastric emptying in noninsulin-dependent diabetic patients. Am J Clin Nutr 1983;37(3):376-81.
162. Rydning A, Berstad A, Berstad T, Hertzenberg L. The effect of guar gum and fiber-enriched wheat bran on gastric emptying of a semisolid meal in healthy subjects. Scand J Gastroenterol 1985;20(3):330-4.
163. Sandhu KS, el Samahi MM, Mena I, Dooley CP, Valenzuela JE. Effect of pectin on gastric emptying and gastroduodenal motility in normal subjects. Gastroenterology 1987;92(2):486-92.
164. Tiwary CM, Ward JA, Jackson BA. Effect of pectin on satiety in healthy US Army adults. J Am Coll Nutr 1997;16(5):423-8.
165. Tomlin J. The effect of the gel-forming liquid fibre on feeding behaviour in man. Br J Nutr 1995;74(3):427-36.
166. Van Nieuwenhoven MA, Kovacs EM, Brummer RJ, Westerterp-Plantenga MS, Brouns F. The effect of different dosages of guar gum on gastric emptying and small intestinal transit of a consumed semisolid meal. J Am Coll Nutr 2001;20(1):87-91.
167. Wilmshurst P, Crawley JC. The measurement of gastric transit time in obese subjects using 24Na and the effects of energy content and guar gum on gastric emptying and satiety. Br J Nutr 1980;44(1):1-6.
168. Holt S, Heading RC, Carter DC, Prescott LF, Tothill P. Effect of gel fibre on gastric emptying and absorption of glucose and paracetamol. Lancet 1979;1(8117):636-9.
169. Shimahara H, et al. Isolation and Characterization of Oligosaccharides from an Enzymic Hydrolysate of Konjac Glucomannan. Agri Biol Chem 1975;39(2):293-9.

170. Kato K, Matsuda K. Studies of the Chemical Structure of Konjac Mannan. Part I. Isolation and Characterization of Oligosaccharides from the Partial Hydroyzate of the Mannan. Agr Biol Chem 1969;33(10):1446-53.
171. Kato Kea. Isolation of Oligosaccharides Corresponding to the Branching-point of Konjac Mannan. Agr Biol Chem 1973;37(9): 2045-51.
172. Kato KWT, Matsuda K.,. Studies of the Chemical Structure of Konjac Mannan. Part II. Isolation ana Characterization of Oligosaccharides from the Enzymatic Hydrolyzate of the Mannan. Agr Biol Chem 1970;34(4):532-9.
173. Garcia M, Charlez M, Fauli C, et al. Physicochemical comparison of some dietary fibres glucomannan, galactomannan, carboxymethylcellulose, pectin, and wheat bran. Curr Ther Res 1988;43:1010-3.
174. Doi K. Effect of konjac fibre (glucomannan) on glucose and lipids. Eur J Clin Nutr 1995;49 Suppl 3:S190-7.
175. Vuksan V, Sievenpiper JL, Xu Z, et al. Konjac-Mannan and American ginsing: emerging alternative therapies for type 2 diabetes mellitus. J Am Coll Nutr 2001;20(5 Suppl):370S-80S; discussion 81S-83S.
176. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22(9):1462-70.
177. Cho S, Devries, JW., Prosky, L. Dietary Fiber Analysis and Applications Gaithersburg, Maryland: AOAC International; 1997.
178. Casiraghi MC, Garsetti M, Testolin G, Brighenti F. Post-prandial responses to cereal products enriched with barley beta-glucan. J Am Coll Nutr 2006;25(4):313-20.
179. Hasson DA, BB. Validation and FIndins Comparing VAS vs. Likert Scales for Psychosocial Measurements. International Electronic Journal of Health Education 2005;8:178-92.
180. Holt SH, Miller JC, Petocz P, Farmakalidis E. A satiety index of common foods. Eur J Clin Nutr 1995;49(9):675-90.
181. Wolever TM, Jenkins DJ. The use of the glycemic index in predicting the blood glucose response to mixed meals. Am J Clin Nutr 1986;43(1):167-72.
182. Heaton KW, Marcus SN, Emmett PM, Bolton CH. Particle size of wheat, maize, and oat test meals: effects on plasma glucose and insulin responses and on the rate of starch digestion in vitro. Am J Clin Nutr 1988;47(4):675-82.
183. O'Dea K N, PJ, Antonoff, L. Physical Factors influencing postprandial glucose and insulin response to starch. Am J Clin Nutr 1980;Apr;33(4):760-5.
184. O'Donnell LJ, Emmett PM, Heaton KW. Size of flour particles and its relation to glycaemia, insulinaemia, and colonic disease. Bmj 1989;298(6688):1616-7.
185. Read NW, Welch IM, Austen CJ, Barnish C, Bartlett, CE, Baxter AJ, Brown G, Compton ME, Hume KE, Stone I, et al. Swallowing food without chewing; a simple way to reduce postprandial glycaemia. Br J Nutr 1986;55(1):43-7.
186. Behall KM, Scholfield DJ, Hallfrisch J. Comparison of hormone and glucose responses of overweight women to barley and oats. J Am Coll Nutr 2005;24(3):182-8.
187. Davis J, Hodges VA, Gillham MB. Normal-weight adults consume more fiber and fruit than their age- and height-matched overweight/obese counterparts. J Am Diet Assoc 2006;106(6):833-40.
188. Edwards CA, Blackburn NA, Craigen L, et al. Viscosity of food gums determined in vitro related to their hypoglycemic actions. Am J Clin Nutr 1987;46(1):72-7.
189. Wolever TM, Vuksan V, Eshuis H, et al. Effect of method of administration of psyllium on glycemic response and carbohydrate digestibility. J Am Coll Nutr 1991;10(4):364-71.
190. Wood PJ, Braaten JT, Scott FW, Riedel KD, Wolynetz MS, Collins MW. Effect of dose and modification of viscous properties of oat gum on plasma glucose and insulin following an oral glucose load. Br J Nutr 1994;72(5):731-43.
191. Wood PJ. Physicochemical properties and physiological effects of the (1----3)(1----4)-beta-D-glucan from oats. Adv Exp Med Biol 1990;270:119-27.
192. Wood PJ BM, Butler G. Evaluation of role of concentration and molecular weight of oat beta-glucan in determining effect of viscosity on plasma glucose and insulin following an oral glucose load. Br J Nutr 2000(84 (1)):19-23.

193. Holt S, Brand J, Soveny C, Hansky J. Relationship of satiety to postprandial glycaemic, insulin and cholecystokinin responses. Appetite 1992;18(2):129-41.
194. Anderson J, Akanji A. Treatment of DIabetes with High Fibre Diets. In CRC Handbook of Dietary Fibre in Human Nutrition 2nd ed; 1993.
195. Castiglia-Delavaud C, Verdier E, Besle JM, et al. Net energy value of non-starch polysaccharide isolates (sugarbeet fibre and commercial inulin) and their impact on nutrient digestive utilization in healthy human subjects. Br J Nutr 1998;80(4):343-52.
196. Whistler R. Introduction to industrial gums. In: JN WRaB, ed. Industrial Gums. 3rd ed: Academic Press; 1993.
197. Morris ER. Fiber in Foods. In: Kritchevsky D BC, Anderson JW eds., ed. Dietary Fiber in Health and Disease. St. Paul: Eagan Press; 1995.
198. Breitman P, Sievenpiper, J, Lyon, M., Vuksan, V. Chronic Feeding of a Viscous Dietary Fibre Blend (PGX) Improves Insulin Sensitivity and Reduces Body Fat Composition in Individuals With Hyperinsulinemia and Metabolic Syndrome. In: First Annual Natural Health Products Conference; 2004 February; Montreal, Quebec; 2004.
199. Tapola N, Karvonen H, Niskanen L, Mikola M, Sarkkinen E. Glycemic responses of oat bran products in type 2 diabetic patients. Nutr Metab Cardiovasc Dis 2005;15(4):255-61.
200. Wolever TMS JD, Jenkins AL, Josse RG:. The glycemic index: methodology and clinical implications. Am J Clin Nutr 1991;54:846-854.
201. Tappy L, Gugolz E, Wursch P. Effects of breakfast cereals containing various amounts of beta-glucan fibers on plasma glucose and insulin responses in NIDDM subjects. Diabetes Care 1996;19(8):831-4.
202. Biorklund M, van Rees A, Mensink RP, Onning G. Changes in serum lipids and postprandial glucose and insulin concentrations after consumption of beverages with beta-glucans from oats or barley: a randomised dose-controlled trial. Eur J Clin Nutr 2005;59(11):1272-81.
203. Liljenberg H GY, Bjorck I. Metabolic responses to starch in bread containing intact kernels versus milled flour. Eur J Clin Nutr 1992;46(8):561-75.
204. Drapeau V, Blundell J, Therrien F, Lawton C, Richard D, Tremblay A. Appetite sensations as a marker of overall intake. Br J Nutr 2005;93(2):273-80.
205. Rolls BJ, Kim S, McNelis AL, Fischman MW, Foltin RW, Moran TH. Time course of effects of preloads high in fat or carbohydrate on food intake and hunger ratings in humans. Am J Physiol 1991;260(4 Pt 2):R756-63.
206. Vuksan V JD, Hogg R, Sievenpiper JL, Vidgen E, Jenkins AL, Leiter LA, Josse RG. Viscous dietary fiber may improve metabolic control in individuals with impaired glucose tolerance (IGT) and low HDL cholesterol. In: FASEB J; 1999; 1999. p. A54.
207. Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. JAMA 2003;289(2):187-93.
208. Fontaine KR. Health-related quality of life among obese subgroups. Obes Res 2002;10(8):854-5.
209. surgeon General's call to action to prevent and decrease overweight and obesity. In: US dept of health and human services. Rockville, MD; 2001.
210. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 2003;289(1):76-9.
211. Allison DB, Fontaine KR, Manson JE, Stevens J, VanItallie TB. Annual deaths attributable to obesity in the United States. JAMA 1999;282(16):1530-8.
212. Seidell JC, Visscher TL, Hoogeveen RT. Overweight and obesity in the mortality rate data: current evidence and research issues. Med Sci Sports Exerc 1999;31(11 Suppl):S597-601.
213. Jia WP, Xiang KS, Chen L, Lu JX, Wu YM. Epidemiological study on obesity and its comorbidities in urban Chinese older than 20 years of age in Shanghai, China. Obes Rev 2002;3(3):157-65.
214. Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the United States. JAMA 2001;286(10):1195-200.
215. Holbrook TL, Barrett-Connor E, Wingard DL. The association of lifetime weight and weight control patterns with diabetes among men and women in an adult community. Int J Obes 1989;13(5):723-9.

216. Colditz GA, Willett WC, Stampfer MJ, et al. Weight as a risk factor for clinical diabetes in women. Am J Epidemiol 1990;132(3):501-13.
217. Hanson RL, Narayan KM, McCance DR, et al. Rate of weight gain, weight fluctuation, and incidence of NIDDM. Diabetes 1995;44(3):261-6.
218. Wannamethee SG, Shaper AG. Weight change and duration of overweight and obesity in the incidence of type 2 diabetes. Diabetes Care 1999;22(8):1266-72.
219. Moore LL, Visioni AJ, Wilson PW, D'Agostino RB, Finkle WD, Ellison RC. Can sustained weight loss in overweight individuals reduce the risk of diabetes mellitus? Epidemiology 2000;11(3):269-73.
220. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344(18):1343-50.
221. Leibson CL, Williamson DF, Melton LJ, 3rd, et al. Temporal trends in BMI among adults with diabetes. Diabetes Care 2001;24(9):1584-9.
222. O'Brien PE, Dixon JB. The extent of the problem of obesity. Am J Surg 2002;184(6B):S4-8.
223. Khan MA, St Peter JV, Breen GA, Hartley GG, Vessey JT. Diabetes disease stage predicts weight loss outcomes with long-term appetite suppressants. Obes Res 2000;8(1):43-8.
224. Macdonald SM, Reeder BA, Chen Y, Despres JP. Obesity in Canada: a descriptive analysis. Canadian Heart Health Surveys Research Group. CMAJ 1997;157 Suppl 1:S3-9.
225. Mokdad AH, Ford ES, Bowman BA, et al. The continuing increase of diabetes in the US. Diabetes Care 2001;24(2):412.
226. Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP. The spread of the obesity epidemic in the United States, 1991-1998. JAMA 1999;282(16):1519-22.
227. Steinberger J, Daniels SR. Obesity, insulin resistance, diabetes, and cardiovascular risk in children: an American Heart Association scientific statement from the Atherosclerosis, Hypertension, and Obesity in the Young Committee (Council on Cardiovascular Disease in the Young) and the Diabetes Committee (Council on Nutrition, Physical Activity, and Metabolism). Circulation 2003;107(10):1448-53.
228. Travers SH, Labarta JI, Gargosky SE, Rosenfeld RG, Jeffers BW, Eckel RH. Insulin-like growth factor binding protein-I levels are strongly associated with insulin sensitivity and obesity in early pubertal children. J Clin Endocrinol Metab 1998;83(6):1935-9.
229. Rolls BJ, Morris EL, Roe LS. Portion size of food affects energy intake in normal-weight and overweight men and women. Am J Clin Nutr 2002;76(6):1207-13.
230. Young LR, Nestle M. The contribution of expanding portion sizes to the US obesity epidemic. Am J Public Health 2002;92(2):246-9.
231. JP F. McCollum Award Lecture. Diet, lifestyle and weight maintenance. Am J Clin Nutr 1995;62:820-36.
232. McGuire MT, Wing RR, Hill JO. The prevalence of weight loss maintenance among American adults. Int J Obes Relat Metab Disord 1999;23(12):1314-9.
233. Wing RH, JO. Successful Weight Loss Maintenance. Annu Rev Nutr 2001;21:323-41.
234. Hanley AJ, Harris SB, Gittelsohn J, Wolever TM, Saksvig B, Zinman B. Overweight among children and adolescents in a Native Canadian community: prevalence and associated factors. Am J Clin Nutr 2000;71(3):693-700.
235. Drewnowski A, Riskey D, Desor JA. Measures of restraint: separating dieting from overweight. Appetite 1982;3(3):282.
236. Polivy J, Herman CP, Warsh S. Internal and external components of emotionality in restrained and unrestrained eaters. J Abnorm Psychol 1978;87(5):497-504.
237. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.
238. Hill AJ, Blundell JE. Nutrients and behaviour: research strategies for the investigation of taste characteristics, food preferences, hunger sensations and eating patterns in man. J Psychiatr Res 1982;17(2):203-12.
239. Delargy HJ, O'Sullivan KR, Fletcher RJ, Blundell JE. Effects of amount and type of dietary fibre (soluble and insoluble) on short-term control of appetite. Int J Food Sci Nutr 1997;48(1):67-77.

240. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA 2002;287(18):2414-23.
241. Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB. High glycemic index foods, overeating, and obesity. Pediatrics 1999;103(3):E26.
242. Ball SD, Keller KR, Moyer-Mileur LJ, Ding YW, Donaldson D, Jackson WD. Prolongation of satiety after low versus moderately high glycemic index meals in obese adolescents. Pediatrics 2003;111(3):488-94.
243. Burton-Freeman B. Dietary Fire and Energy Regulation. J Nutr 2000;130:272S-5S.
244. Burton-Freeman B, Schneeman BO. Lipid infused into the duodenum of rats at varied rates influences food intake and body weight gain. J Nutr 1996;126(11):2934-9.
245. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV. Impaired insulin action in puberty. A contributing factor to poor glycemic control in adolescents with diabetes. N Engl J Med 1986;315(4):215-9.
246. Arslanian SA, Kalhan SC. Protein turnover during puberty in normal children. Am J Physiol 1996;270(1 Pt 1):E79-84.
247. Caprio S, Cline G, Boulware S, et al. Effects of puberty and diabetes on metabolism of insulin-sensitive fuels. Am J Physiol 1994;266(6 Pt 1):E885-91.
248. Goran MI, Ball GD, Cruz ML. Obesity and risk of type 2 diabetes and cardiovascular disease in children and adolescents. J Clin Endocrinol Metab 2003;88(4):1417-27.
249. Moran A, Jacobs DR, Jr., Steinberger J, et al. Insulin resistance during puberty: results from clamp studies in 357 children. Diabetes 1999;48(10):2039-44.
250. Canada S. Canadian Community Health Survey: Obesity among children and adults. The Daily 2006 Wednesday July 6, 2005.
251. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 2006;295(13):1549-55.
252. Shields M. Overweight and obesity among children and youth. Health Rep 2006;17(3):27-42.
253. Parker BA, Sturm K, MacIntosh CG, Feinle C, Horowitz M, Chapman IM. Relation between food intake and visual analogue scale ratings of appetite and other sensations in healthy older and young subjects. Eur J Clin Nutr 2004;58(2):212-8.
254. Mattes R. Hunger ratings are not a valid proxy measure of reported food intake in humans. Appetite 1990;15(2):103-13.
255. Drapeau V, King N, Hetherington M, Doucet E, Blundell J, Tremblay A. Appetite sensations and satiety quotient: predictors of energy intake and weight loss. Appetite 2007;48(2):159-66.
256. Heading RC, Nimmo J, Prescott LF, Tothill P. The dependence of paracetamol absorption on the rate of gastric emptying. Br J Pharmacol 1973;47(2):415-21.
257. Willems M, Quartero AO, Numans ME. How useful is paracetamol absorption as a marker of gastric emptying? A systematic literature study. Dig Dis Sci 2001;46(10):2256-62.
258. Yip PM, W. Walsh, T. Banka and Z. Verjee . . High Sensitivity Method for the Measurement of Acetaminophen in Plasma and Cerebrospinal Fluid Samples by UV-HPLC and EMIT Immunoassay. . In: 9th International Congress of Therapeutic Drug Monitoring & Clinical Toxicology; 2005; 2005. p. 261.
259. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 1999;402(6762):656-60.
260. Kacinik V JA, Vuksan V, Lyon M. . The reduction of the glycemic index when a Viscous Polysaccharide Blend is added or incorporated into
commonly consumed foods. . In: Natural Health Product Research
Conference Proceeding; 2008; Toronto, Ontario; 2008.
261. Raben A. Should obese patients be counselled to follow a low-glycaemic index diet? No. Obes Rev 2002;3(4):245-56.
262. Hospers JJVA, J.M.M; Weststrate, J.A. Amylose-to-Amylopectin Ratio in Pastas Affects Postprandial Glucose and Insulin Responses and Satiety in Males. Journal of Food Science 1994;59(5):1144-9.
263. Raben A, Tagliabue A, Christensen NJ, Madsen J, Holst JJ, Astrup A. Resistant starch: the effect on postprandial glycemia, hormonal response, and satiety. Am J Clin Nutr 1994;60(4):544-51.

264. Raben A, Holst JJ, Christensen NJ, Astrup A. Determinants of postprandial appetite sensations: macronutrient intake and glucose metabolism. Int J Obes Relat Metab Disord 1996;20(2):161-9.
265. Horowitz M, Edelbroek MA, Wishart JM, Straathof JW. Relationship between oral glucose tolerance and gastric emptying in normal healthy subjects. Diabetologia 1993;36(9):857-62.
266. Blackburn NA, Redfern JS, Jarjis H, et al. The mechanism of action of guar gum in improving glucose tolerance in man. Clin Sci (Lond) 1984;66(3):329-36.
267. Lembcke B, Ebert R, Ptok M, et al. Role of gastrointestinal transit in the delay of absorption by viscous fibre (guar). Hepatogastroenterology 1984;31(4):183-6.
268. Meier R, Beglinger C, Schneider H, Rowedder A, Gyr K. Effect of a liquid diet with and without soluble fiber supplementation on intestinal transit and cholecystokinin release in volunteers. JPEN J Parenter Enteral Nutr 1993;17(3):231-5.
269. Morgan LM, Tredger JA, Shavila Y, Travis JS, Wright J. The effect of non-starch polysaccharide supplementation on circulating bile acids, hormone and metabolite levels following a fat meal in human subjects. Br J Nutr 1993;70(2):491-501.
270. Morgan LM, Tredger JA, Wright J, Marks V. The effect of soluble- and insoluble-fibre supplementation on post-prandial glucose tolerance, insulin and gastric inhibitory polypeptide secretion in healthy subjects. Br J Nutr 1990;64(1):103-10.
271. Glerup H, Bluhme H, Villadsen GE, Rasmussen K, Ejskjaer N, Dahlerup JF. Gastric emptying: a comparison of three methods. Scand J Gastroenterol 2007;42(10):1182-6.
272. Camilleri M, Malagelada JR, Brown ML, Becker G, Zinsmeister AR. Relation between antral motility and gastric emptying of solids and liquids in humans. Am J Physiol 1985;249(5 Pt 1):G580-5.
273. Collins PJ, Horowitz M, Cook DJ, Harding PE, Shearman DJ. Gastric emptying in normal subjects--a reproducible technique using a single scintillation camera and computer system. Gut 1983;24(12):1117-25.
274. Houghton LA, Read NW, Heddle R, et al. Relationship of the motor activity of the antrum, pylorus, and duodenum to gastric emptying of a solid-liquid mixed meal. Gastroenterology 1988;94(6):1285-91.
275. Flourie B, Vidon N, Chayvialle JA, Palma R, Franchisseur C, Bernier JJ. Effect of increased amounts of pectin on a solid-liquid meal digestion in healthy man. Am J Clin Nutr 1985;42(3):495-503.
276. Iftikhar SY, Washington N, Wilson CG, Macdonald IA, Homer-Ward MD. The effect of pectin on the gastric emptying rates and blood glucose levels after a test meal. J Pharm Pharmacol 1994;46(10):851-3.
277. Himaya A, Louis-Sylvestre J. The effect of soup on satiation. Appetite 1998;30(2):199-210.
278. Rolls BJ, Fedoroff IC, Guthrie JF, Laster LJ. Foods with different satiating effects in humans. Appetite 1990;15(2):115-26.
279. Spiegel TA, Hubert CD, Fried H, Peikin SR, Siegel JA, Zeiger LS. Contribution of gastric and postgastric feedback to satiation and satiety in women. Physiol Behav 1997;62(5):1125-36.
280. Almiron-Roig E, Chen Y, Drewnowski A. Liquid calories and the failure of satiety: how good is the evidence? Obes Rev 2003;4(4):201-12.
281. Hulshof T, De Graaf C, Weststrate JA. The effects of preloads varying in physical state and fat content on satiety and energy intake. Appetite 1993;21(3):273-86.
282. Tournier A, Louis-Sylvestre J. Effect of the physical state of a food on subsequent intake in human subjects. Appetite 1991;16(1):17-24.
283. Gannon MC, Nuttall FQ. Factors affecting interpretation of postprandial glucose and insulin areas. Diabetes Care 1987;10(6):759-63.
284. Boulby P, Gowland P, Adams V, Spiller RC. Use of echo planar imaging to demonstrate the effect of posture on the intragastric distribution and emptying of an oil/water meal. Neurogastroenterol Motil 1997;9(1):41-7.
285. Batterham RL, Cowley MA, Small CJ, et al. Gut hormone PYY(3-36) physiologically inhibits food intake. Nature 2002;418(6898):650-4.
286. Goodlad RA, Ratcliffe B, Fordham JP, et al. Plasma enteroglucagon, gastrin and peptide YY in conventional and germ-free rats refed with a fibre-free or fibre-supplemented diet. Q J Exp Physiol 1989;74(4):437-42.

287. Lomenick JP, Clasey JL, Anderson JW. Meal-related changes in ghrelin, peptide YY, and appetite in normal weight and overweight children. Obesity (Silver Spring) 2008;16(3):547-52.
288. Stock S, Leichner P, Wong AC, et al. Ghrelin, peptide YY, glucose-dependent insulinotropic polypeptide, and hunger responses to a mixed meal in anorexic, obese, and control female adolescents. J Clin Endocrinol Metab 2005;90(4):2161-8.
289. Weickert MO, Spranger J, Holst JJ, et al. Wheat-fibre-induced changes of postprandial peptide YY and ghrelin responses are not associated with acute alterations of satiety. Br J Nutr 2006;96(5):795-8.
290. Bourdon I, Olson B, Backus R, Richter BD, Davis PA, Schneeman BO. Beans, as a source of dietary fiber, increase cholecystokinin and apolipoprotein b48 response to test meals in men. J Nutr 2001;131(5):1485-90.
291. Heini AF, Lara-Castro C, Schneider H, Kirk KA, Considine RV, Weinsier RL. Effect of hydrolyzed guar fiber on fasting and postprandial satiety and satiety hormones: a double-blind, placebo-controlled trial during controlled weight loss. Int J Obes Relat Metab Disord 1998;22(9):906-9.
292. Boyd KA, O'Donovan DG, Doran S, et al. High-fat diet effects on gut motility, hormone, and appetite responses to duodenal lipid in healthy men. Am J Physiol Gastrointest Liver Physiol 2003;284(2):G188-96.
293. Mohlig M, Koebnick C, Weickert MO, et al. Arabinoxylan-enriched meal increases serum ghrelin levels in healthy humans. Horm Metab Res 2005;37(5):303-8.
294. Juntunen KS, Niskanen LK, Liukkonen KH, Poutanen KS, Holst JJ, Mykkanen HM. Postprandial glucose, insulin, and incretin responses to grain products in healthy subjects. Am J Clin Nutr 2002;75(2):254-62.
295. Bakhoj S, Flint A, Holst JJ, Tetens I. Lower glucose-dependent insulinotropic polypeptide (GIP) response but similar glucagon-like peptide 1 (GLP-1), glycaemic, and insulinaemic response to ancient wheat compared to modern wheat depends on processing. Eur J Clin Nutr 2003;57(10):1254-61.
296. Raben A, Christensen NJ, Madsen J, Holst JJ, Astrup A. Decreased postprandial thermogenesis and fat oxidation but increased fullness after a high-fiber meal compared with a low-fiber meal. Am J Clin Nutr 1994;59(6):1386-94.
297. Gruendel S, Garcia AL, Otto B, et al. Carob pulp preparation rich in insoluble dietary fiber and polyphenols enhances lipid oxidation and lowers postprandial acylated ghrelin in humans. J Nutr 2006;136(6):1533-8.
298. Nedvidkova J, Krykorkova I, Bartak V, et al. Loss of meal-induced decrease in plasma ghrelin levels in patients with anorexia nervosa. J Clin Endocrinol Metab 2003;88(4):1678-82.
299. Erdmann J, Lippl F, Schusdziarra V. Differential effect of protein and fat on plasma ghrelin levels in man. Regul Pept 2003;116(1-3):101-7.

# **CHAPTER 9.** APPENDICES

**APPENDIX 1**

1. Particle size and Dose Study appetite, palatability and side effect scale 148
2. Clinical Questionnaire Adolescent study 149
3. Subjective Physical Comfort Adolescent study 150
4. Telephone Screening Questionnaire Mechanistic Study: 151
5. Rating of study food Enjoyment Mechanistic and Adolescent Study 152
6. Clinical Questionnaire Mechanistic Study 153

1. Particle size and Dose Study appetite, palatability and side effect scale

| Subject Initials | Test | Date | Weight | Start Time | Height | DOB |
|---|---|---|---|---|---|---|
| \|_\|_\|_\| | \|___\| | \|_\|_\|_\|_\| M D Y | \|___Kg\| | \|___\| | \|___\| | \|_\|_\|_\|_\| M D Y |

**Pre-Test Information**:

Was yesterday a usual day? Yes/No If no, describe: _____

Any unusual events prior to test? _____

**Please describe the dinner and snack you had last night:**

| Time | Amount | Food |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

**For the Satiety use the following scale:**

Extremely Hungry -3 -2 -1 0 +1 +2 +3 Uncomfortably full

| 0 | 15 | 30 | 45 | 60 | 90 | 120 |
|---|---|---|---|---|---|---|
| | | | | | | |

**Place an X on the line which best represent the palatability of the meal:**

Extremely dislike 1-----2------3-----4-----5-----6------7------8-----9------10 Delicious

**Eating time of meal:.....**

**Test Symptoms: Indicate whether you experienced any of the following symptoms, placing an X on the line if "yes"**

| | |
|---|---|
| **Bloating:** ☐ Yes ☐ No If yes, then | Low 1-------2-------3-------4-------5-------6-------7 High |
| **Belching:** ☐ Yes ☐ No If yes, then | Low 1-------2-------3-------4-------5-------6-------7 High |
| **Nausea**: ☐ Yes ☐ No If yes, then | Low 1-------2-------3-------4-------5-------6-------7 High |
| **Headache:**☐ Yes ☐ No If yes, then | Low 1-------2-------3-------4-------5-------6-------7 High |
| **Dizziness:**☐ Yes ☐ No If yes, then | Low 1-------2-------3-------4-------5-------6-------7 High |
| **Diarrhea**:☐ Yes ☐ No If yes, then | Low 1-------2-------3-------4-------5-------6-------7 High |

2. Clinical Questionnaire Adolescent study

Date:_____
Session #:_____

Ht (cm)_____
Wt (kg)_____

## Preclinical

**Fasting/Food Intake**
Have you had anything to eat or drink since 9:00 last night? Yes__ No__
Please describe every food you ate from lunch yesterday until you began your fast. Please include the TIME (e.g. 7:00p.m.), FOOD ITEM and QUANTITY consumed.

_____
_____
_____
_____

**General:**
1. Are you experiencing any feelings of illness this morning, other than hunger?
Yes__ No__
If yes, please specify _____

2. Are you under unusual stress this morning (e.g. exams/report deadlines, personal stress)
Yes__ No__
If yes, please briefly describe_____

3. Did you take any medications (prescription, over the counter, remedies, supplements or recreational, including drugs or alcohol) yesterday?
***Please note that this information is confidential***
Yes__ No__

4. Did you do anything last night or this morning that is not part of your regular routine? This may include social activities, exercise, or use of alcohol, medications or supplements. ***Please note that this information is confidential***
Yes__ No__
If yes, then please describe_____

5. How long ago did you last:
empty your bladder ____
empty your bowels_____

6. What was your mode of transportation to the clinic this morning_____
how long did this take _____? Is this different from other clinic mornings? Yes__ No__

7. What was the date of the 1st day of your last menstrual period?

**Sleep:**
Did you have a normal night of sleep last night Yes__ No__
How many hours of sleep did you have last night _____Hours

**Physical Activity**
Have you been engaged in any physical activity, unusual to your normal routine, within the past 24 hours Yes__ No__ If yes, please describe briefly:_____

Time consumption of breakfast drink began_____a.m.
Time taken to finish drink: _____ (please keep this consistent for all 3 visits)
Time taken to finish drink on last visit was _____
Today I thought I consumed the high/medium/low fibre drink (please circle one)
Time lunch began_____a.m.

3. Subjective Physical Comfort Adolescent study

## PHYSICAL COMFORT QUESTIONNAIRE

**Symptoms:** Indicate whether you experienced any of the following

| SYMPTOMS | PRESENCE | SEVERITY | Comment |
|---|---|---|---|
| **Bloating** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Belching** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Diarrhoea** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Flatulence** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Hyper-urination** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Nausea** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Headache** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Dizziness** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Insomnia** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Disorientation** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Anxiety** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Poor wound healing** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Excessive bleeding after cuts** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Impaired vision** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Heart flutters** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Racing Heart** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Joint pain** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Numbness** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |
| **Other (specify):** | ☐ Yes ☐ No | Low 1---------2---------3---------4---------5---------6---------7 High | |

ıptoms during the test.

Name: _____
Telephone

## 4. Telephone Screening Questionnaire Mechanistic Study:

If the individual does not meet the inclusion criteria for the study, please thank them for their interest in the study and explain that the protocol must follow strict inclusion and exclusion criteria because of the specific research question we are interested in.

1. Have you been diagnosed by a doctor with type 2 diabetes? Must answer NO
2. Are you overweight? Must answer YES. what is your height_____ weight _____ calculate BMI _____( 25-30)
3. Are you currently taking any hypoglycemic agents, herbal remedies or supplements of any kind? If YES, please list:
   a. _____
   b. _____
   c. _____
   d. _____
   e. _____
   f. _____
   g. _____

   *** MAY NOT INCLUDE; (Mulberry Extract, β-blockers, HT medication, acarbose, miglitol, hormonal drugs, antidepressants, glucocorticoids, thiazide diuretics, lipid lowering agents, investigational drugs, copious amounts of dietary fibre/day,
4. Have you been diagnosed with depression? Must answer NO
5. Are you between the ages of 35-55? Must answer YES
6. Do you have any kidney or liver problems? Must answer NO
7. Are you pregnant? Must answer NO
8. Do you have any other major illnesses or gastrointestinal problems (eg: Irritable Bowel Syndrome, Crohn's disease, Colitis)? Must answer NO.
9. Do you have high blood pressure? May answer YES (if on medications, exclude them. If it is significant on exam (screening), exclude them, if borderline, okay).
10. Do you consume > 3 alcoholic drinks per day? Must answer NO
11. Do you smoke? Must answer NO
12. Have you used insulin, alpha-glucose inhibitors (i.e. Acarbose), hormonal drugs, antidepressant medication, glucocorticoids, beta blockers, thiazide diuretics or lipid lowering agents within the last 4 weeks? Must answer NO
13. Do you use any laxatives? Including bulk-forming laxatives and dietary fibre? Must answer NO
14. Do you have cancer (must answer NO) unless superficial (i.e. skin). Are you on Cancer therapeutic agents (must answer NO).
15. Do you have unstable angina, have you had a M.I. or stroke within the previous 6 months? Must answer NO
16. Have you had a weight change within the previous 6 months that is greater than 10% of your body weight? Must answer NO
17. Have you been actively dieting within the last month to lose weight? If YES – under discretion of interviewer (i.e. if they have lost 1 pound in the last month then they may be included but if they have lost more than 5 pounds do not include them.
18. Do you currently have an eating disorder (anorexia or bulimia)? Must answer NO.
19. Are you able to eat pasta? Must answer YES. Are you allergic to eggs or any other foods? Must answer NO
20. Are you able to give blood samples? Must answer YES
21. Are you able to come to the clinic for 3 separate appointments that will begin between 7:30am and 8:30 am and take between 4 and 5 hours? Must answer YES.
22. Are you able to arrive at these visits in a fasted state (i.e. having not eaten or consumed any liquid within 10-12 hours prior to arriving at the clinic? Must answer YES.

5. Rating of study food Enjoyment Mechanistic and Adolescent Study

These six questions relate to the palatability of the food you just ate. Please rate the pleasantness of the food by placing a small "x" across the horizontal line at the point which best reflects your present feelings.

Time: _____
Date _____
Participant ID:_____
Food:_____

**1. How pleasant have you found the food?**

Not pleasant at all _____ Very pleasant

**2. How would you rate the taste of the food?**

Not pleasant at all _____ Very pleasant

**3. How do you rate the smell of the food?**

Not pleasant at all _____ Very pleasant

**4. How is the visual appearance of the food?**

Not pleasant at all _____ Very pleasant

**5. How is the mouth feel of the food (i.e. gritty or smooth)?**

Not pleasant at all _____ Very pleasant

**6. How do you rate the aftertaste of the food?**

Not pleasant at all _____ Very pleasant

## 6. Clinical Questionnaire Mechanistic Study

### Clinical Questionnaire

Date:_____
Session #:_____
**Preclinical**

Ht (cm)_____
Wt (kg)_____

**Fasting/Food Intake**
Have you had anything to eat or drink since 9:00 last night? Yes__ No__
Please describe every food you ate from lunch yesterday until you began your fast. Please include the TIME (e.g. 7:00p.m.), FOOD ITEM and QUANTITY consumed. If applicable, please record the brand name of the food and the amount of any condiments (butter, mustard, ketchup) you ate.

_____
_____
_____
_____

**General:**
1. Are you experiencing any feelings of illness this morning, other than hunger?
Yes__ No__
If yes, please specify _____

2. Are you under unusual stress this morning (e.g. exams/report deadlines, personal stress)
Yes__ No__
If yes, please briefly describe_____

3. Did you take any medications (prescription, over the counter, remedies, supplements or recreational, including drugs or alcohol) yesterday?
Yes__ No__

4. Did you do anything last night or this morning that is not part of your regular routine? This may include social activities, exercise, or use of alcohol, medications or supplements.
Yes__ No__
If yes, then please describe_____

5. How long ago did you last:
empty your bladder ____hours ago
empty your bowels_____hours ago

6. What was your mode of transportation to the clinic this morning_____
how long did this take _____? Is this different from other clinic mornings? Yes__ No__

**Sleep:**
Did you have a normal night of sleep last night Yes__ No__
How many hours of sleep did you have last night _____Hours

**Physical Activity**
Have you been engaged in any physical activity, unusual to your normal routine, within the past 24 hours Yes__ No__ If yes, please describe briefly:_____ _____

Time consumption of breakfast drink began_____a.m.
Time taken to finish drink: _____ (please keep this consistent for all 3 visits)
Time taken to finish drink on last visit was _____
Time lunch began_____a.m.

**APPENDIX 2**

Table A2.1: Mean Symptom Ratings for Study 1 155
Table A2.2 Mean Symptom Ratings for Study 2 155
Table A2.3 Mean Symptom Ratings for Study 3. 156
Table A2.4 Mean Symptom Ratings for Study 4. 157
Inclusion and Exclusion Criteria: 158

Table A2.1: Mean Symptom Ratings for Study 1
Preloads were provided fasting and consisted of 200ml of Glucodex® plus control (3g gelatin) or a granulated soluble fiber blend (SFB), of which the glucomannan particle size was varied to be either: large, medium, small or mixed. Following consumption, participants rated symptoms for 180 minutes using a visual analog scale.

| Treatment | Bloating | Belching | Nausea | Headache | Diarrhea | Flatulence | Hyperurination |
|---|---|---|---|---|---|---|---|
| Control | 0.4±0.3 | 0.5±0.2 | 0.1±0.1 | 0.6±0.4 | 0.0±0.0 | 0.4±0.4 | 0.7±0.5 |
| Large | 0.3±0.3 | 0.5±0.2 | 0.0±0.0 | 0.2±0.1 | 0.0±0.0 | 0.6±0.4 | 0.2±0.2 |
| Medium | 0.2±0.2 | 0.6±0.3 | 0.1±0.1 | 0.4±0.2 | 0.0±0.0 | 0.3±0.3 | 0.6±0.3 |
| Small | 0.3±0.2 | 0.6±0.2 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.4±0.2 | 0.1±0.1 |
| Mix | 0.7±0.5 | 0.6±0.4 | 0.2±0.2 | 0.1±0.1 | 0.0±0.0 | 0.6±0.4 | 0.9±0.5 |

Values represent means ± SD
Treatments refer to: Control, Large, Medium, Small and Mixed Particle sizes.
Means represent values converted from the 100 mm to a 10 cm scale.

Table A2.2 Mean Symptom Ratings for Study 2
Participants consumed preload treatments consisted of 289ml of Boost™ meal replacement plus granulated fibers of either control (1.2g of wheat bran), or treatment soluble fiber blend (SFB) in 2 gram, 4gram or 6 gram doses. Fibers were mixed with Boost™ prior to consumption to prevent lump formation. For 120 minutes after consumption, satiety ratings and symptoms were rated by participants using visual analog scales.

| | Bloating | Belching | Nausea | Headache | Dizziness | Diarrhea |
|---|---|---|---|---|---|---|
| Control | 0.1±0.1 | 0.1±0.1 | 0.0±0.0 | 0.4±0.4 | 0.2±0.2 | 0.0±0.0 |
| 2 grams | 0.0±0.0 | 0.3±0.2 | 0.3±0.2 | 0.4±0.4 | 0.2±0.2 | 0.0±0.0 |
| 4 grams | 0.2±0.0 | 0.6±0.4 | 0.2±0.1 | 0.8±0.6 | 0.3±0.2 | 0.0±0.0 |
| 6 grams | 0.0±0.2 | 0.4±0.3 | 0.4±0.3 | 0.6±0.4 | 0.2±0.2 | 0.0±0.0 |

WB: Wheat bran. Values represent means ± SEM. Means represent values converted from the 100 mm to a 10 cm scale.

Table A2.3 Mean Symptom Ratings for Study 3.

Participants were provided with preload meal replacement drinks consisting of either high (soluble fiber blend), medium (glucomannan) or low (cellulose) viscosity fiber. For 90 minutes after consumption of the meal replacement, participants recorded their ratings of motivation to eat and symptoms using visual analog scales. After 90 minutes pizza was provided as a measure of the effect of meal replacement fiber on energy intake. After 90 minutes participants completed another set of visual analog scales and left the clinic with instructions to record food intake long-term. Treatments: GM: Glucomannan, SFB: Soluble Fiber Blend. Values represent means ± SEM. Means represent values converted from the 100 mm to a 10 cm scale.

| Treatment | | 0 | 15 | 30 | 45 | 60 | 75 | 90 | Postprandial |
|---|---|---|---|---|---|---|---|---|---|
| **SFB** | bloating | 0.0±0.0 | 0.5±0.2 | 0.5±0.2 | 0.3±0.2 | 0.3±0.2 | 0.1±0.1 | 0.1±0.1 | 0.3±0.2 |
| **GM** | | 0.0±0.0 | 0.7±0.2 | 0.4±0.2 | 0.3±0.1 | 0.1±0.1 | 0.2±0.1 | 0.0±0.0 | 0.4±0.2 |
| **Cellulose** | | 0.1±0.1 | 0.9±0.3 | 0.6±0.2 | 0.4±0.1 | 0.4±0.2 | 0.2±0.1 | 0.1±0.1 | 0.5±0.2 |
| **SFB** | belching | 0.1±0.1 | 0.5±0.2 | 0.4±0.2 | 0.4±0.2 | 0.3±0.2 | 0.2±0.2 | 0.2±0.2 | 0.4±0.2 |
| **GM** | | 0.0±0.0 | 0.5±0.2 | 0.3±0.2 | 0.3±0.1 | 0.1±0.1 | 0.1±0.1 | 0.1±0.1 | 0.3±0.1 |
| **Cellulose** | | 0.0±0.0 | 0.8±0.3 | 0.4±0.2 | 0.5±0.2 | 0.4±0.2 | 0.3±0.2 | 0.1±0.1 | 0.4±0.2 |
| **SFB** | diarrhea | 0.1±0.1 | 0.1±0.1 | 0.1±0.1 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **GM** | | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **Cellulose** | | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **SFB** | flatulence | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.1±0.1 | 0.1±0.1 | 0.0±0.0 | 0.0±0.0 |
| **GM** | | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.1±0.1 |
| **Cellulose** | | 0.0±0.0 | 0.1±0.1 | 0.1±0.1 | 0.1±0.1 | 0.0±0.0 | 0.1±0.0 | 0.1±0.1 | 0.1±0.1 |
| **SFB** | excessive urination | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.2±0.1 | 0.4±0.2 | 0.2±0.2 | 0.2±0.1 | 0.1±0.1 |
| **GM** | | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.2±0.1 | 0.3±0.2 | 0.0±0.0 | 0.0±0.0 | 0.1±0.1 |
| **Cellulose** | | 0.0±0.0 | 0.1±0.1 | 0.1±0.1 | 0.2±0.1 | 0.2±0.2 | 0.3±0.2 | 0.1±0.1 | 0.1±.0.0 |
| **SFB** | nausea | 0.0±0.0 | 0.5±0.2 | 0.3±0.2 | 0.2±0.2 | 0.2±0.2 | 0.2±0.2 | 0.2±0.2 | 0.1±0.1 |
| **GM** | | 0.1±0.1 | 0.4±0.2 | 0.2±0.1 | 0.2±0.1 | 0.2±0.1 | 0.1±0.1 | 0.1±0.1 | 0.0±0.0 |
| **Cellulose** | | 0.0±0.0 | 0.6±0.2 | 0.2±0.1 | 0.1±0.1 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **SFB** | headache | 0.0±0.1 | 0.1±0.1 | 0.1±0.1 | 0.1±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **GM** | | 0.1±0.1 | 0.1±0.1 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **Cellulose** | | 0.0±0.0 | 0.2±0.1 | 0.1±0.0 | 0.1±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.1±0.1 |
| **SFB** | dizziness | 0.0±0.0 | 0.0±0.0 | 0.1±0.1 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **GM** | | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **Cellulose** | | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.1±0.0 |
| **SFB** | disorientation | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **GM** | | 0.0±0.0 | 0.1±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **Cellulose** | | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **SFB** | anxiety | 0.1±0.1 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **GM** | | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **Cellulose** | | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **SFB** | vision problems | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **GM** | | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **Cellulose** | | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **SFB** | heart | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **GM** | | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **Cellulose** | | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **SFB** | joint pain | 0.1±0.1 | 0.0±0.0 | 0.1±0.1 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **GM** | | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **Cellulose** | | 0.1±0.1 | 0.1±0.1 | 0.1±0.1 | 0.1±0.1 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **SFB** | numbness | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **GM** | | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **SFB** | | 0.0±0.0 | 0.1±0.1 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |

Table A2.4 Mean Symptom Ratings for Study 4.

Participants consumed a breakfast with a bagel, cream cheese, orange juice, 3 extra strength Tylenol and water. Cream cheese was mixed with either granulated soluble fiber blend (SFB) or cellulose control. After completion of the breakfast blood samples were collected for measurement of glucose, insulin, acetaminophen (Tylenol) and growth hormone and visual analog scales were completed for motivation to eat and symptoms. A pizza lunch was provided at 210 minutes. After completion of the study visit, participants were asked to record symptoms for 24-hours using a visual analog scale.

| | Treatment | 0 | 15 | 30 | 60 | 90 | 120 | 150 | 180 | 210 | 240 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Bloating** | Cellulose | 9.97±4.30 | 15.00±5.67 | 10.34±4.25 | 5.74±3.16 | 6.29±2.37 | 3.16±1.33 | 4.55±1.96 | 2.95±1.21 | 4.42±2.12 | 5.32±2.39 |
| | SFB | 10.55±4.04 | 17.93±6.44 | 11.32±5.25 | 5.50±3.04 | 7.55±3.41 | 8.95±4.43 | 4.63±2.52 | 5.03±2.90 | 4.67±2.43 | 10.47±5.83 |
| **Belching** | Cellulose | 5.05±2.98 | 9.21±3.64 | 5.00±2.92 | 5.45±2.95 | 8.87±3.63 | 4.37±1.73 | 4.50±2.12 | 4.50±1.80 | 4.81±2.65 | 4.11±2.47 |
| | SFB | 6.11±3.21 | 11.65±4.79 | 10.82±5.02 | 8.32±3.80 | 11.00±4.65 | 10.68±4.88 | 5.44±2.29 | 7.16±3.42 | 6.89±3.11 | 11.42±5.88 |
| **Nausea** | Cellulose | 9.82±4.39 | 5.53±3.16 | 3.71±2.32 | 2.13±0.90 | 2.26±1.25 | 2.66±1.38 | 1.76±0.72 | 1.26±0.47 | 1.86±0.62 | 1.63±0.89 |
| | SFB | 12.29±5.96 | 3.62±1.74 | 3.95±2.86 | 1.82±0.83 | 2.53±1.14 | 2.08±0.76 | 1.64±0.57 | 1.42±0.50 | 1.89±0.58 | 3.84±2.80 |
| **Diarrhea** | Cellulose | 1.87±0.54 | 1.03±0.31 | 0.90±0.30 | 1.42±0.53 | 1.74±0.68 | 0.95±0.35 | 1.13±0.39 | 1.34±0.47 | 1.15±0.53 | 1.00±0.42 |
| | SFB | 1.66±0.70 | 1.48±0.68 | 1.03±0.44 | 1.08±0.38 | 2.18±1.04 | 1.87±0.73 | 1.51±0.50 | 1.13±0.33 | 0.98±0.33 | 1.03±0.32 |
| **Stomach Pain** | Cellulose | 7.26±4.13 | 3.76±2.22 | 2.63±1.72 | 1.71±0.93 | 3.68±1.36 | 1.29±0.43 | 1.76±0.71 | 2.92±1.83 | 1.74±0.83 | 1.61±0.96 |
| | SFB | 8.37±4.57 | 4.32±1.72 | 3.37±1.54 | 1.68±0.69 | 3.32±1.34 | 3.08±1.36 | 2.65±1.53 | 2.21±1.05 | 1.82±0.83 | 1.90±0.63 |
| **flatulence** | Cellulose | 6.97±4.04 | 6.61±3.56 | 3.90±1.76 | 3.18±1.92 | 4.13±1.54 | 4.08±1.78 | 3.53±1.34 | 5.16±2.23 | 2.51±1.53 | 5.32±3.21 |
| | SFB | 7.24±2.71 | 6.27±2.48 | 6.66±3.32 | 7.13±3.21 | 10.29±3.90 | 9.42±4.67 | 5.86±3.01 | 5.63±2.77 | 6.98±3.27 | 6.74±3.01 |

Values represent means ± SEM. Means from the 100 mm scale were used.

Inclusion and Exclusion Criteria:

**Study 1:** Inclusion criteria: individuals who were greater than 18 years of age, with normal renal and liver function, and clinically euthyroid. Exclusion criteria were: pregnant females, individuals with bowel disease (e.g. malabsorption, disorders of the GI tract, including motility problems and inflammatory bowel disease), major illnesses, use of drugs that alter GI motility, presence of any condition which, in the opinion of the investigator, might jeopardize the health and safety of the participants or study personnel or adversely affect the study results. Individuals following a specific dietary regimen, or those who smoked, drank alcohol heavily, exercised competitively and those having a BMI>30kg/m2 were excluded from participating in the study. Informed consent was obtained from all participants.

**Study 2:** Inclusion criteria: Healthy participants Exclusion criteria: Previously diagnosed liver or kidney disease, diagnosed diabetes, dysglycemia, pregnant females, individuals younger than 18 years of age and those with a body mass index (BMI) of >30kg/$m^2$.

**Study 3:** Inclusion criteria: Healthy, healthy weight, age 13-18 years, breakfast eaters, relatively active. Exclusion Criteria were: 1) Use of insulin, alpha-glucose inhibitors (i.e. Acarbose), hormonal drugs or antidepressant medication; 2) use of drugs that influence carbohydrate metabolism (e.g. systemic glucocorticoids, beta blockers, thiazide diuretics); presence of any significant disease or condition, including emotional or psychiatric disorders and substance abuse, that, in the opinion of the investigator, is likely to alter metabolic state or interfere with the participant's ability to complete the study; 4) presence of gastrointestinal diseases associated with abnormal gut motility (e.g. gastroparesis), altered nutrient absorption (malabsorption syndrome), chronic diarrheal states or chronic enteropathies; 5) use of any investigational drug, special dietary treatments or fiber supplements within 4 weeks of screening; 6) use of drugs which alter appetite, gastrointestinal motility or anti-constipation agents; 7) weight change (±10% body weight) within the previous 6 weeks; 8) alcohol abuse (≥ 4 drinks/day) or smoking (≥ 1 pack/week); 9) a score of ≥ 9 on the Beck Depression Inventory 10) Restrained eating habits (score of ≥ 15 on the Eating Habits Questionnaire).

**Study 4**: Inclusion criteria: BMI: 25-30, Otherwise healthy, males and females, aged 20-55 years, palatability score on study foods >50% , Exclusion: Type 2 diabetes, obese (BMI > 31), hypoglycemic agents, taking herbal remedies, supplements (besides vitamins), other medications, depression, pregnant, consume > 3 alcoholic drinks/day, smokers, restrained eaters, eating disorders, laxative users, has had a significant (>10%) weight change w/i last 6 mo.