Comparison of

Low Glycemic Index High Carbohydrate, High Glycemic Index

High Carbohydrate and Monounsaturated Fat Enriched Diets on

insulin Sensitivity in the Treatment of

Impaired Glucose Tolerance

by

Christine Mehling

A thesis submitted in conformity with the requirements

For the Degree of Master of Science

Graduate Department of Nutritional Sciences

University of Toronto

The author has granted a non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of this thesis in microform, paper or electronic formats.

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de cette thèse sous la forme de microfiche/film, de reproduction sur papier ou sur format électronique.

The author retains ownership of the copyright in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

L'auteur conserve la propriété du droit d'auteur qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

0-612-54157-6

Canada

Comparison of

Low Glycemic Index High Carbohydrate, High Glycemic Index

High Carbohydrate and Monounsaturated Fat Enriched Diets on Insulin

Sensitivity in the Treatment of Impaired Glucose Tolerance

Christine Mehling RD, Master of Science, 2000

Graduate Department of Nutritional Sciences, University

Abstract

The purpose of this thesis was to compare the effects of altering the source and amount of carbohydrate on insulin sensitivity (S_i) and mean insulin levels in subjects with impaired glucose tolerance (IGT).

IGT subjects (n=34) were randomized to either a high-glycemic-index-high-carbohydrate (high-GI), low-glycemic-index-high-carbohydrate (low-GI) or high-monounsaturated-fat-low-carbohydrate diet (MUFA) for four months using a randomized parallel design.

No significant difference in S_i was found on any of the dietary treatments. The glucose disposition index ($S_i \times AIR_{glu}$) improved by 56% on the low-GI group compared to a 16% reduction in the MUFA group (p=0.01). Free fatty acid levels decreased significantly by 25% (p=0.027) on the low-GI diet, but not on the other diets. There were no differences in fasting blood lipids, glucose, HbA1c or insulin. If these changes were sustained (over the long-term), a low-glycemic-index-high-carbohydrate diet would be expected to reduce the rate of progression of IGT to diabetes.

Acknowledgements

Foremost, I would like to thank Dr. Wolever for his support, encouragement, patience and generosity while having provided a worthwhile, interesting challenging experience.

I would like to thank Dr. Jenkins and Dr. Vuksan for their valued input as co-supervisors for the project. Thank you to Dr. Singer for appraising the thesis and Dr. Archer for chairing the defence. Thanks also go to the department's support staff Janette Campbell and Margaret Hardy for their assistance during my studies.

My gratitude and appreciation is also sent out to my work colleagues Tina Parker and Dorothea Faulkner at the Risk Factor Modification Centre for their assistance and accommodation during the clinical aspect of the trial.

Thanks goes out to Bonnie Kennedy, the principal study nurse, for her flexibility, excellent care and friendly service towards the patients on clinic test days.

Special thanks to Rana for her technical support and Elizabeth for her humour and assistance.

With out the assistance of the many student helpers especially Heather Bell, my food records would still be sitting and waiting to be coded and entered.

A special mention should go to Gordon, whose patience and support during the study, especially during the writing process was truly appreciated. This clinical trial was made possible by the support of the Canadian Diabetes Association and Olive Oil Council of Canada.

ii

Table of Contents

Chapter 3.0 Results

Chapter 4.0 Discussion and Conclusions

List of Tables

List of Figures

Abbreviations

ADA:	American Diabetes Association
Air_{glu}:	Pancreatic responsivity
ANOVA:	Analysis of variance
AUC:	Area under the curve
BP:	Blood pressure
BMI:	Body mass index
CHD:	Coronary heart disease
CHO:	Carbohydrate
CI:	Confidence interval
CV:	Coefficient of Variance
DI:	Disposition index
DCCT:	Diabetes Control and Complications Trial
FBG:	Fasting blood glucose
FFA:	Free fatty acid
FSIGT:	Frequently sample intravenous glucose tolerance test
GI:	Glycemic index
HbA1c:	Glycosylated hemoglobin
HDL:	High density lipoprotein
HRT:	Hormone replacement therapy
IGT:	Impaired glucose tolerance
kg:	kilogram
LDL:	Low density lipoprotein

m:	meters
MUFA:	Monounsaturated fat
NCEP:	National Cholesterol Education Program
NHANES III:	Third National Health and Nutrition Examination Survey
OGTT:	Oral glucose tolerance test
PUFA:	Polyunsaturated fat
SCFA:	Short chain fatty acids
sem:	Standard error of the mean
SFA:	Saturated fatty acids
S_G:	Glucose effectiveness
S_I:	Insulin sensitivity
TC:	Total cholesterol
TG:	Triglyceride
UKPDS:	United Kingdom Prospective Diabetes Study
WHO:	World Health Organization

1.0 Introduction

Type 2 diabetes is well recognized as a major health problem associated with increased morbidity and mortality and high health care costs (1). The number of people with diabetes is predicted to explode and reach epidemic proportions as the population ages and 3rd world countries become more industrialized, less active and more obese (2). Considering the financial burden to the health care system and the devastating effects of diabetes on the individual, preventing the onset of the disease would be ideal (1,2,3).

Impaired glucose tolerance (IGT) is a stage between normal and abnormal glucose tolerance and they are at higher risk for developing type 2 diabetes than the average healthy individual (4). Like type 2 diabetes IGT is characterized by a decrease in the effect of insulin on peripheral tissues (insulin resistance) and by the inability of the pancreas to compensate for this resistance (relative insulin deficiency) (5).

It is hypothesised that any therapeutic intervention that can decrease insulin resistance (decrease insulin demand) or protect the β-cell or both could prevent or delay the progression to type 2 diabetes (1,5).

Attention has focused on the role of dietary factors, in particular the role of fat and carbohydrate, which could affect/influence/facilitate insulin action or secretion. (5,6). Currently there is a great deal of controversy as to whether a diet high in monounsaturated fat would be more beneficial than a high carbohydrate low fat diet in reducing hyperinsulinemia and improving insulin resistance. Some epidemiological and clinical studies show that glucose tolerance deteriorates as the proportion of fat calories, in particular saturated fat, relative to carbohydrate calories increases (6,7,8,9). Other

1

short term clinical studies show that high carbohydrate low fat diets increase insulin demand, raise triglyceride levels and lower HDL levels (both risk factors for heart disease), while high monounsaturated fat diets do not have these negative aspects (5,10,11).

During this debate regarding the level of carbohydrate intake, little consideration has been given to the quality of the carbohydrate. Many metabolic studies have documented differences in insulin demand generated by various foods, depending largely on the type or degree of digestibility of the starch content (5). The glycemic index (GI), a relative measure of glycemic response to a given amount of carbohydrate, takes the quality rather than the quantity of carbohydrate into account (5,12). High GI foods are absorbed more quickly than low GI foods. Studies that refer to the detrimental effects of carbohydrates usually refer to a diet high in high GI foods. Meanwhile, studies comparing the effects of a low GI versus high GI high carbohydrate diets show that low GI diets improve the glycemic and cholesterol profile of the diabetic compared to a high GI diet (12). Lowering meal GI and raising meal carbohydrate content has also shown to reduce free fatty acid levels, which may improve insulin resistance (13,14). Looking through the literature, rarely have these three different dietary approaches (high monounsaturated fat (MUFA), high GI high carbohydrate, and low GI high carbohydrate) been tested together. Nor have many studies looked at whether diet can change insulin sensitivity rather the studies have looked at surrogate markers such as fasting glucose and insulin levels.

Thus, this study sets to investigate the effect of varying the quantity and quality of carbohydrate on insulin secretion and sensitivity in a group of impaired glucose tolerant subjects, a group known to be at higher risk for developing diabetes.

1.2 Literature Review

1.2.1 Type 2 Diabetes

Type 2 diabetes is recognized as a major health problem associated with increased morbidity and mortality and high health care costs (1). Coronary heart disease (CHD) in the diabetic population is 2-3 times that of the normal population. Fifty percent of deaths in type 2 diabetes are due to CHD (15). Diabetic retinopathy is the major cause of adult blindness in North America, while diabetic nephrophathy is the number one cause of end stage renal failure in the western world (3). The Diabetes Control and Complications Trial (DCCT) in Type 1 diabetics showed that tight blood glucose control reduced the development and progression of long-term microvascular complications such as retinopathy by 75% in the primary prevention group and 54% in the secondary prevention group. Combining the two groups, microalbuminia was reduced by 39% while albuminuria was reduced by 54% (16). In type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS) showed that tight blood glucose control reduced the development of diabetes related complications by 12% (15). It is estimated, that one in seven Canadian health care dollars is spent on diabetes (3). Currently 5% of Canadians have been diagnosed with diabetes of which 90% have type 2 diabetes (3). Roughly half of those with type 2 diabetes remain undiagnosed (17,18). This number is estimated to explode and reach epidemic proportions as the population ages and as 3rd world countries become more industrialized, less active and more

obese. By the year 2020, an estimated 250 million people will be suffering from this disorder (2). Considering, the financial burden and personal cost of diabetes to society, it appears that slowing the progression to diabetes would seem prudent.

1.2.2 Impaired Glucose Tolerance (IGT)

It is believed that all type 2 diabetics must pass through a phase of impaired glucose tolerance before they develop diabetes (1). IGT was first recognized as an entity and uniformly defined in 1979 by the National Diabetes Data Group (19) and the World Health Organization (WHO) Expert Committee on Diabetes (20). IGT is considered a transitional stage between normal and abnormal glucose levels (4). According to the WHO, IGT is defined by a fasting plasma glucose value within the normal range (<7.8mmol/L) and a value at 2 hours after a 75 g glucose load that lies between that of normal and diabetes (7.8 mmol/L-11.1mmol/L) (20).

The prevalence of IGT varies widely around the world ranging from 1-3% in rural China and Papua New Guinea to over 20% in specific ethnic groups such as the Pima Indians and the Nauruans (1,21). The prevalence varies between 3-10% in Europe and 11-20% in North American (1,21).

Although IGT is not associated with diabetes-specific complications per se, it is important to diagnosis the condition because those who test positive are at higher risk for developing diabetes and heart disease than the normal population (1,18,21). Many prospective studies have shown that the progression of IGT to type 2 diabetes can vary between 1.5-7.3% per year in different ethnic groups and in various regions of the world (1,21). This means that over a 10-year period up to 50% of individuals testing positive with IGT will have progressed to type 2 diabetes (22). Saad et al conducted a study

on the Pima Indians which showed that within their group of subject with IGT type 2 diabetes developed in 31% within 10 years of follow up compared to 3.3% in the control group of Pima Indians (22,23). IGT is associated with a 1.5-2 fold increase in risk of macrovascular and cardiovascular disease (24). In a 20 year follow up of the combined Whitehall, Paris Prospective and Helsinki Policeman studies, they showed after an adjustment for age, that glucose levels in the upper 2.5% quartile of normal non-diabetic men, were associated with a higher risk of death from coronary heart disease. The hazard ratio for fasting and 2 hour glucose was 1.8 (1.4-2.4) and 2.7 (1.7-4.4) (25). A study of older women in the Framingham population demonstrated a gradient of risk for heart disease as glycosylated hemoglobin (HbA1c) increased within the non-diabetic range (26). Considering the complications and risks associated with IGT and diabetes it would seem wise to diagnose and treat the condition as early as possible.

Risk Factors for the development of IGT include older age, obesity, physical inactivity and family history of type 2 diabetes, selected race and ethnicity, a history of IGT or gestational diabetes and lipid abnormalities (high triglycerides (TG), low high density lipoproteins (HDL) (1,2,18). The Third National Health and Nutrition Examination Survey (NHANES III) study in the USA showed clearly that the rise in IGT was associated with increasing age. The rate of IGT in Caucasians aged 65-74 years is 5 times higher than that in individuals aged 25-34 years (17). Other studies have also shown that as body mass index (BMI), especially when it exceeds 27, increases the risk for developing IGT increases (18). A combined analysis of six prospective studies found that fasting and post load glucose concentrations measured at the time of IGT

5

recognition were the most consistent and strongest predictors of the progression from IGT to type 2 diabetes (18).

1.2.3 Etiology and Pathophysiology of Type 2 Diabetes

The etiology of NIDDM is very complicated and involves both genetic and environmental aspects; genes confer predisposition and the environment provides the accelerants (7). Environmental factors include: increased age, obesity and diet and lack of exercise (18). For example, diabetes was virtually unknown among the Pima Indians when they lived as subsistence farmers 100 years ago. Today, the prevalence of type 2 diabetes in the Pima Indians is the highest in the world. Approximately 50% of adults over the age of 35 suffer from type 2 diabetes (7). Accompanying this rise in diabetes was a change in the Pima Indians lifestyle. Their traditional diet that was high in complex carbohydrates and fibre and low in fat and it changed to a typical American diet that was high in fat and low in fibre. The Pima Indians have also become overweight and more sedentary (7).

Type 2 diabetes is a heterogeneous metabolic disorder that is characterized by raised blood glucose levels due to insulin resistance and relative insulin deficiency (27,28). The earliest detectable abnormality in type 2 diabetes is an impairment of the body's ability to respond to insulin. Insulin resistance can be defined as a state in which a normal amount of insulin produces a subnormal biological response in key organs such as muscles, liver and fat (28,29,30). Insulin stimulated glucose uptake in muscles and fat are decreased (31). With insulin resistance in the peripheral tissues, the plasma glucose rises and the pancreas responds by increasing circulating insulin concentrations (hyperinsulinemia) in an attempt to maintain glucose homeostasis.
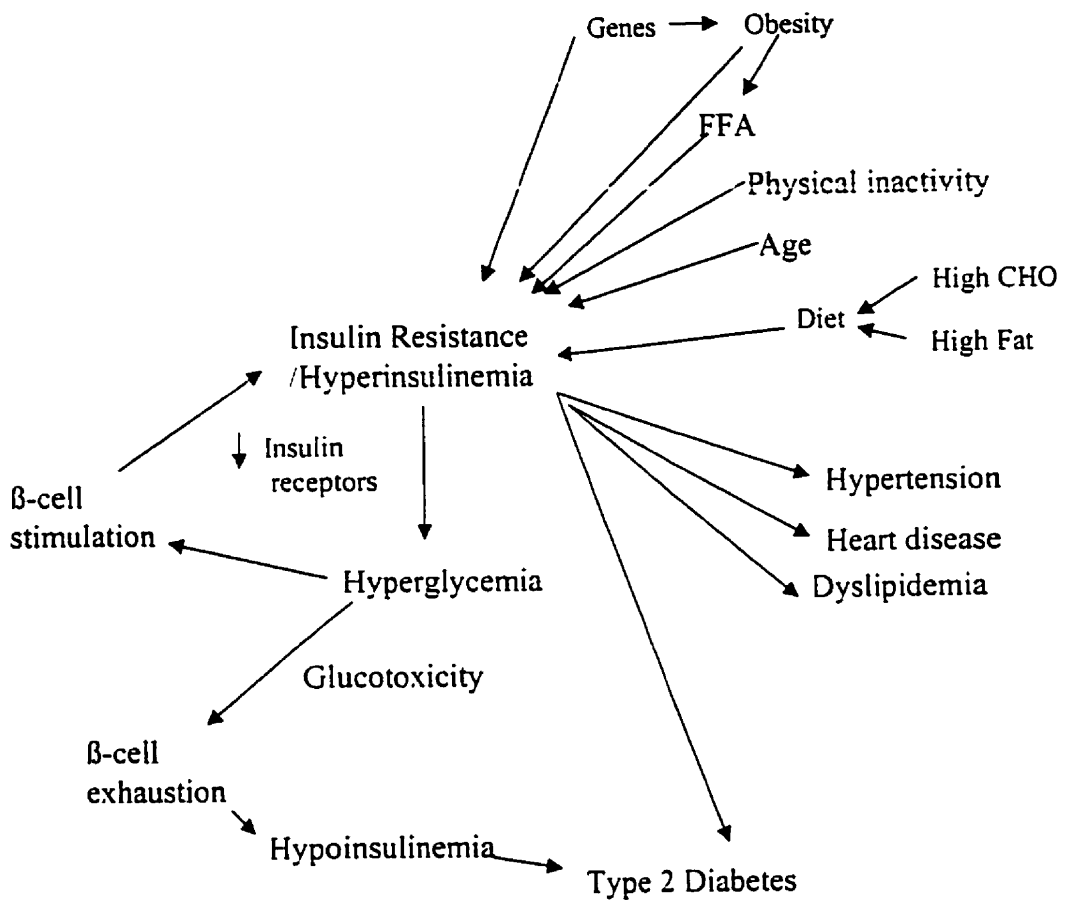
Figure 2.1: Schematic representation of the risk factors in the development of insulin resistance and the sequence of events leading up to the development of type 2 diabetes

Hyperinsulinemia, a manifestation of insulin resistance, is one of the best predictors of type 2 diabetes (5,28,32). This rise in insulin causes down regulation of the insulin receptors and exacerbates the tissue insensitivity to insulin. As long as the β-cell can compensate by increasing insulin secretion, normal glucose tolerance is maintained (1,28). Only when the β-cell fails to compensate does IGT develop resulting initially in post-prandial hyperglycemia (1,28). A vicious cycle ensues with a progressive rise in plasma glucose to a point, at which time the β-cell decompensates, insulin secretion falls and hyperglycemia is further exacerbated resulting in deterioration of glucose tolerance through IGT to diabetes (32). Thus, before the onset of diabetes both insulin resistance and a defect in insulin secretion (insulin deficiency) must be present (33).

Possible causes of insulin resistance include an abnormal β-cell secretory product, circulating insulin antagonists such as free fatty acids (FFAs), or a target tissue defect in insulin action (32). Target tissue defects include both binding and post-binding defects in insulin action (28,32). Diminished insulin binding occurs primarily in individuals with IGT or with very mild diabetes and results secondarily to a down regulation of the insulin receptor by chronic sustained hyperinsulinemia (28). Once fasting glucose levels are greater than 7.7 mmol/L post-binding defects are primarily responsible for insulin resistance. Post-binding defects include tyrosine kinase activity, decreased glucose transport, impaired glycogen synthase activity, and reduced pyruvate dehydrognease activity. Evidence points to a reduced glucose transport and impaired glycogen synthesis as the major defects (28,31,32).

Insulin resistance is not only a risk factor for the development of type 2 diabetes but may also play a role in the development of many other chronic diseases such as hypertension, atherosclerosis, and dyslipidemia such as hypertriglyceridemia and low HDL levels, hyperuricemia, upper-body obesity, and elevated plasminogen activator inhibitor (PAI)-1 levels (31,31,33). Each of the components is in itself a risk factor for the development of heart disease and the cluster of risk factors has been coined Syndrome X or The Metabolic Syndrome (1,34). Therefore, it is extremely important to treat insulin resistance.

1.2.4 Glucotoxicity

Elevated glucose levels are thought in themselves to be deleterious and lead to defects in both insulin secretion and insulin action. The glucoto xicity hypothesis states that chronic hyperglycemia may cause a generalized desensitization of all cells in the body through down regulation of the glucose transport system. In muscle, and adipocytes this would be reflected by a defect in insulin action, whereas at the level of the β-cell, this would be manifested by an impairment in insulin secretion (28).

Elevated glucose levels have been shown to impair the β-cells ability to respond to an acute hyperglycemic challenge. For example, Kosaka et. al took a group of obese type 2 diabetic patients and treated them with either a weight loss diet, insulin or sulfonureas to improve glycemic control. Each treatment led to a marked and similar improvement in glycemic control. After their treatment they were tested with a 100 g oral glucose tolerance test (OGTT). The insulin response improved twofold, suggesting that improving the glucose profile will lead to an improvement in insulin secretion (28,35). Other investigators found similar results. Other support for this concept comes

from animal studies treated with phlorizin. Phlorizin is a potent inhibitor of renal tubular glucose transport. It restores normoglycemia without altering plasma insulin, amino acids, free fatty acids, or other substrate/hormone concentrations. Rats had 90% of their pancreas removed. As a result early insulin secretion was completely lost while the second phase of insulin secretion was impaired. When phlorizin was given to these rats' glucose levels went back to normal. Researchers found that with the normalization of glucose levels, first and second phase insulin secretion also returned to normal. These results suggest that even with 90% of the pancreas removed, the pancreas was still functional in nature but when overburdened with the level of glucose it was unable to secrete enough insulin and as a result glucose levels rose and insulin levels decreased (28,36). In another series of studies Weir and Leahy et al. (28,37,38) showed in pancreatectomized and neonatal streptozocin induced diabetic rats that the insulin response to hyperglycemia was impaired in diabetic rats while the insulin response to arginine, isobutyl methylxanthine and isoproterenol was normal or increased. The researchers caused glucose levels to rise as little as 15 mg/dl and found a 75% inhibition of insulin secretion by the invitro perfused pancreas. These results again showed that the decrease in insulin secretion was a result of hyperglycemia (37).

Chronic hyperglycemia is also thought to play an important role in deterioration of insulin resistance. In the same phlorizin pancreatised rats described above the investigators also checked insulin sensitivity. Insulin mediated glucose uptake during a 100uU/ml euglycemic insulin clamp was performed. When treated with phlorizin, the glucose uptake in the partially pancreatized rats returned too normal. When phlorizin

was removed, and glucose levels increased, glucose uptake decreased, and the rats became insulin resistant (38). In a human study, investigators took well-controlled Type 1 diabetics receiving chronic subcutaneous insulin infusion, and did euglycemic insulin clamp protocols on them. In the initial study, plasma glucose concentrations were maintained at the basal level for 24 hours before performing the insulin clamp (99mg/dl). For the second study participant glucose levels were elevated to 281 mg/dl 24 hours before the insulin clamp. Results showed that 24 hours of hyperglycemia was sufficient to induce a 20% decline in the rate of insulin mediated glucose disposal (28,39).

These results provide evidence for the glucose toxicity hypothesis and show that chronically elevated glucose levels can in themselves lead to impairment in insulin secretion and impairment in insulin action (insulin resistance). Thus, elevated glucose levels should no longer be considered only a manifestation of diabetes but also considered as a pathogenic factor in the development of diabetes and that treatments and more emphasis should focus on improving glucose levels more aggressively (28).

1.2.5 Free Fatty Acids (FFA)

While it is the standard way of thinking that type 2 diabetes is a disorder of carbohydrate metabolism, many feel that the evidence points to abnormalities in fat metabolism. Supporting this notion are the well-known facts that approximately 85% of patients with type 2 diabetes in the United States are obese, and that obesity is virtually always associated with insulin resistance. Studies have also shown that when obese individuals lose weight, insulin sensitivity improves (14,40). It is elevated FFAs, found in obesity and type 2 diabetes that are thought to play a pivotal role in the development of insulin resistance (14).

FFAs are long chain fatty acids bound to albumin that are found in the plasma

(41). FFAs make up only 5% of the total plasma fatty acid profile but are considered the

most metabolically active of the plasma lipids (cholesterol, phospholipid, triacylglycerol,

FFA). FFA levels rise in the plasma from lipolysis of TG in adipose tissue or as a result

of the action of lipoprotein lipase during uptake of plasma TG into tissues (41).

Normal concentrations range from 0.I-2 meq/ml of plasma. Low levels of FFAs

are recorded in the fully fed condition rising to about 0.5 meq/mL in the post absorptive

stage and 0.7-0.8 meq/mL in the fully fasting state (41).

FFA removal from the plasma is rapid. Some of the uptake is oxidized and

produces 25-50% of the fasting energy requirements. The remainder is stored. The

rate of FFA production in adipose tissue controls the FFA concentration in plasma,

which in turns determines the FFA uptake by other tissues. The level of plasma FFA

has the most profound effects upon the metabolism of other tissues. In normal

individuals, circulating FFA concentration is suppressed quickly by insulin acting on

hormone sensitive lipase. Insulin enhances lipogenesis and the synthesis of

acylglycerol and increases the oxidation of glucose to CO_2 via the pentose phosphate

pathway. Small changes in insulin levels have profound effects on plasma FFA

concentrations (41).

Type 2 diabetes, obesity and other insulin resistant disorders are known to have

elevated levels of FFAs. In uncontrolled type 2 diabetes FFA levels may rise to as high

as 2 meq/ml. By mass action effect, the elevated plasma FFA level enhances cellular

FFA uptake and stimulates lipid oxidation (28). Elevated FFAs have been shown to

inhibit insulin stimulated peripheral glucose uptake and carbohydrate oxidation, reduce

stimulation of insulin secretion and increase hepatic glucose output (14,40,42). All these factors are thought to play a role in the development of diabetes.

The idea that elevated FFAs could inhibit peripheral glucose uptake and prevent carbohydrate oxidation was first proposed in the early 1960's by Randle (43). He showed that in striated heart muscle glucose mediated uptake and carbohydrate oxidation was inhibited by fatty acids. The key points of the hypothesis are that increased plasma fatty acid levels cause increased β-oxidation of FFAs, resulting in increased muscle concentration of acetyl-CoA which allosterically inhibits pyruvate dehydrogenase (PDH) and thus pyruvate oxidation. At the same time, an increase in muscle citrate concentration inhibits phosphofructokinase-1 and thus glycolysis resulting in accumulation of glucose-6-phosphate that inhibits hexokinase and glucose phosphorylation and uptake (42,43). This intriguing concept remained controversial mainly because investigators were unable to reproduce the effects that Randle found until recently.

Boden et al. along with other groups of investigators have finally been able to confirm Randle's ideas in vivo in normal and diabetics by using indirect calorimetry, (in order to determine rate of carbohydrate and fat oxidation) in combination with hyperinsulinemic clamping (to determine insulin sensitivity). The different investigators found that raising FFA levels increased fat oxidation and inhibited carbohydrate oxidation. These studies were able to demonstrate that FFA mediated inhibition of insulin stimulated carbohydrate oxidation occurred early (120 min), while the inhibition of glucose uptake developed only after 3-4 hours of fat infusion. Boden et al. conducted further studies and were also able to show that FFAs produce insulin resistance in a

13

dose dependant fashion throughout the physiological range of plasma FFA concentrations (42,44,45). Interestingly, Boden found that under conditions of comparable euglycemia and low plasma FFAs, insulin stimulated glucose uptake was 2 times higher in normals, than in patients with type 2 diabetes. These results indicate that FFAs could account for only about 50% of the insulin resistance in diabetic patients and that the remainder of insulin resistance is due to another mechanism (14). These results contribute to the data that is accumulating about the role that FFAs play in inhibiting glucose uptake and carbohydrate (CHO) oxidation.

At the level of the liver, high FFA levels stimulate gluconeogenesis and increases hepatic glucose output (14,28). Although not all the data supports this idea (14) there is much in favour of this notion. When plasma FFAs were raised during euglycemic or hyperglycemic hyperinsulinemic clamping in normal controls or patients with type 2 diabetes, the insulin suppression of hepatic glucose production was partially inhibited (14,45,46). In another series of experiments done in normal weight individuals who had their FFA levels elevated by an infusion of TGs while insulin levels were clamped at basal levels after an overnight fast, hepatic glucose production and plasma glucose levels rose dramatically. This evidence provides further proof of the role of FFA in insulin resistance (14,47).

FFAs are known to play a role in basal and glucose stimulated insulin secretion (48). Investigators have been able to potentate glucose stimulated insulin secretion by elevating FFA levels in normal individuals for as long as 48 hours. More recent studies done by Boden et al, showed that basal plasma FFA levels supported 25-33% of post-absorptive insulin secretion in obese non-diabetic and diabetic subjects and possibly

contributed to the hyperinsulinemia (44). In another series of experiments Dobbins et al., took non-obese subjects and fasted them for 24 or 48 hours after which he gave them a dose of nicotinic acid to deplete FFA stores followed by a bolus of glucose. Basal insulin levels concentrations were 35 and 45% less while the area under the insulin response curve to glucose decreased by 47% and 42%. When an infusion of intra-lipid plus heparin (maintains FFA levels) was added to the nicotinic acid, basal insulin and area under the curve remained normal. This study showed that FFAs are important for stimulating insulin secretion. In another experiment, after an overnight fast, a group of normal and obese individuals were given either saline or nicotinic acid followed by a hyperglycemic clamp. The insulin area under the curve in response to glucose was unaffected by lowering of FFA levels in non-obese subjects, but fell by 29% in the obese group. These results complement other studies revealing that chronic exposure to very high levels of exogenous FFAs increases basal insulin levels and impairs glucose stimulating insulin secretion. The authors suggest as an explanation that obese individuals are starting to show a partial dependence on elevated FFAs for their glucose stimulating insulin secretion (48). The developing picture is that in obese, genetically predisposed individuals to diabetes, the pancreas gradually fails to secrete appropriate amounts of insulin in response to FFAs and develops increasingly larger FFA induced insulin resistance/secretion deficits. To compensate for the deficits, plasma glucose levels rises and eventually over time leads to diabetes (41). To support this hypothesis, Boden tested in both normals and diabetics, using a euglycemic clamp, the effects of elevating FFA levels on insulin stimulating rates. Insulin stimulation rate rose similarly in both groups, but in the diabetic group ketone bodies rose more than in

the normal groups. Ketone bodies are insulin stimulating (49). Correlating insulin

stimulation rates with FFA and ketone bodies indicated that patients with type 2

diabetes secreted 28% less insulin than non-diabetic controls. Loss of pancreatic

responsiveness to FFA plus ketone bodies correlated with the duration of diabetes. The

longer the duration of the disease the poorer the response to elevated FFAs levels was.

Thus it appears that the insulin stimulation rate becomes progressively more defective

in type 2 diabetes (14,49).

To summarize, type 2 diabetics may eventually lose their ability to increase

insulin secretion to elevated FFA levels. As a result, FFA induced stimulation of hepatic

glucose production becomes unchecked and together with peripheral insulin resistance

result in early and late hyperglycemia. A vicious cycle ensues with hyperglycemia

producing progressively more β-cell desensitization and eventual failure and more

peripheral insulin resistance (14,48).

1.2.6 Treatment

Considering the negative metabolic impact of insulin resistance, it would seem

prudent to try to reverse the effects as early as possible. Thus, if progression could be

slowed, the incidence of diabetes would be reduced and the onset of its complications

prevented or delayed (50). Much work has been done on ways to slow down or prevent

the progression of insulin resistance. Along with numerous medications, insulin

resistance can be treated with diet, exercise, and weight reduction (31,51).

Acarbose is an α-glucosidase inhibitor that delays the absorption of starch and

sucrose and to a lesser extent maltose from the small intestine. This drug works on the

premise that spreading the nutrient load, (ie by slowing absorption of the carbohydrate)

decreases the post-prandial rise in plasma glucose, which may decrease the strain on the pancreas and perhaps theoretically protect the ß-cells. In a randomized, double blind, placebo controlled trial lasting 4 months in a IGT population, acarbose was shown to significantly improve insulin sensitivity as measured by the insulin suppression test, and significantly decrease post-prandial plasma glucose and insulin levels (1,52). Currently investigators are testing acarbose in a worldwide study to decisively determine whether the development of diabetes can be delayed or prevented (1).

In a lifestyle intervention trial, in the city of Da Qing, China, Chinese investigators showed that the progression of IGT to diabetes could be slowed by diet and exercise intervention. 110,660 men and women were screened for IGT of which 577 tested positive. IGT participants were randomized to 1 of 4 groups: the control group, diet group, exercise group or the diet and exercise group. Dietary advice consisted of recommending a 55-65% carbohydrate, 10-15% protein, 25-30% fat diet with approximately 25-30 kcal/kg body weight. If the participants BMI was greater than 25 they were encouraged to lose weight. Participants in the exercise group were asked to exercise daily the equivalent of one unit. One unit of activities included 30 minutes of walking or 5 minutes of jumping rope, etc. Participants were followed for 6 years. The results showed that there was a reduction in the risk of developing diabetes by 31% (p<0.03) in the diet group, by 46% (p<0.0005) in the exercise group and 42% (p<0.005) in the diet and exercise group compared to the control group. The Da Qing study is the first randomized controlled clinical trial to demonstrate that changes in lifestyle such as diet and exercise decreased the conversion rate to diabetes by approximately 40% (50).

1.2.7 Nutrition

Lifestyle and dietary modifications are the cornerstone to the treatment of IGT

and diabetes. The aim of nutritional recommendations for diabetes is to help prevent

short and long term complications, particularly coronary heart disease (53). Up until

1996 the American Diabetes Association (ADA) recommendations for the dietary

management of type 2 diabetes was a high carbohydrate (55-60%), low fat (total <30%,

saturated fat (SFA) <10%) diet (54,55). These recommendations were based on the

premise that eating a high carbohydrate diet would lower saturated fat intake, which

would help to reduce low density lipoproteins (LDL) cholesterol levels and the risk of

cardiovascular complications along with improving glucose metabolism (54,56). Since

diabetics have a 2-4 times higher chance for developing heart disease compared to the

average individual this advise seemed prudent (3). Studies done by numerous

investigators demonstrated that replacing saturated fat with carbohydrate improved LDL

values (56). While some clinical trials showed that a high carbohydrate diet improved

glycemic control, decreased insulin requirements and enhanced insulin sensitivity

(56,57,58,59) other studies showed the opposite (5,56,57).

Numerous investigators felt that a high carbohydrate diet was not necessarily the

best answer since these types of diets while lowering LDL levels accentuated

hypertriglyceridemia, reduced HDL, and were thought to even worsen glycemic control

by raising glucose levels and insulin demands (5,57,60). Since dyslipidemia in type 2

diabetes patients often manifests itself as hypertriglyceridemia, and low HDL levels,

both of which are also known risk factors for the development of heart disease, this was

not considered acceptable (56,61,62). Accentuation of hyperglycemia and

hyperinsulinemia has been shown to aggravate insulin resistance and worsen diabetic control and in the long term contribute to the complications associated with the disease (34).

To prevent the metabolic complications of a high carbohydrate diet, alternative dietary therapies including increased dietary protein, increased polyunsaturated fat intake (PUFA) or increased monounsaturated fat intake or perhaps changing the quality of carbohydrate were considered. A high intake of protein was not really considered acceptable because protein is usually associated with saturated fat, which would increase LDL levels and increase the risk of heart disease. In addition, type 2 diabetics are known to be at risk for developing renal disease, and a high protein intake has been shown to compromise renal function (53,63). A high PUFA intake was also not considered acceptable, because while lowering LDL levels, it also lowers HDL levels (53,63). Numerous clinical studies in humans and animals also suggest that high PUFA intake may increase the risk for developing some types of cancer. Epidemiological studies were also not available to support high intakes of PUFA (63,64). Interest turned to high MUFA intake for one group of scientists while another group of researchers focused on the quality of carbohydrates.

1.2.8 High MUFA

Numerous metabolic and ad-libitum clinical trials ranging from 2-6 weeks in length with one study going as long as 14 weeks, have shown that increasing MUFA intake and decreasing carbohydrate intake improves TG levels (56,57,60,65, 66,67, 68,69) and some studies demonstrated a slight increase in HDL levels (56,66). Some studies show acute improvement in glycemic control such as improved fasting blood

glucose (70) improved meaned glucose levels (64,66,68), or lower meaned insulin levels (65,68,70). To date none of the studies have found a change in HbA1c, an indicator of long-term blood glucose control. In the two trials that measured insulin sensitivity one of the studies found an improvement on the high MUFA diet compared to a high carbohydrate diet (56,68). In the longest study to date, Garg et al. studied 42 patients in a multi-centre randomized cross over designed study for 14 weeks. Participants went on a 55% carbohydrate, 30% fat, 10%SFA, 10% MUFA diet and than took the other diet which was 40% CHO, 45% fat 10% SFA, 25% MUFA. The other macronutrients were similar in the diet. Each session was 6 weeks long and a sub group of 21 continued on with their 2nd dietary treatment for an additional 8 weeks. The high carbohydrate diet increased fasting plasma triglyceride levels and very low density lipoproteins (VLDL) levels by 24% (p>.001) and 23% (P=.001) respectively and increased daylong plasma TG, glucose, and insulin levels by 10% (P=0.3), 12% (P>.001) and 9%(P=0.02) respectively. No differences in total cholesterol, LDL, and HDL or HbA1c were observed between the diets. The effects of both diets on plasma glucose, insulin and TG levels persisted for 14 weeks (57).

Recently a meta-analysis by Garg et al. was published summarizing the results of nine different high MUFA versus high carbohydrate studies. Fat intakes on the high MUFA diets ranged from 40-50%, and carbohydrate intake ranged from 35% to 40%. Results showed that compared to a high carbohydrate diets, high MUFA diets lowered TG by 19%, reduced VLDL levels by 22%, caused modest increases in HDL levels with no adverse effects of LDL concentration. An improvement in glycemic control was also found. The meta-analysis found a significant improvement in fasting plasma glucose

levels of 0.23 mmol/L (95% confidence interval (CI) –0.39-0.06 mmol/L). Some of the studies found improvement in mean pre-prandial plasma glucose, while others found improvement with post-prandial plasma glucose, 24 hour plasma glucose and insulin profiles. No improvement was found with fasting insulin levels or glycosolated proteins (11).

The supporters of a high MUFA diet feel that there is sufficient evidence to promote this type of diet. In fact, in 1994, the ADA changed their nutrition recommendations to reflect the current change in philosophy with regards to MUFA and carbohydrate intake. The current guidelines no longer emphases a specific percentage of carbohydrate and MUFA intake rather a range of these two macronutrients, between 60-70% of the total calories are recommended. The distribution of calories from fat and carbohydrate can vary and be individualized based on the nutrition assessment and treatment goals. The emphasis is on quantity of carbohydrate consumed versus the source or quality of carbohydrate (54,71).

A debate continues to be waged regarding the efficacy of a high MUFA diet, since several important issues have yet to be resolved. Issues such as: the high level of fat required for these beneficial effects to be seen, no change in long term glycemic control has yet been measured, and no consideration of the carbohydrate source has been taken into consideration in the studies. High MUFA diets have been able to show a reduction of TG levels and a minor, if at all, rise in HDL levels in type 2 diabetes as compared to a high carbohydrate diet. The levels of dietary fat that show these benefits are at a fat intake of 40-50%, which according to present guidelines for lipid management would not be recommended. Current National Cholesterol Education

Program (NCEP) guidelines for Americans (72) and Canadian guidelines (73)

recommend that fat intake not be greater than 30% for those with high LDL or TG

levels. Even the guidelines for healthy eating in both Canada and the United States

also support the recommendation of keeping fat to approximately 30% of the daily

intake (74,75). Since diabetics are at higher risk for developing heart disease, and often

have cholesterol or TG problems, they should be following the low fat guidelines. In one

clinical trial a 30% fat diet with a high MUFA intake showed the beneficial effects of a

high MUFA diet were reduced when fat intake was reduced. TG levels in the 30% fat

study improved by 16.6% (P=0.006) (76) rather than the 20-28%, which was observed

in the high MUFA diets when fat intake was closer to 40-50% (56,57,66). The beneficial

effects of MUFA diets have also been interpreted to mean that hypertriglyceridemics

would benefit from this type of a diet (53). But, so far, the majority of studies that have

tested this hypothesis use subjects with normal TG levels and in only 2 studies have

mildly hypertriglyceridemic subjects participated (56,66). Lastly, studies have yet to

show whether improving TG levels that are within the normal range have any clinical

benefits (53,77). For example, populations with a high carbohydrate intake do not tend

to have a high prevalence of CHD. Mexicans living in Mexico City, Mexico, consume

more carbohydrates and have higher serum TG than Mexicans living in San Antonio,

Texas. However, the Mexicans in Mexico also are less obese, have 26% less diabetes

and have lower serum cholesterol concentrations (53,78).

High MUFA diets have yet to show any significant change in HbA1c levels or any

other glycosolated protein, which are major indicators of overall glycemic control

(11,53). Investigators state that no change was found because the studies were not

long enough. If the studies were not long enough, that suggests that longer clinical trials should be done in order to answer this question. One questions whether the dietary recommendations should have been changed with such an important issue still unresolved. In addition, some of the studies were 4 weeks or more in length and that is adequate time to see changes in HbA1c and yet none were observed. Some studies have shown a difference in day- long plasma glucose, or fasting glucose levels, but in the absence of any difference in HbA1c, the results could be interpreted as an acute effect of reduced carbohydrate intake (53).

Other measurements such as FFA and insulin sensitivity, both of which provide important information about glucose homeostasis, have been rarely measured in the studies. In the one study that looked at FFA levels, the study found that FFA levels were significantly worse on the high MUFA compared to the high carbohydrate diet (70). In only 1 of the 2 cases that looked at insulin sensitivity was there an improvement observed on the high MUFA diet otherwise no changes were observed. Improvement in either of these measurements would be important because that would suggest that there was an improvement in the metabolic condition.

Furthermore, studies comparing the effects of a high MUFA and high carbohydrate diet have used high glycemic or quickly absorbed carbohydrates. Only one study has compared high MUFA diets with a diet containing slowly absorbed carbohydrates or also known as low glycemic index carbohydrate foods (79). Slowly absorbed carbohydrates have shown to be just as or more beneficial than MUFA diets and do not have the possible negative affects of the standard high carbohydrate diets.

Thus, before any conclusions regarding the ideal diet for the prevention and treatment of diabetes is made, these issues described above should be resolved.

1.2.9 Low Glycemic Index High Carbohydrate

When discussing the merits of a high MUFA diet versus a high carbohydrate diet the discussion usually does not take into consideration the source of carbohydrate. Many studies have found that different foods containing an equal amount of carbohydrate produce a wide range of glycemic responses (79,80). The glycemic index has been proposed as a method of classifying the blood glucose response to foods (81).

1.2.9.1 The Glycemic Index (GI)

It is a well-known fact that different foods containing the same amount of carbohydrate produce a wide range of glycemic responses (79,80). Developed in 1981, the GI is a qualitative method of assessing and classifying the blood glucose raising potential of foods. The glycemic response of a food is indexed as a percentage against a standard of either white bread or glucose (82,83). The concept of the GI allows for the comparison of different foods on the basis of their physiological effects rather than on their chemical composition, fibre content or chain length (79,81).

The GI of a food is defined as (81):

Incremental area under blood glucose response curve for food   * 100
Corresponding area after an equivalent carbohydrate portion of white bread or glucose

The GI works on the principle that a food with a low GI is digested and absorbed more slowly than a high GI food and consequently reduces post-prandial glucose and insulin levels and cholesterol levels (81). Short-term in-vitro and in-vivo studies along with longer-term studies support this (81,84,85).

To date more than 600 foods have been tested. Values range from 30 to 140. Foods that produce a flat or low glycemic response are legumes, pasta, barley, bulgur, parboiled rice, and whole grain breads such as pumpernickel, milk, some fruits and vegetables and nuts. Typical high GI foods include instant mashed potatoes, most processed cereals such as cornflakes, regularly milled bread, and most types of rice (81).

Many factors, apart from the macronutrients and fibre content, affect glycemic responses. Nutritional factors that may affect the glycemic index of a food include the type of dietary fibre (soluble vs insoluble), nature of starch (amylose vs amylopectin / degree of gelatinization and retrogradation) enzyme inhibitors and antinutrients, food form (method of cooking, degree of hydration, particle size) and starch-protein/lipid interactions (81,86). For example, different types of rice have different GI values ranging from, 68 for parboiled rice, 81 for brown rice, to 121 for instant rice. Parboiled rice has the lowest value in the rice group and this is probably due to the processing (12).

1.2.9.2 Benefits

Epidemiological, short and long term clinical trials provide evidence which support the beneficial effects for following a low GI diet for the treatment or prevention of diabetes and other chronic disease such as heart disease. Low GI diets have been shown to improve glycemic control such as improve insulin sensitivity, reduce blood glucose and insulin levels, reduce FFA levels, improve glycosylated hemoglobin (HbA1c) and fructosamine levels, and improve cholesterol levels.

1.2.9.2.1 Epidemiological Studies

Two large scale prospective longitudinal studies; the Health Professional Follow-up Study and the Nurses Health Study demonstrated that diets with a high GI or a high glycemic load (GI*carbohydrate content) and low cereal fibre content when consumed in combination increased the risk of developing type 2 diabetes after controlling for known risk factors such as age and BMI (5,87). The relative risk doubled, as the glycemic load was greatest and dietary fibre intake lowest. Independent of cereal fibre intake, the GI correlated with the increased risk of diabetes. The lower the GI, the lower the risk for developing diabetes (87). Interestingly, the total carbohydrate and refined sugar content, and the amount and type of fat in the diet, were not found to be independent risk factors in these studies. Like this study, previous prospective studies have not found a relationship between carbohydrate and risk of diabetes. This may be due in part, to the fact that the glycemic index, which takes into consideration the glycemic impact or insulin demand of the carbohydrate food, was not taken in to account (5). The underlying mechanism postulated by these authors is that the increased demand for insulin generated by high GI foods and low fibre foods creates an environment prone to diabetes especially if exacerbated by insulin resistance (87,88).

In another prospective study, investigators of the San Luis Valley Diabetes Study followed a group of normal individuals between the years 1984 to 1992. Participants were seen for up to three visits. 24 hours dietary recalls were done at each visit. Results showed that high total and saturated fat intake were associated with higher fasting insulin levels after adjusting for age, sex, ethnicity, body mass index, waist circumference, total energy intake and physical activity. On the other hand dietary fibre

and starch intake were inversely associated with high fasting serum levels. The same investigators also followed a group of IGT participants, and found similar results in that a high fat low carbohydrate diet increased the risk for developing diabetes by 3.4 fold after adjusting for fasting glucose, insulin and 1 hour insulin (8). These studies, along with other epidemiological studies support the role of increased carbohydrates, in particular slowly absorbed carbohydrates, and low fat dietary intake in the prevention of diabetes.

1.2.9.2.2 Clinical Trials

To date there have been many well designed, randomized clinical trials, ranging from 2 to 12 weeks testing the benefits of low glycemic index diets on diabetes control (79,89,90,91,92,93,94,95). The Calle-Pascual study is the only study to date showing no benefit (96). Some studies had the participants on metabolically controlled diets, while others were given advice and followed for the duration of the study. The diets were well matched and the only difference between the test and control phases was the glycemic index and in some of the studies an accompanying increase of dietary fibre on the low GI phase. The GI difference from low to high GI diets ranged from as little as 7 to as great as 28. Improvement in blood glucose control was found by either improvement in fructosamine (89,90,91,94,95), HbA1c (90,91), reduced fasting blood glucose (within groups) (89,90) or mean daylong plasma glucose (91). On average low GI diets are thought to improve HbA1c by approximately 10%. This improvement is of the same magnitude, as one would expect to achieve when taking oral hypoglycemic agents or insulin in the treatment of type 2 diabetes (83,82). Low GI diets also appear to be either lipid neutral or to reduce concentration of total cholesterol (89,93,95) TG

(12,89). Low GI diets have also been tested in hyperlipidemic (97) and normal populations with similar results (98).

Not all studies found improvements in HbA1c or fructosamine. In two studies done by Jenkins (90,98) the length of each phase was 2 weeks, which would have been too short of a time to see changes in either fructosamine or HbA1c. In the study by Calle-Pasucal, perhaps no change in HgA1c was found because the difference in GI was very small at only 7 (96). Perhaps the combination of the small change in GI and study length of one month was not long enough to measure changes in HbA1c, since it can take up to 2-3 months to change (12). More recently in an ad-libitum study by Luscombe et al., the only change found was that the low fat, low GI and high GI high MUFA diet showed a significantly higher HDL (8%, p=0.05) than the high GI diet (79). The authors provided several reasons for their lack of observed changes in glucose metabolism. They stated that the subjects differed considerable in glycemic control, age, gender and BMI and that these variations might have masked any effects from the dietary changes made. The authors also suggested that since the participants were not well controlled, the small decrease in carbohydrate load over the day may only have had a minor influence on average blood glucose levels in comparison to the hepatic contribution (79). Another concern is in the choice of foods that the investigators used on their low GI diets. They considered certain low GI fruits and vegetables as part of their test diet and decided not to include legumes, which is a particularly good low GI food. Reducing the glycemic impact of the diet by using foods high in sugars, such as fruit, vegetables or dairy product, may reduce average blood glucose levels, but may not yield the same beneficial effects on insulin and blood lipids as low glycemic index

starchy foods (12). Fructose may stimulate insulin secretion, raise serum TG levels and increase LDL levels (99,100).

Low GI diets have also been shown to improve free fatty acid levels. In a study by Wolever et al., 4 breakfast test meals were given to normal individuals (13). The breakfast test meals had either a high GI low carbohydrate, high GI high carbohydrate, low GI low carbohydrate or low GI high carbohydrate content. Results showed that FFA levels were similar after breakfast for each test meal but rebounded differently. Low carbohydrate breakfasts resulted in more marked FFA rebound and impaired carbohydrate tolerance to lunch compared with high carbohydrate breakfasts. A low GI high carbohydrate breakfast was most effective in suppressing FFAs and improving second meal carbohydrate tolerance. The results from Wolever's study confirm previous studies showing that high carbohydrate and low GI breakfasts improve blood glucose responses to the subsequent meal (13,101). On the other hand, Frost et al., found no change/difference in FFA levels in his study with insulin resistant women on a low GI diet (102,103). Further studies need to be conducted to determine whether an improvement in FFA levels are found in the long term in diabetics and other insulin resistant individuals.

Low GI, high carbohydrate diets have also been shown to improve insulin sensitivity in normal, women with a family history of heart disease, obese individuals and diabetics (102,103). This sort of effect is extremely desirable because it suggests a decrease in insulin resistance. For example, Frost et al. took fat biopsies from a group of pre-menopausal women. He was able to categorize them as either having a family history of heart disease before the age of 55 (suggesting reduced insulin sensitivity) or

not. Part of the group agreed to follow either a high GI high carbohydrate diet or a low GI high carbohydrate diet 3 weeks prior to the surgery. Frost measured insulin stimulated glucose uptake in isolated subcutaneous and omental (visceral) adipocytes obtained during elective surgery of the whole group. In addition, insulin sensitivity was measured with a short insulin tolerance test in the groups who followed the dietary treatment prior to surgery. The short insulin test has been validated against the gold standard for assessment of insulin sensitivity the hyperinsulinemic euglycemic clamp and also Bergman's minimal model. The results showed that a low GI diet improved adipocyte insulin sensitivity in women with a family history of early heart disease. In-vivo insulin sensitivity also improved in those who followed a low GI diet even though no changes were found in fasting glucose or insulin concentrations. More data is required to determine whether insulin sensitivity does in fact improve on low GI diets (103).

The epidemiological and clinical trials compliment each other and support the use of low GI diets for the improvement of blood glucose metabolism and cholesterol levels in type 2 diabetes. The data appears to be just as strong and stronger in the case of longer-term improvement in glucose metabolism than the high MUFA and low carbohydrate diets. Although many studies have been done in diabetics and hyperlipidemics, most of the studies are short term ranging in time from 2-4 weeks. Longer studies, with a larger number of subjects are needed to examine whether the long-term effects are the same as in the short term. In particular, studies showing improvement in HbA1c and FFAs and insulin sensitivity would be important to provide stronger support for this type of dietary advice.

1.2.9.3 Objections to the GI

There are numerous objections against the clinical use of the GI. Criticisms range from concerns over the technical way that the GI of a food is determined, to the lack of long term clinical trials providing evidence about the benefits, to the lack of clinical utility for the average individual (54,82,104,105). Technical problems include large intra individual variation, and not ensuring that glucose levels return to normal when testing to determine the GI of a food. Some investigators feel that there are not enough clinical trials, and that the clinical trials are not long enough. Others feel that asking people to follow a low glycemic index diet would be too complicated and reduce food choice. Other issues of contention include: that the GI may not apply to mixed meals, fat and protein intake within the meal may affect the glycemic response, and that hypo and hyperglycemia have a greater affect on the rate of digestion and subsequent glycemic response than the glycemic index of a meal (82,104,105). Proponents of the GI have shown that the concerns are not warranted (82). For every concern there is a rebuttal, but the debate still wages on. Perhaps when a mechanism of action has been confirmed, or more supportive data has been collected from clinical trials will the debate be resolved.

1.2.9.4 Mechanism

Although, the mechanism of action for the observed beneficial effects of the low GI diet remains to be elucidated, two possible mechanisms have been proposed. The first is a slowed/reduced rate of absorption of carbohydrates and the second is that following an low GI diet increases the amount of malabsorbed starch that reaches the colon and increases colonic fermentation (12,81,89).

1.2.9.4.1 Colonic Fermentation

On low GI, high carbohydrate diets as much as 20% of the carbohydrate arrives in the colon for fermentation compared to the 1-2% that arrives on a high GI, high carbohydrate diets (12,81). Short chain fatty acids (SCFA) such as acetate, propionate and butyrate are the 3 prominent products produced from colonic carbohydrate fermentation. 75% of the SCFAs produced in the colon are absorbed into the blood stream and used as substrates and may have effects on carbohydrate, lipid and protein metabolism. In experimental animal and human studies the SCFA propionate has been shown to inhibit hepatic cholesterol synthesis, stimulate insulin secretion and be a substrate for gluconeogenesis and decrease fasting serum glucose levels. Although proprionate is gluconeogenic the amount it produces is so small that it would not make an important contribution to glucose production (12,106). Acetate has been shown to reduce blood glucose and FFA levels in animals and in humans (12,106) and has also been found incorporated into skin lipids in favour of glucose (81,89). In a study done by Thorburn, she showed that when a significant amount of slowly absorbed fermentable carbohydrates are ingested the evening before an oral glucose tolerance test there is an enhanced suppression of hepatic glucose production and FFAs creating a more insulin sensitive environment (89,102,107). These effects would be beneficial for insulin resistant individuals because improving glucose levels, reducing cholesterol levels and reducing FFA levels would make for a more insulin sensitive environment. More studies need to be done to determine the effects of a low GI diet and SCFA metabolism and how this may affect insulin sensitivity.

1.2.9.4.2 Slowed Absorption

One of the key benefits of including low GI foods into the diet is that these types of foods are more slowly absorbed than foods with a high GI (81,84). Because of their slow absorption these foods produce less rapid of a rise of blood glucose and smaller insulin response and have less of a tendency for the blood glucose to undershoot than does the more quickly absorbed high GI carbohydrate foods (12,81,102). This results in a smaller counter regulatory response and improved glucose disposal after the next meal. In the case of rapidly absorbed carbohydrates, there is a large rise in blood glucose and insulin levels. The large insulin response causes peripheral glucose utilization to increase to such an extent that absorption from the gut cannot keep up so that the blood glucose level undershoots the baseline. The undershooting causes a rise in FFA and relative insulin resistance (81). There is a lot of evidence that supports the slowed absorption hypothesis. First, the rate of digestion of foods in vitro is directly related to their blood glucose and insulin responses in vivo. The slower the rate of food digestion, the lower the blood glucose and insulin response is (81,83,84). In a model for slowed absorption, participants were given a 50 gram glucose solution and asked to either drink it as a bolus or sip it at an even rate for 3.5 hours. Four hours after the start of glucose consumption an intravenous glucose load was administered. The disposal of intravenous glucose was markedly improved, despite identical peak serum insulin levels, after sipping glucose than after the glucose bolus. After glucose sipping serum glucagon, catecholamine, growth hormone and FFA levels were lower than after the glucose bolus. These effects show that slowing the absorption of glucose has marked metabolic effects that are evident well after the end of the post-prandial blood glucose

response (88,108). A similar study was done with a mixed test meal and similar results were found (88,109). In another study, healthy subjects were given the same amount of food and either nibbled it as 17 small meals or three meals over the day. The nibbling resulted in 28-32% reductions in serum insulin responses, and 10-25% reductions in urinary C-peptide excretion (88,93,110). Other evidence supporting the hypothesis of slowed absorption includes studies that show the effects of low GI foods on post-prandial glucose, insulin and GIP responses are similar to those treatments known to reduce the rate of absorption of carbohydrate from the small intestine, including viscous fibre, and α-glucosidase inhibitors (93). Thus these studies demonstrate that slowing absorption of nutrients can reduce glucose, day long insulin and fatty acids levels all of which when elevated have been shown to cause insulin resistance (86).

1.2.10 Summary

It is well known that the pathogenesis of type 2 diabetes involves defects in both insulin action and insulin secretion (28). Those with IGT have been shown to have signs of both of these defects and are at higher risk than the average individual for developing diabetes (1,23). Diets that facilitate the maintenance of insulin secretion and insulin action would be preferred for individuals at risk for developing type 2 diabetes (1,5,28). Both epidemiological and clinical trials have shown that diet plays an important role in the development of the disease. Weight loss and exercise has been shown to improve insulin resistance (51). High fat, in particular saturated fat diets can lead to elevated insulin levels, (5,7,8,103) which can increase the risk for developing diabetes. While high GI high CHO diets have in some studies shown improvements in insulin sensitivity and cholesterol levels (57,58,59) other studies suggest a worsening of

glycemic control and raised triglyceride levels (11,63). High MUFA diets while improving cholesterol levels have shown little effect on long-term glycemic control (11,53). High CHO low GI diets have shown promise in that these types of diets improve HbA1c (12,53,88) and acute studies show improvements in FFA levels (13). While all these indicators provide important information, more conclusive evidence would be if a change in insulin sensitivity could be measured. Insulin sensitivity improved when subjects took acarbose, a drug that leads to malabsorption of starch, but very few nutrition studies have tested for insulin sensitivity (52). Searching through the literature, very few studies have been conducted which actually compares the effects of a high MUFA, high GI high CHO and low GI high CHO diet, especially over the long term. Therefore, the purpose of our study was to compare the effects of altering the source and amount of dietary CHO on insulin sensitivity in subjects with impaired glucose tolerance.

1.3 Research Hypothesis and Objectives

1.3.1 Research Hypothesis

1. A high CHO low GI diet will reduce mean insulin levels and improve insulin sensitivity in subjects with impaired glucose tolerance compared to a low CHO high MUFA diet and a high carbohydrate high GI diet.

2. A high CHO low GI diet will improve total serum cholesterol, LDL, HDL, TG, total cholesterol/HDL ratio, FFA, insulin, glucose to insulin ratio, fasting and post prandial blood glucose levels compared to a high MUFA low CHO and high CHO high GI diet.

1.3.2 Research Objectives

The primary objective was to compare the effects of altering the source and amount of dietary CHO on insulin secretion and insulin sensitivity in subjects with impaired glucose tolerance. Using the FSIGT test to measure insulin sensitivity, pancreatic responsivity, glucose effectiveness and the Disposition Index, a high CHO low GI diet, a high MUFA low CHO diet, and a high CHO high GI diet were compared.

The secondary objectives of the study were to determine the long-term effects of the different dietary protocols on:

1) Fasting serum glucose

2) HbA1c

3) Fasting and post-prandial glucose, insulin, FFA, and TG levels in response to a 8 hour metabolic day profile

4) Serum total cholesterol, LDL, HDL, TG levels

5) BP

2.0 Materials and Methods

2.1 Ethics

St. Michael's Hospital Research Ethics Board approved all procedures in the study. All participants gave informed consent (see Appendix A).

2.2 Study Design and Duration

The study design is a randomized, controlled, parallel design with a 4 to 6 week run-in period followed by 4 months of treatment (see Figure 2.1). Due to the nature of the treatment (i.e. different foods given in the test groups) the study was not blinded. The study consisted of a minimum of one pre study visit for an initial dietary assessment. The second and third visits were the 8 hour metabolic profile and a 4 hour Frequently Sampled Intravenous Glucose Tolerance Test (FSIGT). Randomization occurred after both tests were completed. Follow-up visits were at week 2, 4, 8, 12, 14, and 16. On the last two visits the 8 hour metabolic day profile and 4 hour FSIGT were done once again.

2.3 Randomization

Participants were randomized to one of three treatments; 1) low GI high CHO (low GI) (50-60% CHO, 30% fat, 70-75 GI), 2) high GI high CHO (hi GI) (50-60% CHO, 30% fat, 85 GI) high monounsaturated fat low CHO (high MUFA) (40% CHO, 45% fat, 20-25% MUFA, 85 GI). Using a stratified randomization process sex, BMI and age were taken into consideration since these three variables have a potential for interaction with the primary end point of insulin sensitivity. Thus the objective for the stratified randomization was to have the 3 groups as evenly matched with regard to these 3 variables.

2.4 Screening

Subjects were recruited through advertisements in local newspapers (see appendix 2.1). The advertisement asked for men or women who were at risk for developing diabetes. Interested participants were initially screened over the telephone. Exclusion criteria included those on medications for diabetes, those on thiazide and β-blocker medications, pregnancy and any metabolic disorder that may affect carbohydrate absorption. Those who qualified were asked to come to an information session when a brief overview of the study and time requirements was laid out. Interested volunteers were than asked to sign up to complete a two-hour oral glucose tolerance test. Participants were informed to bring a list of medications, doctors name and address and asked to eat regularly for 3 days prior to the test and fast on the day of the OGTT. Tests were done between 8-10 am in the morning. The 75-gram glucose drink (Glucodex) was drunk in approximately 5 minutes. Blood was drawn at time 0 and two hours. Liver enzymes, kidney function, cholesterol levels, uric acid, HbA1c and fasting blood glucose (FBG) levels were drawn at fasting. Participants were asked to sit for the duration of the test. Blood was analyzed at St. Michael's Hospital in their main laboratory.

Inclusion criteria into the study was anyone who had IGT according to World Health Organization criteria but otherwise healthy. IGT is defined as a fasting blood glucose level <7.8 mmol/L and a two-hour value between 7.8 and 11.0 mmol/L inclusive on one occasion (20). Participants were informed over the telephone as to whether they were included into the study. If they were interested in participating they were asked to come in for an initial nutritional assessment.

	Run-In		Treatments	High GI n=11	
				Low GI n=13	
				High MUFA n=11	

↑   ↑   ↑   ↑   ↑   ↑   ↑   ↑   ↑
-4   -2   0   2   4   8   12   14   16
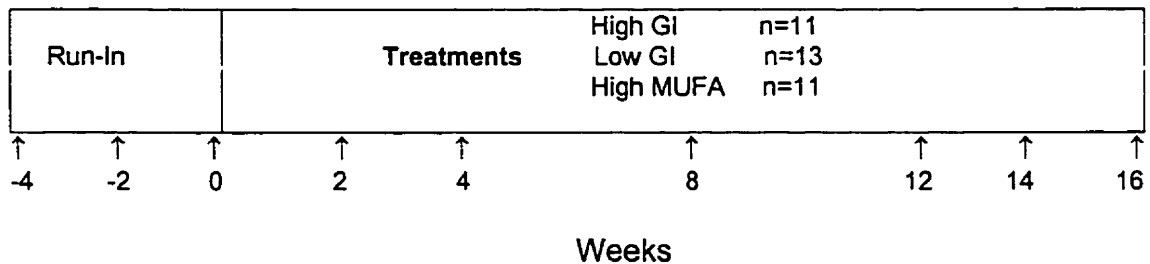
Weeks

Visits

Weeks
-4   Nutrition counselling
-2,0   **Start:** FSIGT, 8 hour Metabolic Day Profile
2,4,8,12   Follow-up
14-16   **End:** FSIGT, 8 hour Metabolic Day Profile

All Visits during the study: Blood, weight, BP, nutrition counselling, compliance
                              assessment

Figure 2.1: Study design

2.5 Pre Study Nutrition Assessment

Participants completed a 3-7 day food record. This information was compared to the NCEP diet of 30% fat, 10% SFA, 10% MUFA, 10% PUFA diet (72). If the subject's food record indicated that they were not following a Step 1 NCEP diet, they were provided with suggestions to assist them in that direction. The nutritional information was also used to personalize the study diets to the individual preferences.

2.6 Dietary Guidelines for the Study

On the second of their two metabolic tests, participants were prescribed on an ad-libitum basis the dietary regime that they were to follow for the duration of the study. The 3 dietary regimes were: 1) low GI high carbohydrate (low GI) (50-60% carbohydrate, 30% fat, 70-75 GI), 2) high GI high carbohydrate (high GI) (50-60% carbohydrate, 30% fat, 85 GI) high monounsaturated fat low carbohydrate (MUFA) (40-45% carbohydrate, 40-45% fat, 20-25% MUFA). The aim the study was to produce a difference of 10% between the high carbohydrate diet groups and MUFA group for total fat, MUFA and available carbohydrate. For the GI the aim was to have a difference of 10 between the low GI group and the high GI and MUFA group. Both oral and written educational information was provided to the subjects about the type of nutritional changes that they were to make for the study (see appendix B). To help participants follow the diet, key food supplements were provided to participants if they wanted them. The high GI diet group was asked to include instant mashed potatoes, cold cereals, and regular rice and avoid low GI foods. The low GI subjects were asked to include a serving of low GI foods at each meal. Examples of low GI starchy foods include oatmeal, bran buds with psyllium, legumes (dried beans, peas, lentils), barley, pasta or

parboiled rice. The GI of the diet was not lowered through the use of low GI foods rich in simple sugars (eg. milk, fruit). For the high monounsaturated fat participants, 10% of their daily energy intake as assessed by the LRC requirements was taken as olive oil or high MUFA margarine. Containers marking the level of oil to be taken daily, or measuring spoons were given to participants to help them measure the oil.

2.7 Follow Up Visits (Week 2, 4, 8, 12, 14, 16)

Participants came in fasting. Fasting body weight, blood pressure and a blood sample were taken. Total cholesterol, LDL, HDL, TG and FBG, and HbA1c were measured. Blood was also spun down and the serum was saved for later analysis. Participants were asked about compliance and their health status. Questions such as changes in medications, bowel habits, exercise level, or whether there were any unusual events, illnesses, and or vacation were asked (see appendix C).

3-7 day food records were returned at each visit. Food scales were provided if the participant desired to use one in order to help with the measurements and accuracy of the food record. The dietitian reviewed the food record. The dietitian provided suggestions and recipes to the participants to help them follow the dietary regime as closely as possible. To help with compliance key food items such as olive oil, instant mash potatoes and cereal were provided to the participant if they so desired it.

2.8 Anthropometric Measurement

Height and weight was measured to the nearest 0.5 cm and 0.1 kg with the participant wearing indoor clothing and no shoes. Body mass index (BMI) was calculated as the weight (kg) divided by the height (m) squared.

2.9 Energy Requirements

Energy requirements for the metabolic day profile and to assess the quantity of olive oil to recommend to participants were determined according to the Lipid Research Clinic Assessment Values (111).

2.10 Nutrient Analysis

3-7 day food records were coded and entered into a nutrient analysis program called NUTRIPUT Version 2.02 (Thomas Wolever, University of Toronto) by either students or a dietitian. All food records were quality controlled by one dietitian. The nutrient database for the program is based on the USDA database (112). Missing values such as dietary fibre, and the glycemic index were added. An additional database, containing speciality and convenience foods not available on the USDA database was also used. Food labels, nutrient analyses using standard AOC practices were used to create this database. Diet GI was calculated as previously described (113).

2.11 8 hour Metabolic Day Profile

An 8 hour metabolic day profile test was done prior to the beginning of treatment and at the end of the 16-week study at the Clinical Risk Factor Modification Centre at St. Michael's Hospital (see Figure 2.2). Participants were asked to coming in fasting. Fasting weight was taken. Blood pressure was taken at one point over the day. Participants remained seated for the duration of the study and either read, listened to the radio, chatted with other participants or watched a movie. Blood samples were taken at times: 0, 0.5, 1, 1.5 ,2 ,3 ,4 ,5 , 5.5 ,6 ,7 ,8 hour. Cholesterol levels, FBG, HbA1c were measured at fasting. Subjects were given breakfast at time 0 and lunch

after the hour 5 blood sample was taken. A cup of black tea, herbal tea, coffee or water could be drunk half way through the morning and afternoon. Breakfast and lunch made up 45 % of their energy requirement for the day. 45% went for breakfast and 55% was allocated for lunch. Energy requirements were based on Lipid Research Clinic assessment for energy requirements (111). At baseline all participants received a standard high GI breakfast and lunch. The macronutrient profile for breakfast and lunch was 60% available carbohydrate, 12% protein 28% fat, 7% SFA with a GI of 85. The macronutrient profile was based on nutrition recommendations found in the NCEP guidelines and Canadian guidelines for healthy eating (72,74). At the end of the study the high GI group received the same diet as week 0. The olive oil group had the same diet as week 0 except 45% of their daily olive oil intake was substituted in exchange for carbohydrate at breakfast and lunch meals so that overall energy intake remained the same. The nutrient profile for the low GI group for week 16 remained the same as week 0 except for the GI. The GI was changed to represent the best estimate of the subject's GI over the study based on their food records. Appendix D provides an example of the types of foods offered to subjects during the metabolic day profile at week 0 and at the end of the study.

The blood from the metabolic day profile was spun down and the plasma separated and alloquated for analysis at a later date. The blood was analyzed for glucose, insulin, FFAs and TGs.

| 0 | 1 | 11/2 | 2 | 3 | 4 | 5 | 51/2 | 6 | 7 | 8 |

Breakfast
8:00 am

Lunch
1:00 pm
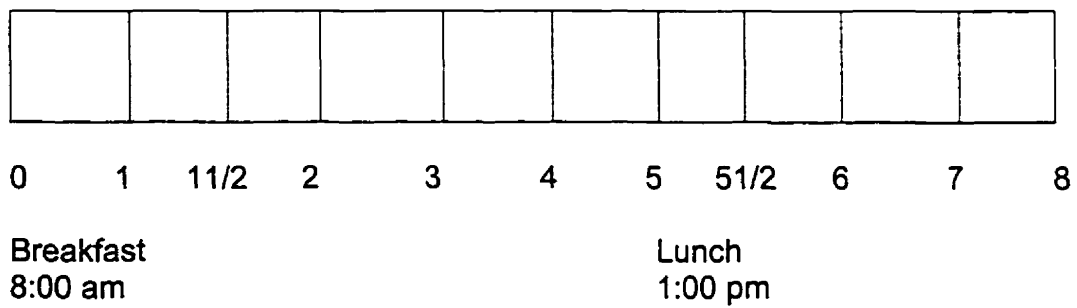
Blood drawn at each time interval. Time given in hours.

Blood drawn for FFA, glucose, insulin and TG at each time interval.

Blood pressure, fasting body weight, nutrition counselling completed during the

8 hour metabolic day profile

Figure 2.2: 8 hour metabolic day profile protocol

44

2.12 Frequently Sampled Intravenous Glucose Tolerance Test (FSIGT)

Insulin sensitivity (S_I), glucose effectiveness (S_G), pancreatic responsiveness (AIR_{glu}) and glucose disposition index ($DI= S_I \times AIR_{glu}$) were assessed by the frequently sampled intravenous glucose tolerance test (FSIGT) (114). Participants completed an FSIGT test at the baseline and end of the study phase. Participants came in after a 12-14 hour over night fast. Studies began between the hours of 7:30 am and 10:00 am. Fasting body weight was measured. Prior to the start of the study blood was drawn and measured for total cholesterol, LDL, HDL, TG, FBG and HbA1c. Intravenous cannulae were placed into a forearm vein on each arm, one side for glucose and insulin injection and the other for blood sampling.

Baseline samples for measurement of plasma glucose and insulin were drawn at –20, -15, and –5 minutes before initiation of the glucose injection (time 0). A 50% glucose solution ($25.1ml/ m^2$ (m^2 = body weight ($kg^{0.425)}$ * height ($cm^{0.0.75}$)*0.0071284)) was rapidly injected at time 0 and the vein was than flushed with saline to prevent clots from forming. Once glucose was injected blood was drawn at the following time intervals: 2, 3, 4, 6, 8, 10, 12, 14, 16, 19. At 20 minutes a mixture of insulin ($1.6U/ m^{2)}$ and the participant's serum was injected. Further blood samples were taken at 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 100, 120, 140, 180, 200, 220 and 240 minutes. Plasma glucose and insulin results were analyzed using the MINMOD computer program for the determination of the parameter S_I and S_G (115). The minimal model assessment of the FSIGT data was done at the Banting and Best Diabetes Centre Core Laboratory Toronto, Ontario.

2.13 Analytical Procedures.

Vacutainer brand blood collection tubes (Becton Dickinson, Rutherford, NJ) were used for blood samples: 5-mL K3EDTA tubes for HbA1c; 10-mL SST gel and clot activator tubes for serum glucose, TG, and total cholesterol; 10-mL no additive tubes for HDL cholesterol; and 5-mL potassium oxalate sodium fluoride tubes for the metabolic day profile and the FSIGT test.

Fasting plasma glucose, total cholesterol and TG were measured at St. Michael's Laboratory enzymatically using a Vitros Analyser 950 (Johnson and Johnson Clinical Diagnostics, Rochester, NY). HDL cholesterol was measured after precipitation of other lipoproteins with dextran sulphate and magnesium chloride. LDL was calculated as Total cholesterol – (HDL+TG/2.2) (only for TG <4.5 mmol/L). HbA1c was measured at St. Michael's Main Laboratory by a Diamat HPLC (Bio-Rad Laboratories (Canada) Ltd., Mississauga, Ontario).

Metabolic day profile and FSIGT blood samples were centrifuged at 3,000 rpm for 15 minutes and the plasma was separated into 2 aliquots, which were frozen and stored at –20 C until analysis. Blood glucose samples from the metabolic day profile were analysed using the YSI model 2300 STAT glucose analyser, (Yellow Springs Instruments, OH). Insulin was measured by at the Banting and Best Diabetes Core Laboratory using a commercially available kit (Insulin RIA, Pharmacia, Dorval, Quebec). TGs from the metabolic day profile were measured using a kit from Triglycerides (GPO-Trinder), Sigma Diagnostics, ST. Louis MO and FFAs were measured using a kit from (NEFA C, ACS-ACOD, WAKO Chemicals USA, Richmond, VA).

2.14 Statistical Analysis

Data are presented as means ± standard error of means (sem). Mean concentrations of metabolites during the 8h metabolic profile were calculated as total area under the curve using the trapezoidal rule and divided by 8 hours. Baseline results were compared for all measurements using one-way analysis of variance (ANOVA) to determine whether there was a difference at baseline. End results and differences between values at baseline and 4 months for the FSIGT (S_I, S_G, AIR_{glu} and DI, insulin and glucose levels) and metabolic day profile results (blood glucose, insulin, TG, FFA) were calculated for each subject in the different dietary test groups and the meaned results were compared by one-way ANOVA. The Newman-Keul method to adjust for multiple comparisons was than done. Similar analyses were made for the fasting cholesterol levels, weight, BP, FBG and HbA1c. Similar statistical tests were also done to compare to the nutrient analyses at baseline and changes over 4 months between the 3 dietary treatments. A one-way ANOVA comparison was done within the dietary treatment to determine whether the different weeks within treatment could be meaned. If results were missing during the 8 hour metabolic day profile, FSIGT or food records were not available, values were imputed using the methods described by Snedecor and Cochran (116). Within the groups a simple paired t-test was also done to compare baseline and treatment values. All statistical tests were 2 tailed with $p \leq 0.05$ being taken as significant.

2.15 Power Analysis

The intent was to enrol 48 subjects (16 per treatment arm) in anticipation that at least 75% (about 12 per treatment) of subjects will complete the study. The primary

47

statistical analysis was based on comparing the differences in insulin sensitivity index within subjects before and after treatment. The reproducibility of the measurement of insulin sensitivity using the minimal model in subjects with IGT is not known, however, in 15 healthy subjects who were studied before and after a 3 week interval, the coefficient of variation (CV) of repeated measures of S_I was 14.4% (117). Thus, the CV of the differences is $14.4 * \sqrt{2} = 20.4\%$. For power analysis the variability of S_I differences in subjects with IGT was assumed to be 20.4% and the probability of a Type II error (two-tailed) set at 0.90. With these assumptions, power analysis suggests that there was a 90% chance of detecting a 20% change in insulin sensitivity, which was considered as being clinically significant with an n of 11 subjects per treatment.

3.0 Results

3.1 Screening

257 people with risk factors for diabetes were screened with an oral glucose tolerance test to determine whether they had IGT. 85 subjects tested positive for abnormal blood glucose results of either IGT or type 2 diabetes. 41 subjects had blood levels in the range of diabetes. 44 subjects had IGT. 172 subjects tested normal. Of the 44 people with IGT, 37 joined the study while 7 individuals were unable to participate.

3.2 Anthropometric and Metabolic Parameters for the IGT Subjects in the 3 Diet Groups; High GI, Low GI and MUFA

Thirty-seven subjects took part and were randomized into the study. Three dropped out during the study: one from the MUFA group and 2 from the high GI group. Thirteen subjects completed the low GI test phase, 11 completed the high GI test phase and 11 completed the MUFA test phase. One participant took part in two phases (high GI and MUFA). Table 3.1 summarizes baseline and end values of the anthropometric and metabolic parameters of the 3 randomized IGT test groups; high GI, low GI and the MUFA group. No significant differences were found between the groups in any of the anthropometric or metabolic parameters at neither baseline, nor when looking at the change from baseline at weeks 4, 8 and 12 or over the whole treatment period. The only significant change was a drop in diastolic BP of 4 mmhg (p=0.03) on the low GI group that was significantly different from the high MUFA group. Figures 3.1, 3.2, 3.3, 3.4 presents the metabolic and anthropometric data from the three different diet groups over the duration of the study.

Table 3.1: Baseline and end results for the anthropometric and metabolic parameters of the high GI, low GI, and MUFA diet groups

	High GI Diet Baseline	High GI Diet End	Low GI Baseline	Low GI End	MUFA Diet Baseline	MUFA Diet End
Number (M:F)	11 (2:9)		13 (3:10)		11 (2:9)	
Age (y)	58.8 ± 4.0		55.2 ± 3.0		55.8 ± 4	
Height (m)	1.61 ± 0.03		1.64 ± 0.02		1.60 ± 0.02	
Weight (kg)	76.3 ± 6.2	76.0 ± 6.1	79.7 ± 3.6	79.4 ± 3.3	77.7 ± 4.8	77.9 ± 4.7
BMI (kg/m^2)	29.4 ± 2.2	29.2 ± 2.1	29.7 ± 1.2	29.7 ± 1.2	30.6 ± 1.7	30.6 ± 1.7
Blood Pressure (mmhg)	127±6/79±3	130±6/80±3[a]	129±5/80±2	125±5/76±2 [*a]	126±6/76±2	131±6/80±3[b]
Cholesterol (mmol/L)	5.50 ± .30	5.45 ± .34	5.42 ± .17	5.33 ± .18	4.72 ± .30	4.74 ± .24
Triglycerides (mmol/L)	2.12 ± .33	2.13 ± .30	1.79 ± .16	1.83 ± .19	1.70 ± .22	1.78 ± .24
HDLCholesterol (mmol/L)	1.19 ± .11	1.26 ± .12	1.20 ± .08	1.19 ± .09	1.20 ± .11	1.24 ± .11
Cholesterol/HDL Ratio	5.02 ± .54	4.77 ± 0.56	4.85 ± .44	4.93 ± .57	4.12 ± .26	4.00 ± .24
LDL Cholesterol (mmol/L)	3.34 ± .25	3.21 ± .30	3.41 ± .18	3.29 ± .18	2.75 ± .24	2.69 ± .17
Fasting Glucose (mmol/L)	5.3 ± .3	5.5 ± .2	5.2 ± .3	5.2 ± .2	4.7 ± .2	4.9 ± .2

Values are means ± sem. [*] refers to a significance of a paired t test p=0.02. [b] Refers to a significance of F value from one-way ANOVA comparing the meaned differences from start to end. [ab] Within each variable, means not sharing a common letter superscript are significantly different.
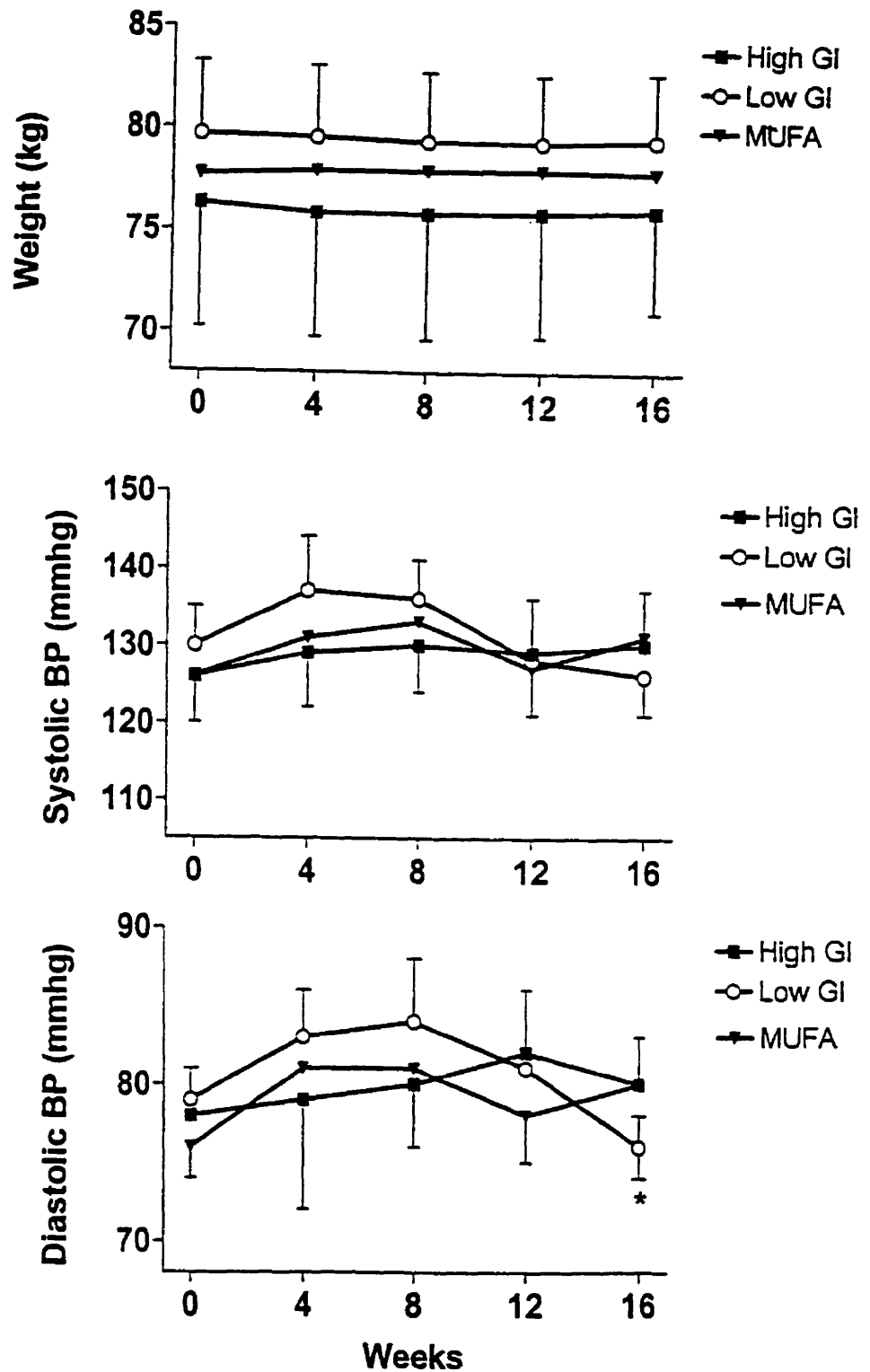
Figure 3.1: Body weight, systolic and diastolic blood pressure over the duration of the study for the high GI, low GI, and MUFA diet groups. Values are means ± sem. Error bars not shown if they are smaller than the symbol or overlap other error bars. * next to symbols denote a significant difference from week 0 within the group (p<0.05).
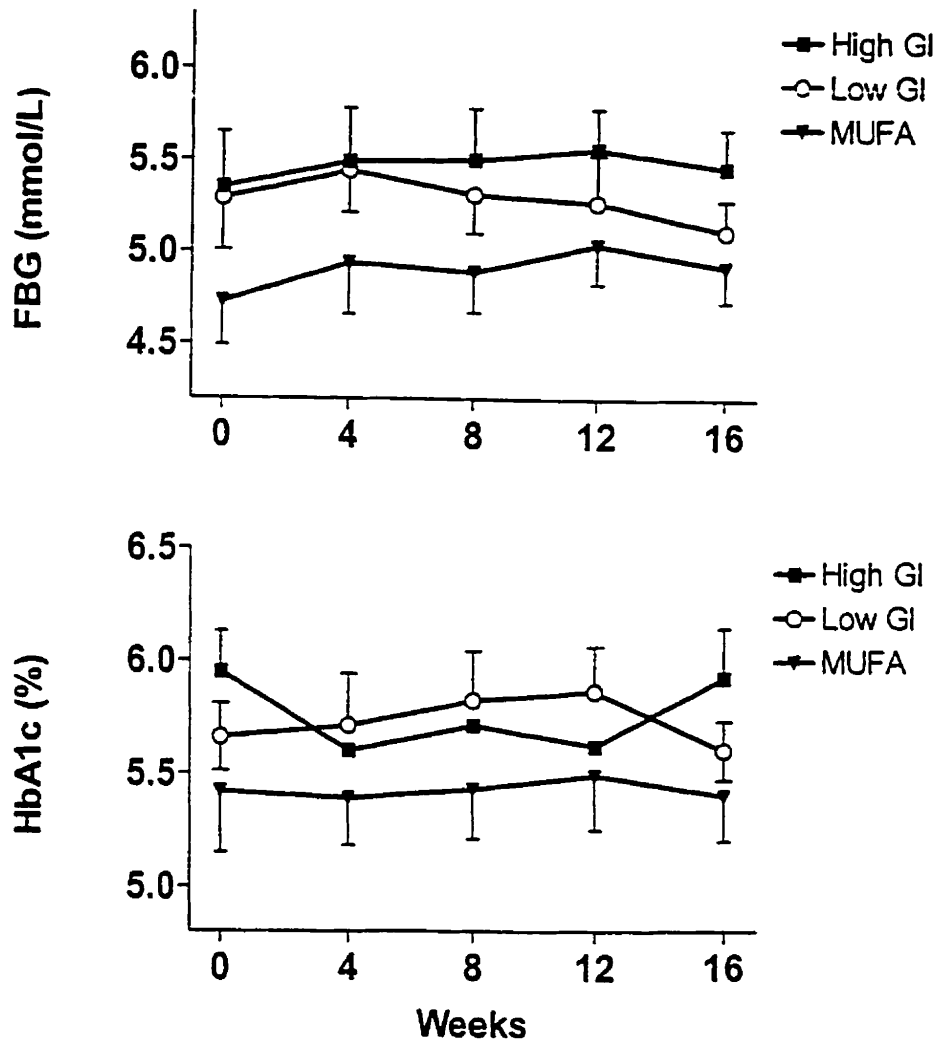
Figure 3.2: Fasting blood glucose and HbA1c levels over the duration of the study for the high GI, low GI, and MUFA diet groups. Values are means ± sem. Error bars not shown if they are smaller than the symbol or overlap with other error bars.
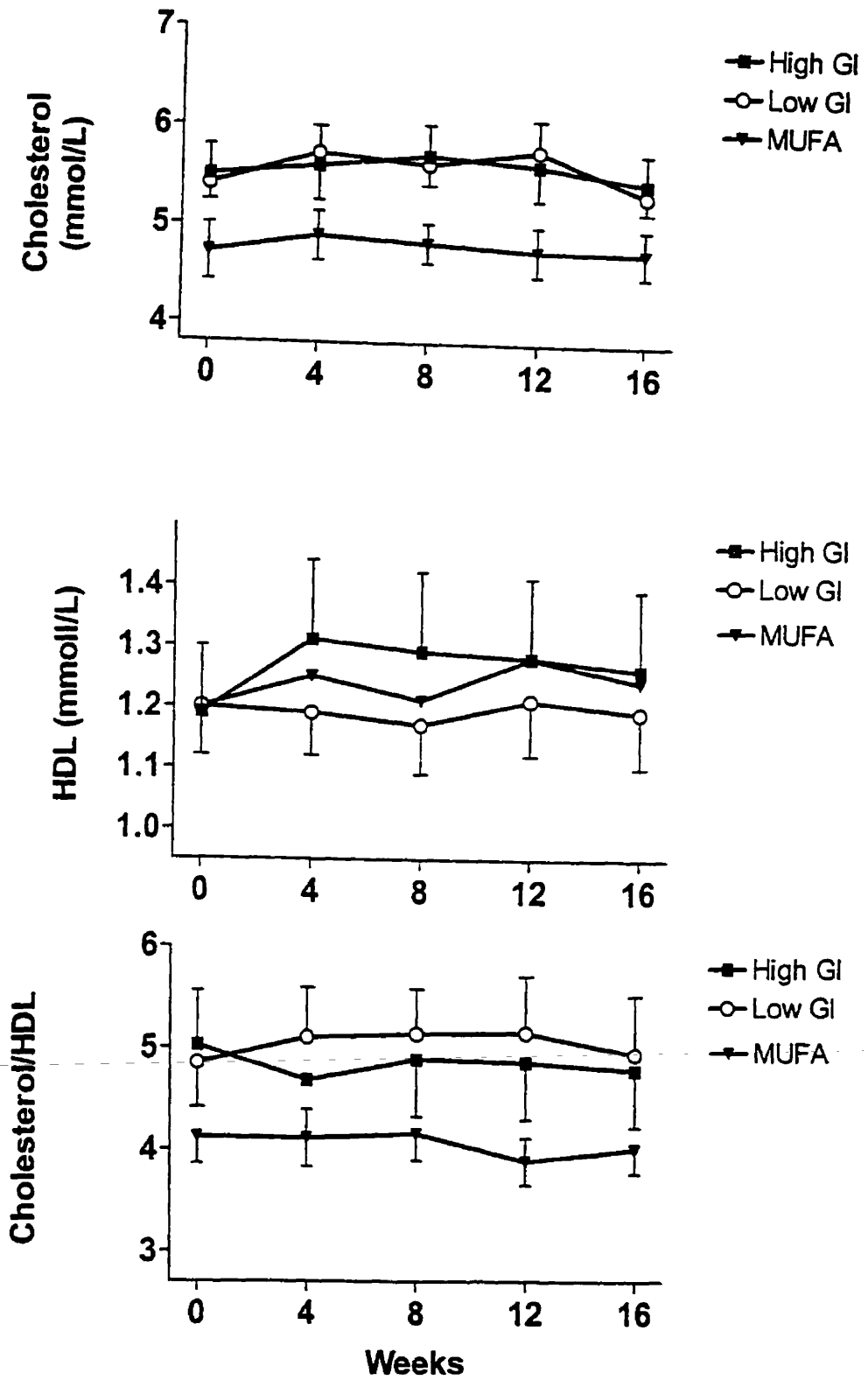
Figure 3.3: Total cholesterol (TC), HDL and TC/HDL ratio over the duration of the study for the high GI, low GI, and MUFA diet groups. Values are means ± sem. Error bars not shown if they are smaller than the symbol or overlap other error bars.
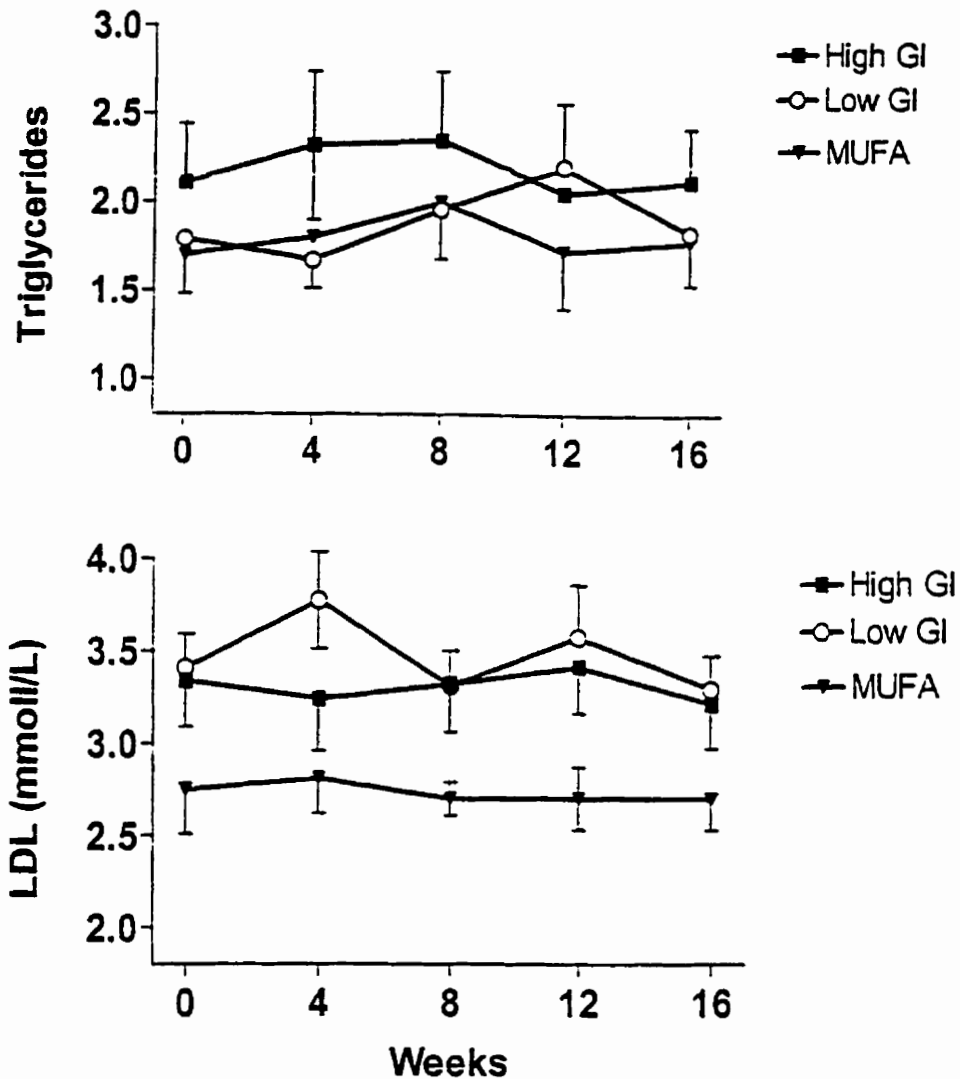
Figure 3.4: LDL and TG levels over the duration of the study for the high GI, low GI and MUFA diet groups. Values are means ± sem. Error bars not shown if they are smaller than the symbol or overlap other error bars.

3.3 Medications

Participants were on various medications (see table 3.2). Seven were on HRT, 2 on birth control, 2 on HmgCoA Reductase Inhibitors, 1 on bile acid sequestrant, 8 on thyroid medications, 4 on calcium channel blockers, 3 on diuretics, 5 on ace inhibitors, 2 on angiotensin II receptor antagonists, 2 on ß-blockers (1 person started half way through the study), 2 on ASA, 1 on fosomax, 2 on antidepressants, 1 on anti-anxiety, 1 on zantac, 1 on coumadin, 2 on tamoxifen, 1 on redux (stopped half way through the study), 1 on urispas, 1 on aldactone and 2 on anti-inflammatories. Except for the two cases mentioned above, study participants had no change in medications while on the study. A decision was made to keep both subjects in the study that were on ß-blockers although it was an exclusion criterion. In one case the subject was on it for the duration of the study. In the second case the subject was on it for a short duration during the middle of the study, and it was felt that if the drug had any effect on glucose metabolism the effect would have been washed out by the time the end tests were done. The data for both these subjects were evaluated and the results fell within the groups average and thus we felt the results could be included.

3.4 Nutrient Analyses of the Food Records

Of the 280 possible 3-7 day food records that were to be completed, 24 food records were missing. Table 3.3 refers to the dietary information for week 0 and meaned treatment values for the 3 different treatment groups. The dietary macronutrient profiles from the 3 different test groups did not differ at baseline. No significant difference was found between the different weeks while on treatment so the food records from week 2, 4, 8, 12, 14, 16 were meaned. Table 3.4, 3.5 and 3.6 shows the nutrient results of the

individual weeks for each of the dietary treatments. When comparing the meaned

energy intake during the study no significant difference was found. But, when

comparing the change in energy intake over the duration of the study, a significant

increase was found in the MUFA group compared to the other two dietary groups

(p=0.02). Within the MUFA phase a significant increase of 213 kcal was observed over

the dietary period (p=0.03). As hoped on the MUFA diet the intake of fat increased

significantly from baseline from 31% to 36% (p<0.05). On the low GI diet total fat intake

decreased significantly by 5.1% and went from 29.8% to 24.7* (p<0.05) and on the high

GI diet total fat intake went from 30.3% to 27.9%. A significant difference in the change

in percent fat intake over the study was found between the 3 diet groups (p=0.00004).

The increase in fat intake in the MUFA group came predominantly from an increase in

MUFA intake. Percent MUFA intake increased from 12.2% at baseline to 18.1% during

treatment in the MUFA group and the change over the treatment was significantly

different from the other two groups. No significant differences in the changes over the

treatment between the groups were found for SFA or PUFA. Available carbohydrate

intake increased significantly by 4.7% from 50% to 54.7% on the low GI group over the

treatment period and decreased significantly on the MUFA group by 4.2% and went

from 51.3 to 47.1%. A significant difference (p=0.0006) in the change over the study

period in percent available carbohydrate was achieved between the high carbohydrate

groups and the MUFA group. The low GI group had a significantly greater increase in

fibre intake over the study (p=0.0002) compared to the high GI and MUFA group. The

intake increased from 13.2 g/1000 kcal to 22.3 g/1000 kcal. A significant reduction in GI

of 6.2 (p<0.0007) was achieved on the low GI group while the GI remained the same in

the other 2 groups. Soluble fibre increased within the low GI group by 3.21 g over the study (p<0.05). The change in soluble fibre was significantly different between the 3 groups. The low GI group experienced the biggest change in soluble fibre over the study compared to high GI and MUFA group (p>0.0001).

Table 3.2 Summary of medications of study participants

Ace Inhibitor   5
    Fosinopril (Monopril)   1
    Ramipril (Altace)   2
    Enalapril (Vasotec)   2

Aldactone   (aldosterone antogonist)   1

Angiotensin II Receptor Antagonist   2
    Cozaar
    Inhibace (Cilazapril)

Anti-anxiety   1
    Stellazine

Antidepressants   2 (1 took 2,1 took 3)
    Adovent
    Lorazapem
    Prozac
    Zoloft
    Trazodone

Anti-inflammatory Drug   2
    Arthrotec
    Sulfasalazine

Aspirin   2

Beta Blocker   1.5
    Metrolol (last 7 weeks)
    Solatol

Bile Acid Sequestrant   1

Birth Control Pill   2

Calcium Channel Blocker   4
    Cardizem   1
    Adalat   1
    Norvasc   2

Coumadin   1

Diuretic-Antihypertensive   3
    Novospirozine   1
    Furosemide   1
    Hydrochorohydrazide   1

Fosamax   1

HmgCoA Reductase Inhibitors   2

Hormone Replacement Therapy   7

Redux   1

Tamoxifen   2

Thyroid   8

Urinary Tract Antispasmodic   1
    Urispas

Zantac   1

Table 3.3: Baseline and meaned study nutrient Intake for the 3-7 day food records for the high GI, low GI and MUFA diet groups

	Variable	High GI	Low GI	MUFA	P value
Energy	Baseline	1751 ± 67	1862 ± 19	1671 ± 116	
(kcal/day)	Study	$1714^{ab} \pm 95$	$1695^{b} \pm 70$	$1894^{*a} \pm 136$	0.02
Protein (g)	Baseline	76.0 ± 4.2	87.2 ± 6.1	73.5 ± 4.7	
	(%)	17.4	18.7	17.9	
	Study	74.3 ± 4.6	81.9 ± 3.2	76.4 ± 3.9	
	(%)	17.4^{ab}	19.3^{a}	16.4^{b}	0.02
Fat (g)	Baseline	59.0 ± 5.6	63.1 ± 6.6	57.4 ± 7.5	
	(%)	30.3	29.8	30.2	
	Study	54.3 ± 5.8	47.4 ± 4.3	75.1 ± 6.6	
	(%)	27.9^{b}	24.7^{*b}	35.6^{*a}	0.00004
AvailCHO g)	Baseline	222.6 ± 11.7	229.6 ± 13.7	212.9 ± 15.5	
	(%)	51.2	50.0	51.3	
	Study	223.8 ± 52.2	230.1 ± 10.2	224.3 ± 19.3	
	(%)	52.8^{b}	54.7^{*b}	47.1^{*a}	0.0006
Fibre (g)	Baseline	24.1 ± 2.0	24.2 ± 1.5	21.9 ± 1.9	
	g/1000 kcal	14.0	13.2	13.6	
	Study	22.6 ± 2.2	36.3 ± 2.7	23.7 ± 2.2	
	g/1000 kcal	13.5^{b}	22.3^{*a}	12.6^{b}	0.0002
Soluble Fibre	Baseline	6.8 ± 0.5	6.7 ± 0.5	6.35 ± 0.5	
	Study	$6.0^{*b} \pm 0.4$	$9.95^{*a} \pm 0.7$	$6.61^{b} \pm 0.5$	<0.0001

Chol (mg)	Baseline	215.3 ± 27.1	246.7 ± 34.4	209.4 ± 24.9	
	mg/1000kcal	123	132.4	125.3	
	Study	206.9 ± 23.1	194.8 ± 18.5	203.4 ± 18.3	
	mg/1000kcal	120.7	114.9	107.4	
SFA (g)	Baseline	18.4± 2.2	20.5 ± 2.2	18.1 ± 2.5	
	(%)	9.3	9.7	9.6	
	Study	17.4 ± 2.3	15.0 ± 1.8	19.6 ± 1.9	
	(%)	8.9	7.8*	9.4	
MUFA (g)	Baseline	23.4 ± 2.18	24.7 ± 2.7	23.4 ± 3.5	
	(%)	11.9	11.7	12.2	
	Study	21.1± 2.3	17.8 ± 1.7	38 ± 3.3	
	(%)	10.9[b]	9.2*[b]	18.1*[a]	<0.0001
PUFA (g)	Baseline	11.9 ± 1.3	12.9 ± 1.9	11.2 ± 1.4	
	(%)	6.0	6.1	5.9	
	Study	10.1 ± 1.1	9.3 ± 0.9	11.9 ± 1.6	
	(%)	5.2*	4.9*	5.5	
GI	Baseline	82.2 ± 1.0	82.2 ± 0.8	82.4 ± 1.1	
	Study	83.1[b] ± 0.8	76.0*[a] ± 1.0	82.1[b] ± 0.5	0.0007

Values are given as grams ± sem. Statistical information given for percentages only for protein, fat, carbohydrate. * Refers to a significance of paired t test p≤ 0.05. [b] Refers to a significance of F value from one-way ANOVA comparing the meaned differences from start to end. [ab] Within each variable, means not sharing a common letter superscript are significantly different.

Table 3.4: Baseline and study nutrient intake for the meaned 3-7 day food records for the low GI diet group

	Wk 0[#]	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 16
Energy (kcal)	1862 ± 119	1738 ± 100	1757 ± 87	1659 ± 77	1656 ± 57	1756 ± 92	1607 ± 115
Protein (%)	18.7^{bc} ± 0.5	20.1^{b} ± 0.7	19.8^{bc} ± 0.4	18.0^{ac} ± 0.5	19.3^{bc} ± 0.8	19.6^{bc} ± 0.5	19.6^{bc} ± 0.7
Total Fat (%)	29.8^{a} ± 1.8	25.5^{ac} ± 1.7	24.1^{ac} ± 1.9	24.6^{ac} ± 1.5	24.7^{ac} ± 2.1	24.3^{ac} ± 2.0	25.0^{bc} ± 2.2
SFA (%)	9.7^{a} ± 0.6	7.9^{b} ± 0.7	7.5^{b} ± 0.8	8.0^{b} ± 0.7	7.8^{b} ± 0.8	7.6^{b} ± 0.8	7.8^{b} ± 0.9
MUFA (%)	11.7^{a} ± 0.7	9.8^{b} ± 0.7	9.0^{b} ± 0.8	9.3^{b} ± 0.6	9.1^{b} ± 0.9	9.1^{b} ± 0.9	9.1^{b} ± 1.0
PUFA (%)	6.1 ± 0.7	5.4 ± 0.5	5.0 ± 0.4	4.3 ± 0.4	4.5 ± 0.5	4.9 ± 0.4	5.4 ± 0.8
Cholesterol (mg)	247 ± 34	211 ± 17	206 ± 25	195 ± 20	174 ± 14	203 ± 24	179 ± 30
Available Carbohydrate (%)	50.0 ± 2.1	53.2 ± 1.8	54.9 ± 2.0	56.3 ± 1.6	54.9 ± 2.1	55.1 ± 2.2	54.4 ± 2.6
Alcohol (%)	1.3 ± 0.6	1.1 ± 0.4	1.1 ± 0.5	0.8 ± 0.3	1.0 ± 0.4	0.9 ± 0.4	0.9 ± 0.5
Dietary Fibre (g)	24.2^{a} ± 1.5	35.0^{b} ± 3.1	39.6^{b} ± 3.5	33.3^{b} ± 2.1	34.3^{b} ± 3.9	37.6^{b} ± 2.9	37.5^{b} ± 2.6
GI	82.2^{a} ± 0.8	75.2^{b} ± 1.1	75.7^{b} ± 1.3	77.9^{b} ± 1.3	76.2^{b} ± 1.0	75.0^{b} ± 1.7	76.7^{b} ± 1.1

Values are given with ± sem. # Indicates mean of 1-2 food records. [abc] Within each variable, means

not sharing a common letter superscript are significantly different (p<0.05). % Indicates percentage

of energy.

Table 3.5: Baseline and study nutrient intake results for the meaned 3-7 day food records for the high GI diet group

	Wk 0[#]	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 16
Energy (kcal)	1751 ± 67	1751 ± 85	1849 ± 152	1572 ± 126	1739 ± 100	1709 ± 111	1678 ± 95
Protein (%)	17.4 ± 0.8	16.9 ± 0.6	17.4 ± 0.5	18.1 ± 0.7	16.8 ± 0.9	17.7 ± 1.0	17.7 ± 0.9
Total Fat (%)	30.0 ± 2.2	27.5 ± 1.9	29.5 ± 2.2	26.3 ± 2.4	27.3 ± 1.9	28.6 ± 2.1	28.3 ± 2.2
SFA (%)	9.3 ± 1.0	8.7 ± 0.8	9.5 ± 0.9	8.7 ± 1.0	8.6 ± 0.9	8.8 ± 1.0	9.0 ± 0.8
MUFA (%)	11.9 ± 0.9	10.0 ± 0.9	11.9 ± 1.1	10.8 ± 1.1	10.9 ± 0.7	10.3 ± 0.7	11.0 ± 1.0
PUFA (%)	6.0 ± 0.5	4.9 ± 0.7	5.2 ± 0.5	4.3 ± 0.4	5.3 ± 0.4	5.7 ± 0.4	5.5 ± 0.5
Cholesterol (mg)	215 ± 27	203 ± 34	217 ± 28	217 ± 31	214 ± 33	205 ± 23	185 ± 22
Available Carbohydrate (%)	51.2 ± 2.6	53.5 ± 2.0	50.8 ± 2.3	54.6 ± 2.6	53.7 ± 2.3	52.6 ± 2.3	51.5 ± 2.4
Alcohol (%)	1.3 ± 0.7	1.9 ± 0.8	2.0 ± 1.0	0.8 ± 0.4	2.1 ± 0.9	1.0 ± 0.6	2.3 ± 1.5
Dietary Fibre (g)	24.2 ± 2.0	26.1 ± 2.1	23.7 ± 2.1	20.8 ± 3.0	22.9 ± 2.4	21.5 ± 2.6	21.4 ± 2.5
GI	82.2 ± 1.0	81.2 ± 1.0	83.8 ± 1.5	83.1 ± 0.7	83.2 ± 1.0	84.2 ± 1.0	82.4 ± 1.2

Values are given with ± sem. # Indicates mean of 1-2 food records. % Indicates percentage of energy.

Table 3.6: Baseline and study nutrient intake results for the meaned 3-7 day food records for the MUFA diet group

	Wk 0[#]	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 16
Energy (kcal)	1671 ± 116	1804 ± 103	1915 ± 190	1951 ± 122	1878 ± 124	1845 ± 159	1893 ± 151
Protein (%)	17.9 ± 1.0	16.2 ± 0.7	16.7 ± 0.4	15.9 ± 0.7	17.0 ± 0.8	16.4 ± 0.7	16.4 ± 0.6
Total Fat (%)	30.2^a ± 2.5	34.5^{bc} ± .0	35^{ac} ± 1.3	35.1^{ac} ± 1.6	34.6^{ac} ± 2.4	36.6^{bc} ± 1.8	36.8^{bc} ± 1.5
SFA (%)	9.6 ± 1.0	9.3 ± 1.0	9.5 ± 0.6	9.3 ± 0.9	9.0 ± 0.9	9.3 ± 0.8	9.2 ± 0.8
MUFA (%)	12.2^a ± 1.2	16.7^b ± 1.1	18.1^b ± 0.7	17.2^b ± 0.7	17.8^b ± 1.3	19.5^b ± 0.9	19.1^b ± 0.8
PUFA (%)	5.9 ± 0.5	5.4 ± 0.4	5.0 ± 0.4	6.1 ± 0.5	5.2 ± 0.5	5.1 ± 0.5	5.9 ± 0.4
Cholesterol (mg)	209 ± 25	205 ± 25	227 ± 33	181 ± 25	196 ± 21	213 ± 20	202 ± 22
Available Carbohydrate (%)	51.3^a ± 2.4	48.8^{ac} ± 2.1	47.8^{ac} ± 1.3	48.1^{ac} ± 1.7	47.5^{ac} ± 2.4	46.8^{ac} ± 1.8	45.5^{bc} ± 2.0
Alcohol (%)	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2	0.8 ± 0.4	0.9 ± 0.4	0.2 ± 0.2	1.1 ± 0.5
Dietary Fibre (g)	21.9 ± 1.9	22.0 ± 1.8	22.5 ± 2.0	25.7 ± 2.4	22.7 ± 2.1	24.2 ± 2.2	24.8 ± 3.7
GI	82.4 ± 1.1	80.5 ± 0.9	82.4 ± 0.7	82.5 ± 0.9	83.4 ± 0.8	82.0 ± 0.8	81.4 ± 0.9

Values are given with ± sem. # Indicates mean of 1-2 food records. [abc] Within each variable, means not sharing a common letter superscript are significantly different ($p<0.05$). % Indicates percentage of energy.

3.5 FSIGT Results: Comparison of the 3 Dietary Treatments

Table 3.7 and Figure 3.5 summarize the results of the FSIGT test. There was no significant difference between the 3 diet groups at baseline with respect to DI, S_I, AIR_{glu} or S_G. When comparing the change in DI over the study period of the three dietary treatments, the low GI and MUFA group were significantly different (p=0.01), while there was no significant difference found between the low GI and high GI dietary treatment nor the high GI and MUFA groups. The DI for the low GI group improved by 56% from the baseline (p=0.02). The high GI group remained the same while the MUFA group worsened by 16% over the test period. S_I and AIR_{glu} tended to improve by 17% and 37 % on the low GI group while they tended to worsen on the high GI and MUFA groups.

Table 3.7: FSIGT and 8 hour metabolic day profile results at baseline and the end for the high GI, low GI, and MUFA diet groups

	High GI Diet Baseline	High GI Diet End	Low GI Diet Start	Low GI Diet End	MUFA Diet Start	MUFA Diet End
S_I (min^{-1}/uU/mL)	0.561±0.089	0.552±0.072	0.447±0.095	0.523±0.115	0.556±0.078	0.501±0.050
S_G (min^{-1})	0.017±0.002	0.019±0.002	0.017±0.002	0.015±0.002	0.017±0.001	0.018±0.002
AIR_{glu} (uU/mLX10 min)	601.8±206.6	547.0±161.0	513.3±124.5	701.9190.8	984.3±269.3	965.4±215.9
DI (no units)	288±116	287±103[a]	221±80	344±103[*a]	478±110	403±64[b]
				*p=0.02,[a]p=0.01		
0-8hr* Glucose (mmol/L)	7.48±0.3	7.53±0.34	7.25+0.2	7.03±0.21	7.06±0.2	6.80±0.27
0-8hr Insulin (pmol/L)	198.6±39.2	160.1±25.9* p=0.04	222.4±30.8	222.3±24.2	228.4±35.6	198.9±26.9
0-8hr FFA (mEq/L)	0.31±0.03	0.27±0.03	0.37±0.04	0.28±0.03 p=0.02	0.32±0.05	0.28±0.03
0-8hr TG (mmol/L)	2.12±0.25	1.96±0.28	1.75±0.16	1.92±0.3	1.56±0.52	1.63±0.21

Values are means ± sem. * refers to a significance of paired t test. [a] refers to a significance of F value from one-way ANOVA. [ab] Within each variable, means not sharing a common letter superscript are significantly different.

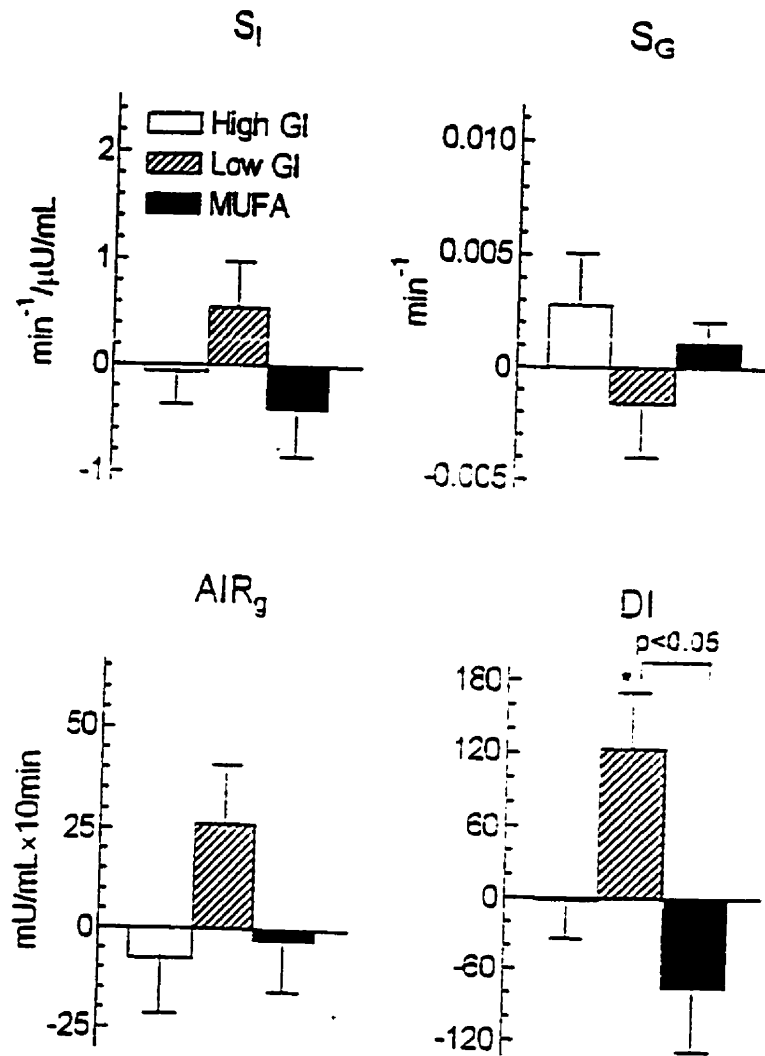**Figure 3.5**: Changes from baseline values for insulin sensitivity (S_I), glucose

effectiveness (S_G), pancreatic responsiveness (AIR_{glu}), and glucose disposition

index (DI) from the FSIGT test for the high GI, low GI and MUFA diet groups.

Values are means ± sem. * Significant change from baseline (paired t-test,

$p < 0.05$). $p < 0.05$ indicates a significant difference in changes between diets by

ANOVA.

3.6 8 hour Metabolic Day Profile Results for the 3 Dietary Groups

3.6.1 Nutrient Profiles for the 8 hour Metabolic Day Profile

The macronutrient compositions of the meals for the metabolic day profiles are given in Table 3.8. The high GI group had the same type of diet at start and finish. Percent total fat and MUFA intake increased significantly by 11.8% and 11.9% respectively on the MUFA diet. The available carbohydrate intake decreased by 11.2% and protein intake decreased by 0.6%. The GI was reduced in the low GI group from 85.6 to 74.4 (p<0.0001) while the available carbohydrate remained the same. Fibre intake on the low GI diet increased by 24.4 grams and saturated fat and monounsaturated fat intake decreased slightly.

3.6.2 Baseline and End Results

Hourly, and 0-8 hour meaned results for FFA, TG, insulin and glucose from the metabolic day profile for the 3 dietary treatments are found in Table 3.7. Fifteen of the possible 1680 results were unavailable and had to be imputed. Baseline results showed no significant differences between the groups.

3.6.2.1 FFAs

Mean FFA levels improved by 25% at week 16 compared to week 0 on the low GI diet group (p=0.027). At hours 3 and 7 a significant decrease of 0.058 mEq/L (p=0.04) and 0.056 mEq/L (p=0.04) (see Figure 3.6) was observed. No significant improvements were observed on the other 2 diets over the treatment period. No significant difference was found when comparing the change from the start and end of the 3 dietary periods.

Table 3.8: Macronutrient profile for the 8 hour metabolic day profile at baseline and end for the high GI, low GI and MUFA diet groups

	IGT group Baseline	High GI End	Low GI End	MUFA End
Sample size	35	11	13	11
Energy (kcal)	977.5±83.5	998.1±66.9	980.1±47.3	938.2±51.7
Protein (%)	12.6	12.8	13.0	12.0*
Fat (%)	27.9	28.3	28.3	39.7*
Available CHO (%)	59.5	58.9	59.6	48.3*
SFA (%)	7.2	7.3	6.4*	8.4*
MUFA (%)	11.4	11.4	10.4*	22.3*
PUFA (%)	8	8.2	8.4	7.3
Fibre (g)	7.6	7.8	32.0*	6.7*
GI	85.6	85.4	74.4*	85.8

Values are given with ± sem. % Indicates percentage of energy. * refers to a significance of paired t test p<0.05.

Comparing the changes from baseline at individual time points, a significant difference was found at hour 6 and hour 7 for the low GI and high GI compared to the high MUFA group. At hour 6, the low GI group improved by 0.11 mEq/L and the high GI group improved by 0.13 mEq/L. At hour 7 the low GI group improved by 0.06 and the high GI group improved by 0.02. In the MUFA group, the FFA went up by 0.08 and 0.06 at hour 6 and 7.

3.6.2.2 TG

No significant differences were found at any of the time intervals or the mean change over the day when comparing the changes from baseline within and between the three groups (Figure 3.7).

3.6.2.3 Insulin

Mean plasma insulin levels over the day decreased by 20% on the high GI diet and went from 199.6 to 160.1 (p=0.04) (see Table 3.7). Insulin levels in the high GI group went down significantly at hours 1, 6 and 7 (p<0.05). Insulin levels remained the same on the low GI and MUFA groups with no significant changes observed at any point in time or with the 0-8 hour meaned levels. No significant differences were observed between the 3 dietary treatments with regards to a mean change in insulin concentration between the baseline and end. At hours 6 and 7 the changes in plasma insulin levels were significantly different on the high GI diet compared to the low GI (p=0.04, p=0.05).

3.6.2.4 Glucose

Mean plasma glucose levels over the day did not change within any of the diet groups or when comparing the change in mean glucose levels over the treatment

period between the three groups (see Figure 3.9, Table 3.7). Glucose levels did improve on the low GI diet at hour 1.5 resulting in a lower post breakfast glucose peak. At 1.5 hours the glucose level improved by 1.33 mmol/L from 9.6 to 8.27 (p=.011). Glucose levels worsened slightly at hour 5 going up from 4.45 to 4.7 (p=0.031). The MUFA group worsened at hour 4 going up .38 mmol/L to 4.82 (p=0.046).

3.6.2.5 Fasting Glucose Insulin Ratio

The fasting glucose insulin ratio was calculated at baseline and at the end of the study for each of the dietary treatments. The ratio for the high GI diet group at baseline was 0.15 ± 0.02 and went to 0.16 ± 0.02 at the end, for the low GI diet group the ratio went from 0.14 ± 0.02 to 0.12 ± 0.01 and in the MUFA diet group the ratio went from 0.12 ± 0.02 at the start to 0.11 ± 0.02 at the end of the study. No significant difference was found when comparing the change in the ratio from the baseline between the 3 dietary periods.

Figure 3.6: The line graph represents baseline (•) and end (o) results of plasma FFA levels over 8 hours during the metabolic day profile in the high GI, low GI and MUFA diet groups. The bar graph represents changes from baseline. Breakfast was consumed at approximately 8:00 am (time 0) and lunch 5 hours later. Values are means ± sem. * On the line graph at a specific time point indicates a significant difference between baseline and end values for pairs of means and on the bar graph indicates a significant change from baseline by paired t-test ($p \leq 0.05$).
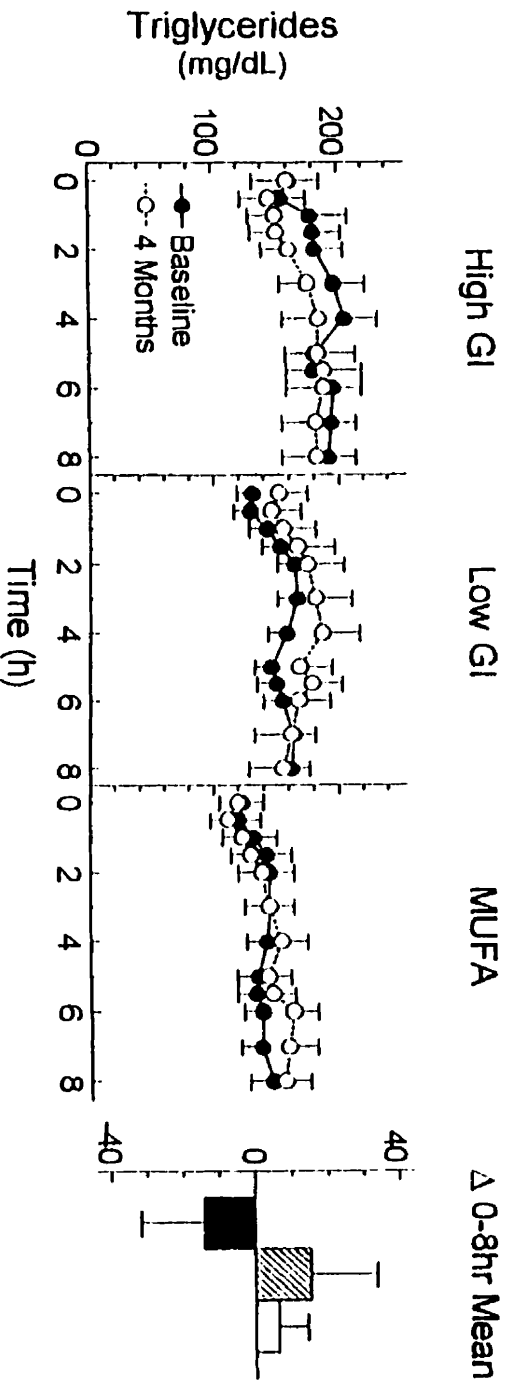
Figure 3.7: The line graph represents baseline (•) and end (o) results of plasma triglyceride levels over 8 hours during the metabolic day profile in the high GI, low GI and MUFA diet groups. The bar graph represents changes from baseline. Breakfast was consumed at approximately 8:00 am (time 0) and lunch 5 hours later. Values are means ± sem.
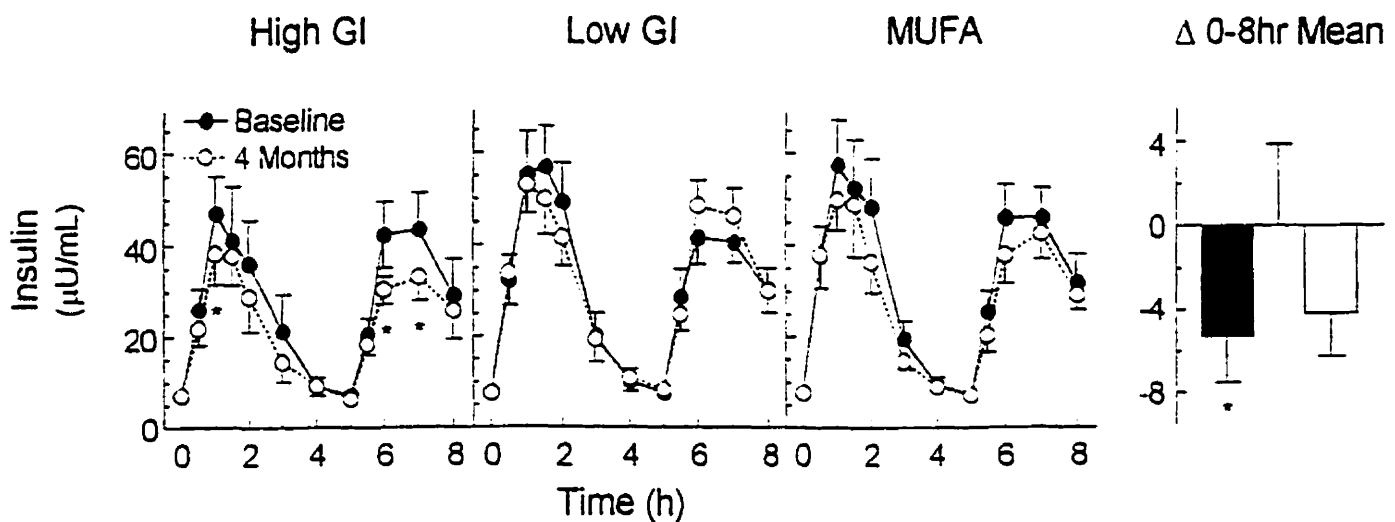
Figure 3.8: The line graph represents baseline (•) and end (o) results of plasma

insulin levels over 8 hours during the metabolic day profile in the high GI, low GI

and MUFA diet groups. The bar graph represents changes from baseline.

Breakfast was consumed at approximately 8:00 am (time 0) and lunch 5 hours

later. Values are means ± sem. * On the line graph at a specific time point

indicates a significant difference between baseline and end values for pairs of

means, and on the bar graph indicates a significant change from baseline by
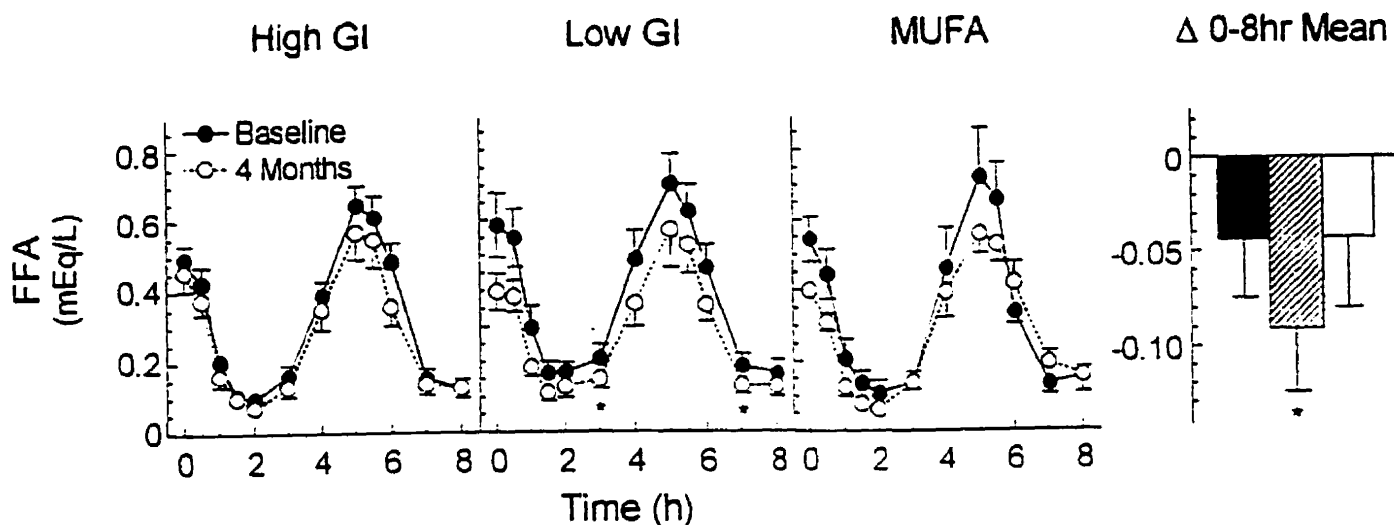
paired t-test (p≤ 0.05).
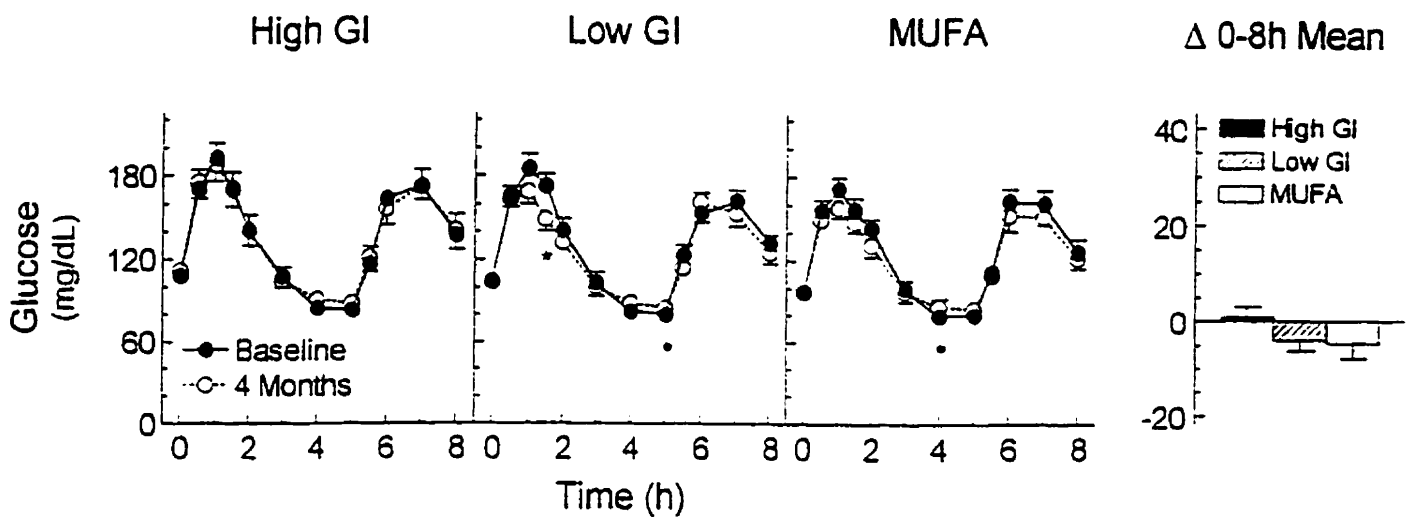
Figure 3.9: The line graph represents baseline (•) and end (o) results of plasma glucose levels over 8 hours during the metabolic day profile in the high GI, low GI and MUFA diet groups. The bar graph represents changes from baseline. Breakfast was consumed at approximately 8:00 am (time 0) and lunch 5 hours later. Values are means ± sem. * On the line graph at a specific time point indicates a significant difference between baseline and end values for pairs of means by paired t-test (p≤ 0.05).

4.0 Discussion and Conclusions

4.1 Discussion

The current study was designed to compare the effects of different dietary approaches on insulin sensitivity as measured by the FSIGT test. Impaired insulin sensitivity or insulin resistance is considered a major etiologic factor in the development of type 2 diabetes and is identified as one of the earliest detectable abnormalities in the disease (28,68,118). Improving insulin sensitivity and reducing hyperinsulinemia has been suggested to reduce the risk for developing diabetes (8,59,119,120). Diet is considered an important environmental factor influencing insulin sensitivity. There is quite a bit of controversy in the scientific literature about what the best diet is to enhance insulin sensitivity. The current study compares three different dietary approaches. The first includes reducing the quantity of carbohydrate and increasing the intake of monounsaturated fat, the second alters the source of carbohydrate by using low GI or slowly absorbed complex carbohydrates while keeping the carbohydrate level high and the third is a high carbohydrate, high glycemic (quickly absorbed foods) index diet. We hypothesised that the low GI diet would improve insulin sensitivity, while the low carbohydrate MUFA enriched diet and high GI high carbohydrate would not. Pharmacological inhibition of carbohydrate absorption, a paradigm for low GI foods, reduces post-prandial insulin and improves insulin sensitivity in subjects with IGT (52). Results of work on increased meal frequency, which is another type of model of delayed carbohydrate absorption, has demonstrated a lower daily glucose and insulin response which could explain improvements in glycemic

and lipid control reported in low GI studies (89,109). High GI high carbohydrate intake is thought to worsen S_I because of increased insulin demand which may accentuate hyperinsulinemia (5). Acute studies that have looked at the effect of reducing carbohydrate intake found that FFAs rebounded to a higher degree after a low carbohydrate breakfast (13). Chronic elevation of FFAs may result in insulin resistance (14). Numerous studies in the past have tested these different dietary approaches on blood glucose and lipid levels but in only one case have these different dietary regimes been compared in one study. More importantly, few dietary studies have looked at a whether a change in quantity and/or quality of carbohydrate has an impact on insulin sensitivity. Therefore, the objective in the present study was to compare the effect of a high carbohydrate low GI diet and a low carbohydrate high MUFA and a high carbohydrate high GI diet on insulin sensitivity.

The inclusion of low GI foods in a high carbohydrate self selected diet of IGT subjects' improved the DI and reduced FFAs compared to a high carbohydrate high GI and a MUFA enriched diet. No deleterious effects on the lipid profile were observed and fasting blood glucose and HbA1c levels and mean plasma insulin levels were maintained. These changes are all conducive to lowering the risk profile for the development of type 2 diabetes. This study contributes to our current knowledge and lends support for the beneficial effects of adding low GI foods to a high carbohydrate diet to improve glycemic control in insulin resistant individuals. These beneficial effects were achieved with a modest amount of dietary change (GI change 6), could be kept up for the

duration of the study, with products that were readily available at the supermarket.

4.1.1 Insulin Sensitivity

We were unable to demonstrate any significant difference of diet on insulin sensitivity and further studies are needed to address this issue. Although, a trend was observed for improving S_I on the low GI diet, a worsening on the low carbohydrate MUFA enriched diet, with no change observed on the high GI diet (see Table 3.7, Figure 3.5). However, we were able to show a significant improvement with the DI of 56% (p=0.02) on the low GI diet and this improvement was significantly different from MUFA diet, whose DI actually worsened over the study period. A significant difference was just missed comparing the high GI to the low GI diet. The DI is the product of S_I and AIR_{gluc} and has been suggested as a measure of overall glucose disposal (7,121,122). The improvement in DI shows that within individuals, the ability to compensate for a particular degree of insulin resistance improved (7). Bergman showed that the DI was more strongly correlated with glucose tolerance than either insulin action or insulin secretion alone (7,122). Lind et al. showed that IGT are a heterogeneous group with different combinations of impairments in insulin secretion and insulin sensitivity (124). Since the development of diabetes requires both insulin resistance and a decrease in insulin secretion, the DI may be a more sensitive measure of overall insulin action and the risk of developing diabetes than is S_I alone (7,122). Thus, we feel that the DI provides important information about the status of insulin resistance.

Supporting our low GI results of an improved DI, are data from the study by Frost who using a modified FSIGT showed improvement in S_I both in-vitro in adipocytes and in-vivo in insulin resistant women at risk for heart disease while on a low GI diet compared to a high GI diet (102). He like in our study, found no accompanying decrease in fasting glucose or insulin concentrations (102). Similar dietary modification has been shown to improve S_I in subjects with CHD, NIDDM, and obesity (102,103). Swinburn et al. showed an improvement in the DI with no change in S_I when he compared a traditional Indigenous Diet (low fat, high carbohydrate, high fibre,) against a modern diet (high total fat, high saturated fat,) (7,91). Low GI diets may improve the DI/S_I because their slowed absorption has been shown to lower and attenuate post-prandial insulin levels which may suppress FFA levels and hepatic glucose production longer, creating a more insulin sensitive environment and thus improve insulin resistance (102,107). Although no change in insulin levels were observed in our study, the low GI group did have a significant reduction in FFA levels during their metabolic day profile (Table 3.7, Figure 3.6).

No change in S_I, DI, AIR_{gluc} was found on the high carbohydrate high GI diet. These results are similar to several other studies that used the euglycemic clamp test to test for S_I (56,119,125,126). Earlier studies found improvements on S_I on a high GI high carbohydrate used dietary extremes that are not tolerated over the long term (119). Often times the studies used indirect methods to test for S_I, such as measuring insulin and glucose levels after an OGTT, making the results difficult to interpret (118,119) and hard to compare with the results from

the euglycemic clamp and FSIGT techniques. For example Himsworth first postulated over 50 years ago that high carbohydrate diets enhance insulin sensitivity. He demonstrated that the glucose tolerance of normal subjects increased as the carbohydrate content of the antecedent diet was progressively increased. He attributed this effect to changes in insulin sensitivity, since the hyperglycemic response to injected insulin varied in parallel with the changes in glucose tolerance. But, closer analysis of his data shows that most of the improvement occurred when carbohydrate intake increased from 10 to 30% of energy intake. Increases from 30 to 60% of energy take levels comparable to what is consumed in our western society today produced few changes (119). In addition he did not measure insulin action as such, but only the plasma glucose response oral glucose (120). Thus the more recent studies, albeit there are not many, tend to show no change with S_I on a high GI high carbohydrate diet.

Along with our study two other studies were conducted comparing a high MUFA, low carbohydrate diet versus a high carbohydrate low fat diet. Parillo et al. found, using a euglycemic clamp, that a high MUFA diet improved S_I compared to a high carbohydrate high GI diet in mild type 2 diabetics, while Garg, also using the euglycemic clamp, found no difference in S_I between the two diets in a type 2 diabetic populations (56,68). Our study found no change in S_I or AIRglu, but found a decrease in the DI by 16% (significantly different from low GI) on the high MUFA diet.

The results of the 3 studies are difficult to compare with each other because of the different population groups and the study lengths. The Parillio and

Garg studies were both short-term cross over studies of 2 weeks in type 2 diabetics with many of the subjects having either no or very little wash out (56,68). With no wash out period, there is always the uncertainty of carry over effects from the first phase into the second and the concern of whether subjects had sufficient time to establish a new steady state on the second phase. The Parillio and Garg studies were conducted on metabolic wards where dietary intake is strictly controlled along with the rest of the lifestyle compared to an ad-libitum outpatient study such as ours and thus their studies may have been able to detect metabolic changes of a lesser magnitude than we would have in ours. (56,68). Some of the subjects on the Parillio study were on sulfonureas which enhance insulin secretion, and may have affected carbohydrate metabolism such as preventing the high carbohydrate intake from raising plasma glucose concentrations (28,127). The difference between fat and carbohydrate intake on the high carbohydrate and high MUFA was also much greater at 20% in the Parillo and 25% on the Garg study than in our study at 7%. The patients in the Parillo and Garg study were diabetic, while the subjects in our study were IGT. Considering the glucotoxic effect of raised glucose levels, diabetics will be more beneficially affected by methods of reducing blood glucose than those with IGT (28). Thus, the 20-25% reduction in carbohydrate intake would result in lower glucose levels and insulin levels in the diabetics, and could be reduced enough as was observed in the Parillio study to improve insulin sensitivity. Hyperglycemia (28,39) and hyperinsulinemia (68,128) has been shown in several studies to reduce insulin sensitivity.

The improvement in S_i found in the Parillio study could be interpreted as only an acute effect since the study was only two weeks long. A lower carbohydrate diet can increase FFA levels as was observed in the study by Rasmussen in type 2 diabetics (70) and acutely by Wolever in normal subjects (13). It is well known that elevated FFA levels can lead to insulin resistance (14). In a 6 month study by Wolever et al in type 2 diabetics mean FFA were significantly higher in the MUFA group compared to the high carbohydrate groups. The study by Wolever also found that insulin levels were reduced and fasting and post-lunch glucose levels on the MUFA group were higher, suggesting a worsening of S_i (129). Since S_i was not measured in Wolever's study, one can only hypothesize that S_i worsened. Therefore, it is unknown whether the effects of a high MUFA diet may initially show an improvement in S_i because of lower glucose and insulin levels, but over the long term elevate FFA levels, which may override the benefit of lower glucose and insulin levels and cause a worsening of S_i (129).

This chronic effect of elevated FFA levels on S_i is what we may be seeing in our study. In the MUFA group, S_i did not change but DI tended to get worse in the MUFA group by 16%. Although not as elevated as in type 2 diabetics, FFA levels were slightly elevated compared to normals and remained so for the duration of the study. More studies looking at the long-term effect of high MUFA and high carbohydrate diets in particular low GI on S_i and the relationship between FFA levels and S_i in the insulin resistant populations are required, since there is very little data looking at this important issue.

4.1.2 Insulin Levels

Dietary metabolic studies have documented differences in insulin demand generated by various foods containing the same amount of carbohydrate, depending largely on the type or degree of digestibility of the starch content (90,91,93,94,95,98,130). Foods with a higher carbohydrate digestibility (high GI) generate a higher insulin demand than slower digested carbohydrate rich foods (low GI foods) (5,83,84,130). Lower carbohydrate diets have a lower insulin demand due to the lower content of carbohydrate (53,131). Considering the evidence in the literature, we were initially somewhat surprised at our insulin results. A significant (within group) reduction of mean insulin levels was found on the high carbohydrate high GI diet with no change on the other two diets.

Previous metabolic low GI studies have found reductions in urinary c peptide, an index for insulin secretion, (93,98) but both these studies were short term 2 week metabolic studies and thus these studies might reflect acute rather than the long term effects. Metabolically controlled studies also provide more control and structure than an ad-libitum diet such as ours. The studies also had a GI difference between the high and low GI limbs of 17 (93) on the Wolever study and 41 in the study by Jenkins (98) while in our study the difference was smaller at 6. The GI on the low GI phase was 60 (93) and 63 (98) while our low GI diet was 75. The lower the GI the smaller the effect of the carbohydrate on postprandial glucose and insulin values. (81,103). Thus it is difficult to compare our study results with the study by Jenkins and Wolever.

In our study what we could be observing is the long-term adaptation of the body to a lower GI diet. One could interpret the lack of change in mean insulin levels on the low GI diet to mean that ß-cell responsiveness was enhanced, consistent with the AIR_{glu} result of the FSIGT test, resulting in a maintenance of the insulin levels. Over the long term, the slightly lower glucose levels (see Figure 3.9) over the day from consuming a lower GI diet, may decrease the glucose toxicity effect on the pancreas and result in better insulin secretion (28). Due to the small dietary changes, changes may occur slowly and also may require time to express themselves and thus would not be observed in the acute studies. The reduction in plasma FFA concentration on the low GI diet may have contributed to the preservation of ß-cell function on this diet, since chronic elevation of FFA levels have been shown to reduce insulin secretion (132).

Previous MUFA enriched, low carbohydrate studies show mixed results with regard to the impact on insulin levels. Reduction in insulin levels depends on the level of fat and carbohydrate exchange. Several studies show reductions in post-prandial insulin levels compared to high GI carbohydrate diets but these studies are metabolically controlled with a difference between carbohydrate and fat intake on the 2 phases being 15% or greater (56,57,65,70). This significant reduction in carbohydrate intake results in lower glucose levels and thus less of an insulin demand. In ad-libitum studies the difference in carbohydrate and fat between the high carbohydrate and high MUFA diet are 15 or less %, no change in mean/post-prandial insulin levels were found (11,64,79,127). Ad-libitum studies are less controlled and the dietary change not as great in magnitude or

rigorous as in the metabolically controlled study. Combining both these factors makes it difficult to detect metabolic changes of lesser magnitude (127). Thus in our study with a difference between the fat and carbohydrate intake of 7-11%, like the other ad-libitum studies, there may be to much noise in the system to detect small changes.

Unlike many a metabolic study that shows an increase in insulin levels on a high carbohydrate high GI diet we did not find this (57,58). Instead, we found a reduction in mean plasma insulin levels of 20% after 4 months on the high GI, high carbohydrate diet that was significantly lower than the low GI but not the MUFA diet (see Table 3.7, Figure 3.8). Combining the day long mean insulin results with the FSIGT results which showed that on the high GI diet S_I and AIR_{glu} tended to get worse, one could hypothesis that the reduction in mean insulin levels represents a decrease in the pancreatic responsivity. This reduction manifested itself into a lowering of plasma insulin levels (i.e. progression of the disease). Short-term (3 day) insulin infusion into healthy subjects has shown to reduce pancreatic responsiveness (128) and this may explain in part, why plasma insulin was significantly reduced after the high GI diet.

4.1.3 Glucose and HbA1c

We found no significant changes for mean glucose and HbA1c levels in any of our groups. Although on the low GI diet looking at the change over 16 weeks during the day profile, there was a significant reduction in blood glucose at time 1½ hr by 14% (p=0.01). Previous metabolic and ad-libitum low GI studies have found reductions in glucose (91,98), and HbA1c/fructosamine levels

(89,90,91,92,93,94,95). There may be several reasons for why they found changes and we did not. The studies that found changes were done in type 2 diabetics. In type 2 diabetics, the disease has progressed further than in IGT, and glucose and HbA1c levels are higher in absolute terms than in the IGT population. Bringing type 2 diabetics under better glycemic control by lifestyle and dietary changes would bring about greater reductions in glucose and improvement in insulin secretion (28). For example, improving hyperglycemia in type 2 diabetes decreases the glucotoxic effect of elevated glucose levels on the pancreas and greatly improves fasting and post-prandial glucose levels and increases insulin secretion (28). Improvements in daylong blood glucose control would reflect in a reduction of HbA1c an indicator of long-term blood glucose control. The disease in the IGT group has not progressed to this stage, so the impact of better metabolic control would reflect in smaller changes. In the studies that found a difference, the change in GI lay between 16-40 compared to our study with a difference of 6 and thus our study would show less dramatic effects (81,92). Lastly, since we were anticipating small changes, any change that may have occurred, could be obscured within the laboratory error. The laboratory coefficient of variance for glucose is 2-3% and HbA1c is 5-8% at St. Michael's biochemistry lab.

Previous MUFA enriched, low carbohydrate studies show mixed results with regard to the impact on glucose levels. Several studies show reductions in post-prandial glucose levels compared to high GI, high carbohydrate diets but these studies are metabolically controlled and have a difference between fat and

carbohydrate of ≥15% between the high carbohydrate and high MUFA diet.

Such a large reduction in carbohydrate intake will manifest itself into lower

glucose levels (53). The question is whether this effect is acute or long term.

With higher fat diets, FFA are elevated (70), and the deleterious effects of

elevated FFA levels such as increased hepatic output, decreased peripheral

glucose utilization and uptake (45), and reduced insulin secretion (132) in the

long term, may counteract any acute changes in mean glucose reductions and

result in the deterioration of IGT to diabetes (14,57,66,70). What is interesting is

that even with the reductions in mean glucose levels, no study has yet found an

improvement in HbA1c or fructosamine. This suggests that perhaps sugar levels

may be high at certain times of the day, thus preventing improvements in HbA1c

from occurring. In the ad-libitum studies when the difference between the fat and

carbohydrate intake is ≤15% and the fat intake is actually at a more reasonable

level for long term consumption of 35-40% fat (77), most of the studies show no

change in post-prandial glucose levels (69,79). With a fat intake of 37%, our

study, like the other ad-libitum studies show no change in glucose and HbA1c

levels.

4.1.4 Fasting Blood Glucose and Insulin levels.

FBG and insulin levels remained the same in all three groups in our study.

These results are not surprising since clinical trials testing low GI diets show

mixed results regarding reductions in fasting blood glucose and insulin levels. A

few studies show significant reductions within the groups (89,90) but the other

studies do not. MUFA studies show a similar pattern in their results. In only one

study by Rasmussen (70) was a reduction in FBG found and none of the studies

found a reduction in insulin levels. These results suggest that the reduction in

fasting levels is probably more related to being closely monitored and more

careful with the food intake than with what actually is being consumed. In

addition in our group of subjects, dietary change was small, and fasting glucose

levels were with in the normal range, and due to the small anticipated changes of

FBG, they may have been missed due to laboratory error.

4.1.5 FFAs

A significant marked reduction of 25% (p=0.02) in the meaned daylong

FFA concentrations within the group was found on the low GI group only. FFA

levels also went down on the other two limbs but not significantly. Elevated FFA

levels are thought to play a role in the pathogenesis of diabetes by contributing to

insulin resistance by preventing glucose uptake and carbohydrate oxidation,

reducing stimulation of basal insulin secretion and increasing hepatic glucose

production (14,40). Considering the role that elevated FFA plays in the

pathogenesis of insulin resistance it would seem prudent to find ways to reduce

levels.

As discussed previously we believe that the reduction in FFA

concentration on the low-GI diet may have contributed to the preservation of the

ß-cell function and improved the DI on the low GI diet. Previous studies show

that slowing the rate of glucose absorption by adding soluble fibre (13) or by

sipping glucose slowly (13,108) both methods paradigms for delayed

carbohydrate absorption, prevents the rebounding effect of FFAs and is

associated with improved carbohydrate tolerance to the next meal. Wolever

found similar results in a study with normal test subjects that were given a low GI,

low carbohydrate, high fat breakfast or a low GI high carbohydrate, low fat

breakfast. A marked FFA rebound occurred after breakfast on the low GI, low

carbohydrate high fat meal and resulted in an impaired carbohydrate tolerance to

lunch compared to the low GI high carbohydrate meal. Tsihlias and Wolever

conducted a long-term study in well-controlled diabetics, which showed a

reduction in daylong FFA levels in the high carbohydrate group and an increase

in the low carbohydrate high MUFA group. The high MUFA group had

correspondingly reduced insulin levels and tended to increase fasting and post-

lunch glucose to the greatest extent (129). These observations are all consistent

with the negative effects of FFAs on glucose metabolism and their role in the

pathogenesis of insulin resistance.

Low GI diets are thought to lower FFA levels because low GI foods are

slowly absorbed, produce less rapid of a rise in glucose and a smaller insulin

response which than prevents the undershooting of glucose and subsequent

release of counter-regulatory hormones that may result in the release of FFA

(81,103) when compared to high GI or more quickly absorbed carbohydrates.

The beneficial effects of low GI diets may also be the results of increased

carbohydrate entry into the colon that may result in higher colonic acetate

production that has been shown to reduce plasma FFA levels (106,107,133). An

increase in SCFA production has also been shown to decrease hepatic

gluconeogenesis and thus reduces fasting and post-prandial blood glucose levels

and improves glucose tolerance (107). Further long-term dietary studies need to be conducted in the insulin resistant population to determine the role of FFAs.

4.1.6 Cholesterol

One of the main arguments against a high carbohydrate diet is that high carbohydrate diets are thought to enhance the risk for the development of heart disease by raising TGs and lowering HDL levels. Instead, a high MUFA low carbohydrate diet is recommended because it counters the negative aspects of a high carbohydrate diet (11,56,57,64,66). Our study found no significant changes in the lipid profile on any of the diets. There may be several reasons for this. No improvement in TG or HDL was observed on the MUFA enriched diet because the reduction in carbohydrate and increase in fat was relatively small compared to the studies that found changes. Studies that have shown lipid improvements usually had greater than 15% difference between the carbohydrate intake on the high carbohydrate versus the low carbohydrate, high MUFA and were metabolically controlled (56,57,64,66,67). No differences were found in non-metabolic studies when the difference in carbohydrate level between the high MUFA and high carbohydrate has been equal to or less than 15% (70,79,127). In an analysis of the studies that were available, Wolever found that the magnitude of the change in TGs is directly related to the amount of carbohydrate replaced. The greater the carbohydrate intake the greater the rise in TG levels (53,77). Other studies have noted that if carbohydrate intake is gradual, the impact on TGs is minimized (77). Since our study was 16 weeks in length any transient changes may have been missed. The TG rising potential of

carbohydrates may also depend on whether high or low GI foods are consumed. Metabolic studies using low GI foods have either shown an improvement in one or more of plasma cholesterol variables such as TG, LDL, cholesterol and HDL (92,94,95,97,100) or no change (90,91). Thus our study results are similar to many other studies found in the literature.

4.1.7 Diet Records

One of the purposes of this study was to determine whether dietary advice could be followed on an outpatient basis and whether improvement in clinical outcomes could be found. There are some who suggests that adding low GI foods reduces food choice and is difficult to incorporate into the diet (105). The dietary instruction that was given was not complex and the subjects (88) considered the diet practical and acceptable. We were able to reduce the GI by 6 with an accompanying reduction in fat of 3%, in particular saturated and monounsaturated fat. A significant increase in fibre was also found. This finding is not unique. In another ad-libitum study the low GI group also found an accompanying reduction in fat and increase in fibre (89). The reasons for finding these changes could be that low GI foods tend to be low fat and/or high in fibre and the low GI foods may have displaced high fat foods in the diet (89). On the MUFA, low carbohydrate diet, fat intake significantly increased by 5% of which all came from an increase in MUFA showing that people followed the dietary advise that was given to them. Dietary carbohydrate went down by 4% and protein by 2%. Although there was an increase in fat intake on the MUFA diet, we did not achieve the 10% increase in fat that we had prescribed to the subjects. This may

be due to inaccurate recording of food records and difficulty in consuming the prescribed quantity of extra olive oil in the diet.

Our dietary analysis shows that the macronutrient profile of the three groups was not significantly different from each other at week 0 and that the changes to their dietary intake occurred after dietary advice was given and maintained for the duration of the study (Table 3.4,3.5,3.6). The change in energy intake on the MUFA group was significantly greater than the other two dietary groups. According to the food records the MUFA group increased their energy intake by approximately 370 kcal extra per day. Considering this increase, one would expect a weight gain of greater than 5 kg to have occurred over the 4 months. This did not occur. This increase in energy level does not make sense because the group experienced a non-significant weight gain of 0.2 kg and no increase in cholesterol levels. Daily walking of 1 hr would be required to expend 370 kcal, which would have also improved S_I (51,134). S_I did not improve and no significant change in exercise level was noted in this or any other group. On average this group was asked to consume an additional 5 tsp of fat (225 kcal) that could in part explain part of the increase in energy found on the food records. Thus this difference appears to be more of a reporting error rather than an actual error in energy level. Underreporting of dietary intakes remains one of the hurdles in the disclosure of valid habitual estimates of food eaten (135,136,137,138). While traditional dietary assessment measures, such as food records, may be inaccurate when it comes to the quantitative aspects (ie energy intake is underestimated), Lissner et al., showed that the assessment measures

may be more adept at getting a picture of the qualitative aspects (ie percent intake) versus actual intake (135). Thus, we believe that the information that was obtained from the food records gave a good impression of the nutrient intake of the three different groups over the study period.

4.2 Why we did not see the Expected Changes

When we set out on this project, our initial hypothesis was that a low GI high carbohydrate would reduce postprandial insulin responses and improve insulin sensitivity when compared to a high GI high carbohydrate, and that both of these diets would improve insulin sensitivity better than the high MUFA diet.

Perhaps significant changes were not observed in our study because our population was not as homogeneous as it could have been, thus making it difficult to see changes. Initially when planning the study, an assumption was made, based on the literature available at the time that suggested that all IGT candidates were hyperinsulinemic. This has turned out not to be the case. Lind et al. showed in their study that IGT is a heterogeneous disorder with different combination of insulin secretion and insensitivity impairments (124). In our study, we found similar results in that some participants were not hyperinsulinemic, but rather had a low first phase insulin secretion and hypoinsulinemic. Therefore, to overcome this problem and obtain a more homogeneous group, candidates should have been screened for IGT and fasting insulin levels and only participants who were IGT and hyperinsulinemic should have been included. Although not significantly different at baseline, fasting blood glucose levels were not as well balanced as they could have been. Studies show that higher fasting

and post-prandial blood glucose values are associated with higher risk of developing type 2 diabetes (18,21,139). Therefore, when randomizing, in addition to taking BMI, age and sex into consideration, fasting and 2 hour post-prandial values should have been taken into account.

Another problem was in our initial power analysis calculation. The initial power analysis based the estimation of the coefficient of variance (CV) for insulin sensitivity on a normal population rather than an insulin resistant population since that information was not available. In the normal population the CV was determined to be 20% (117). In actuality, in our IGT population, it turned out to be greater at 30%. Therefore, given the actual CV a larger sample size would have been needed to give the study more power to detect differences.

We also choose to conduct an ad-libitum study rather than a metabolically controlled study, and thus a larger sample size may have been required in order to see changes. Ad-libitum outpatient studies may not allow for the detection of metabolic changes of a lesser magnitude since patients are not as well controlled and dietary manipulation can not be as great or exact as in studies conducted on metabolic wards (127). In addition food records are known to underestimate energy and portion sizes leading to another degree of error (135,136,137,138). On the other hand, the benefits of an ad-libitum study is that the results reproduce more closely situations encountered in medical practice, allowing for estimations of what will happen when conclusion drawn for more experimental situations are applied to the actual management of patients (127).

4.3 Future Investigations

Our study was unable to answer the question regarding the effect of the quantity and quality of carbohydrate on insulin sensitivity. Considering the amount of debate surrounding the issue and lack of studies comparing the effect of the different dietary treatments, it is an important question to answer and thus further studies are warranted. In addition to looking at the IGT population, similar studies should be conducted in other insulin resistant populations such as the obese and type 2 diabetics to determine if similar or different effects are observed. In addition to looking at the three diet phases tested in this study, a low GI low carbohydrate, high MUFA phase should also be included. Individually both of these dietary components show positive benefits on glucose and cholesterol metabolism (11,12). According to an acute study by Wolever et al., this combination resulted in the highest rebounding of FFAs after breakfast, which if maintained, may cause a worsening of insulin sensitivity (13,14). Thus, it would be interesting to see the long-term effects of a low GI low carbohydrate high MUFA diet on insulin sensitivity.

Following a metabolic diet, using a crossover versus a parallel design, and having tighter inclusion criteria in future studies may help to decrease variability and make differences more obvious to detect.

Our study was one of the longest dietary studies measuring the impact of diet on insulin sensitivity. To better compare our results with acute studies, a study should be conducted which measures insulin sensitivity and other biochemical indices of glucose and cholesterol metabolism acutely (after 1

month) and over the long term. The body may require time to adapt to a new dietary intake, and thus the changes observed at one month may be different than after 4 months. For example, the full effect of colonic adaptation (ie short chain fatty acid production) to an increase in fibre may take time to occur. The negative impact of a high GI high carbohydrate diet on triglyceride and HDL levels often seen during an acute study may be transitional and by 4 months may no longer occur (77).

Support for dietary modification would be greater if a mechanism of action could be elucidated. Proposed mechanisms of action for low GI diets include increased colonic fermentation and slowed absorption (12). Therefore, measuring short chain fatty acids a by -product of colonic fermentation, would be important. The mechanism of action, behind the beneficial effects of a high MUFA diet has yet to be explained.

Measuring the impact of diet on LDL and HDL particle size would also be interesting since some studies show that a high GI high carbohydrate diet is associated with smaller denser LDL and HDL particles while a high MUFA diet does not have this effect (120). Smaller, denser LDL particles are a risk factor for heart disease (10). The impact of a low GI high carbohydrate diet on LDL and HDL particle size is unknown.

4.4 Conclusion

High carbohydrate diets are considered deleterious in the dietary management of type 2 diabetes because they accentuate the metabolic abnormalities of insulin resistance. But little consideration has been given to the

quality of the carbohydrate. Our hypothesis is that a low GI high carbohydrate diet would improve insulin sensitivity and the metabolic profile of subjects with IGT compared to a high GI high carbohydrate and high MUFA low carbohydrate diet. Our study results support our hypothesis in that it shows that a low GI high carbohydrate diet improved the DI, reduced FFA levels, maintained plasma insulin and had no deleterious effects on blood cholesterol levels. If these changes were sustained over the long term, the expected result would be a reduced rate of progression toward the development of type 2 diabetes. We were able to find these changes with modest changes to the dietary intake of the study subjects. We believe our study contributes to the current knowledge in the literature and lends support for the beneficial effects of adding low GI foods to a high carbohydrate diet to improve glycemic control in insulin resistant individuals.

Chapter 5.0 References

1. Chiasson JL, Gomis R, Hanefel M, Josse RG, Karasik A, Laakso M, et al The STOP-NIDDM trial. Diabetes Care 1998;21:1720-25.

2. Goke B. Implications of blood glucose, insulin resistance and β-cell function in impaired glucose tolerance. Diabetes Research and Clinical Practice 1998;40(suppl):S15-S20.

3. Meltzer S, Leiter L, Daneman D, Gerstein HC, Lau D, Ludwig S, et al. 1998 Clinical practice guidelines for the management of diabetes in Canada. CMAJ 1998;159(8 suppl):S1-S29.

4. Alberti KGMM. Impaired glucose tolerance: what are the clinical implications? Diabetes Research and Clinical Practice 1998;40(suppl):S3-S8.

5. Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willet WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. JAMA 1997;227:472-77.

6. Feskens EJM, Loeber JG, Kromhout D. Diet and physical activity as determinants of hyperinsulinemia: The Zutphen Elderly Study. Am J Epidemiol 1994;140:350-60.

7. Swinburn BA, Boyce VL, Bergman RN, Howard BV, Bogardus C. Deterioration in carbohydrate metabolism and lipoprotein changes induced by modern, high fat diet in Pima Indians and Caucasians. J Clin Endocrinol Metab 1991;73:156-65.

8. Marshall JA, Hoag S, Shetterly S, Hamman RF. Dietary fat predicts conversion from impaired glucose tolerance to NIDDM. The San Luis Valley diabetes study. Diabetes Care 1994;17:50-56.

9. Marshall JA, Bessesen DH, Hamman RF. High satuated fat and low starch and fibre are associated with hyperinsulinaemia in a non-diabetic population: The San Luis Valley diabetes study. Diabetologia 1997;40:430-38.

10. Jeppesen J, Schaaf P, Jones C, Zhou-MY, Chen I, Reaven GM. Effects of low-fat, high-carbohydrate diets on risk factors for ischemic heart disease in postmenopausal women. Am J Clin Nutr 1997;65:1027-33.

11. Garg A. High-monunsaturated –fat diets for patients with diabetes mellitus: a meta-analysis. Am J Clin Nutr 1998;67:(suppl) 577S-82S.

12. Wolever TMS. Glycaemic index revisited. In *The Diabetes Annual/7*. Marshall SM, Home PD, Alberti KGMM, Krall Lp, Eds. New York, Elsevier, 1993;258-72.

13. Wolever TMS, Bentum-Williams A, Jenkins DJA. Physiological modulation of plasma free fatty acid concentration by diet. Diabetes Care 1995;18:963-70.

14. Boden G. Role of fatty acids in the pathogenesis of insulin resistance in NIDDM. Diabetes 1997;46:3-10.

15. American Diabetes Association. Implication of the United Kingdom Prospective Diabetes Study Diabetes Care 1998;21:2180-84.

16   The Diabetes Control and Complications Trial Research Group. The effect

of intensive treatment of diabetes on the development and progression of

long-term complications in insulin-dependent diabetes mellitus. N Engl J

Med 1993;329-977-86.

17.   Harris MI, Flegal KM, Cowie CC, Eberhardt, MS, Golstein DE, Little RR, et

al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose

tolerance in U.S. Adults. Diabetes Care 1998;21:518-24.

18.   Edelstein SL, Knowler WC, Bain RP, Andres R, Barrettt-Connor EL,

Dowse GK et al. Predictors of progression from impaired glucose

tolerance to NIDDM an analysis of six prospective studies. Diabetes

1997;46:701-10.

19.   National Diabetes Data Group. Classification and diagnosis of diabetes

mellitus and other categories of glucose intolerance. Diabetes

1979;28:1039-57.

20.   Expert Committee on Diabetes Mellitus, World Health Organization. WHO

Technical Report Series 646. Geneva: WHO;1980:1-80.

21.   Chiasson JL. Impaired glucose tolerance: a risk factor for type 2 diabetes

and cardiovascular disease. Diabetes Research and Clinical Practice

1998;40(suppl):S1-S2.

22.   Saad, MF, Knowler WC, Pettitt DJ, Nelson RG, Mott DM, Bennett PH. The

natural history of impaired glucose tolerance in the Pima Indians. N Engl J

Med 1988;319:1500-06.

23. Golay A, Felber JP. Evolution from obesity to diabetes. Diabetes and Metabolisme 1994;20:3-24.

24 Jarrett RJ, McCartney P, Keen H. The Bedford survey: ten year mortality rates in newly diagnosed diabetics, borderline diabetics and normoglycemic controls and risk indices for coronary heart disease in borderline diabetics. Diabetologia 1982;22:79-84.

25. Balkau B, Shipley M, Jarrett RJ, Pyorala K, Pyorala M, Fohan A, Eschwege E. High blood glucose concentration is a risk factor for mortality in middle-aged non-diabetic men. Diabetes Care 1998l;21:360-67.

26. Singer De, et al. Assoication of HbA1c with prevalent cardiovascular disease in the original cohort of the Framingham Heart Study. Diabetes 1992;41:202-208.

27. O'Rahilly S, Hattersley A, Vaag A, Gray H. Insulin resistance as the major cause of impaired glucose tolerance: a self-fulfilling prophesy? Lancet 1994;344585-89.

28. DeFronzo RA, Bonadonna RC, Ferrannini E. Pathogenesis of NIDDM. Diabetes Care 1992;15:318-68.

29. Reaven GM, Pathophysiology of insulin resistance in human disease. Physiological reviews 1995;75:473-86.

30. Zimet PZ. Hyperinsulinemia-how innocent a bystander? Diabetes Care 1993;16(suppl 3):56-70.

31. Smolar EN. The Insulin Resistance Syndrome. Comprehensive Therapy 1997;23:237-43.

32. Zimmet P, Dowse G, Bennett P. Hyperinsulinaemia is a predictor of non-insulin-dependent diabetes mellitus. Diabete and Metabolisme 1991;17:101-08.

33. Ferrannini E. Insulin resistance versus insulin deficiency in non-insulin-dependent diabetes mellitus: problems and prospects. Endocrine reviews 1998;19:477-90.

34. Reaven GM. Role of insulin resistance in human disease. Diabetes 1988;37:1595-607.

35. Kosaka K, Kuzuya T, Akanuma Y, Hagura R. Increase in insulin response after treatment of over maturity onset diabetes mellitus is independent of the mode of treatment. Diabetologia 1980;18:23-28.

36. Rossetti L, Shulman GI, Zaqalcih W, DeFronzo RA. Effect of chronic hyperglycemia on in vivo insulin secretion in partially pancreatectomized rats. J Clin Invest 1987;80:1037-44.

37. Leahy JI, Bonner-Weir S, Weir GC: Minimal chronic hyperglycemia is critical determinant of impaired insulin secretion after an incomplete pancreatectomy. J Clin Invest 1988;81:1407-14.

38. Leahy JL, Bonner-Weir S, Weir GC. Abnormal glucose reglualtion of insulin secretion in models of reduced β-cell mass. Diabetes 1984;33:667-73.

39. Yki-Jarvinen H, Helve E, Koivisto VA. Hyperglycemia decreases glucose uptake in type I diabetes. Diabetes 1987;36:892-96.

40.	Boden G. Free fatty acids, insulin resistance, and type 2 diabetes mellitus. Proceedings of the Association of American Physicians 1999;111:241-48.

41.	Mayes PA. Lipid transport and storage in Harper's Biochemistry 24th edition. Murray RK, Granner DK, Mayes PA, Rodwell VW editors. 1996, Appleton & Lange publishers: Stamford, Connecticut. Pages:254-270.

42.	Boden, G. Fatty acids and insulin resistance. Diabetes Care 1996;19:394-95.

43.	Randle PJ Hales CN, Garland PB, Newholme EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. The Lancet 1963;I:785-89.

44.	Boden G, Chen X, Iqbal N. Acute lowering of plasma fatty acids lowers basal insulin secretion in diabetic and nondiabetic subjects. Diabetes 1998;47:1609-18.

45.	Boden G, Chen X, Ruiz J, White JV, Rossetti L. Mechanisms of fatty acid induced inhibition of glucose uptake. J Clin Invest 1994;93:2438-46.

46.	Saloranta C, Koivisto V, Widen E, Falholt K, DeFronzo R, Harkonen M, Groop L. Cotnribution of muscle and liver to glucose-fatty acid cycle in humans. Am J Physiol 1993;264:E599-E605.

47.	Boden G, Jadali F. Effects of lipid on basal carbohydrate metabolism in normal men. Diabetes 1991;40:686-92.

48.	Dobbins RL, Chester MW, Daniels MB, McGarry JD, Stein DT. Circulating fatty acids are essential for efficient glucose-stimulated insulin secretion after prolonged fasting in humans. Diabetes 1998;47:1613-18.

49. Boden G, Chen X. Effects of fatty acids and ketone bodies on basal insulin secretion in type 2 diabetes. Diabetes 1999;48:577-83.

50. Pan XR, Li GW, Wang JX, Yang WY, An ZX, Hu ZX, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. Diabetes Care 1997;20:537-44.

51. Yamanouchi K. Shinozaki T, Chikada K, Nishikawa T, Ito K, Shimizu S et al. Daily Walking Combined with Diet Therapy is a useful means for obese NIDDM patients not only to reduce body weight but to improve insulin sensitivity. Diabetes Care 1995;18:775-78.

52. Chiasson JL, Josse RG, Leiter LA, Mihic M, Nathan DM, Palmason C et al. The effect of acarbose on insulin sensitivity in subjects with impaired glucose tolerance. Diabetes Care 1996;19:1190-93.

53. Wolever TMS. Dietary recommendations for diabetes: high carbohydrate or high monounsaturated fat? Nutr Today 1999;34:73-77.

54. Franz JM, Horton ES, Bantle JP, Beebe CA, Brunzell JD, Coulston AM, et al. Nutrition Principles for the management of diabetes and related complications. Diabetes Care 1994;17:490-517.

55. American Diabetes Association: Nutritional recommendations and principles for individuals with diabetes mellitus 1986. Diabetes Care 1987;10:126-32.

56. Garg A, Grund SM, Unger RH. Comparison of effects of high and low carbohydrate diets on plasma lipoproteins and insulin sensitivity in patients with mild NIDDM. Diabetes 1992;41:1278-85.

57. Garg A, Bantle JP, Henry RR, Coulston AM, Griver KA, Raatz SK, et al. Effects of varying carbohydrate content of diet in patients with non-insulin-dependent diabetes mellitus. JAMA 1994;271:1421-28.

58. Brunzell JD, Lerner RI, Hazzard WR, Prote D Jr. Bierman EL. Improved glucose tolerance with high carbohydrate feeding in mild diabetes. N Engl J Med 1971;284: 521-24.

59. O'Dea K, Traianedes K, Ireland P, Niall M, Sadler J. the effects of diet, differing in fat, carbohydrate, and fiber on carbohydrate and lipid metabolism in type II diabetes. J Am Diet Assoc 1989;89:1076-86.

60. Hollenbeck CB, Coulston AM. Effects of dietary carobhdyrate and fat intake on glucose and lipoprotein metabolism in individuals with diabetes mellitus. Diabetes Care 1991;14:774-83.

61. Steiner G. Intermediate-density lipoptroteins, diabetes and coronary artery disease. Diabetes Research and Clinical Practice. 1998;40Suppl:S29-S33.

62. Pietzsch J, Julius U, Nitzsche S, Hanefeld M. In vivo evidence for increased apolipoprotein A-1 catabolism in subjects with impaired glucose tolerance. Diabetes 1998;47:1928-34.

63. Garg A. Dietary monounsaturated fatty acids for patients with diabetes mellitus. Annals New York Academy of Science. 199-206.

64. Campbell LV, Marmot PE, Dyer JA, Borkman M, Storlien LH. The high-monunsaturated fat diet as a practical alternative for NIDDM. Diabetes Care 1994;17:177-82.

65. Parillo M, Giacco R, Ciardullo Av, Rivellese AA, Riccardi G. Does a high-carbohydrate dit have different effects in NIDDM patients treated with diet alone or hypoglycaemic drugs. Diabetes Care. 1996;19:498-500.

66. Garg A, Bonamone A, Grundy SM, Zang A, Unger RH. Comparison of a high-carbohydrate diet with a high-monunsaturated-fat diet in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 1988;319;829-34.

67. Rivellese AA, Giacco R, Genovese S, Patti L, Marotta G, Pacioni D, et al. Effects of changing amount of carbohydrate in diet on plams lipoproteins and apolipoprotiens in type II diabetic patients. Diabetes Care 1990;13:446-48.

68. Parillo M, Rivellese AA, Ciardullo AV, Capaldo B, Giacco A, Genoves S, Riccardi G. A high-monounsaturated-fat/low-carbohydrate diet improves peripheral insulin sensitivity in non-insulin-dependent diabetic patients. Metabolism 1992;41:1373-78.

69. Lerman-Garber I, Ichazo-Cerro S, Zamora-Gonzalez J, Cardoso-Saldana G, Posdas-Romero C. Effect of a high-monunsaturated fat diet enriched with avocado in NIDDM patients. Diabetes Care 1994; 17:311-315.

70. Rasmussen OW, Thomsen C, Hansen KW, Vesterlund M, Winther E, Hermansen K. Effects on blood pressure, glucose and lipids levels of a high-monounsaturated fat diet compared with a high carbohydrate diet in NIDDM subjects. Diabetes Care 1993;16:1565-71.

71.   Franz JM, Horton ES, Bantle JP, Beebe CA, Brunzell JD, Coulston AM, et al. Nutrition Principles for the management of diabetes and related complications. Diabetes Care 1994;17:490-517.

72.   The Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the second report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatmen panel II). JAMA 1993;269:3015-23.

73.   Frohlich MD, Fodor G, McPerson R, et al. Rationale for and outline of the recommendations of the working group on hypercholesterolemia and other dyslipidemias: interm report. Dyslipidemia working group of health Canada. Can J Cardiol 1998;14(suppl A):17a-21a.

74.   Health and Welfare Canada. Nutrition Recommendations: The report of the scientific review committee. Ottawa: Minister of supply and services Canada; 1990.

75.   Dietary guideline for Americans, 3rd edition. US department of agriculture and US department of health and human services. US GPO. 1990 273-930.

76.   Jenkins DJA, Wolever TMS, Vidgen E, Kendall CWC, Ranson TPP, Mehling CC et al. Effect of psyllium in hypercholesterolemia at two monounsaturated fatty acid intakes. AM J Clin Nutr 1997;65:1524-33.

77.   Parks EJ, Hellerstein MK. Carbohydrate-induced hypertriacylglycerolemia: historical perspective and review of biological mechanism. Am J Clin Nutr 2000;71:412-33.

78.   Gonzelez C, Stern MP, Mitchell BD, Valdez RA, Haffner SM, Perez BA. Clinical characteristics of type II diabetic subjects consuming high versus low carbohydrate diets in Mexico City and San Antonio, Texas. Diabetes Care 1994;17:397-404.

79.   Luscombe ND, Noakes M, Clifton PM. Diets high and low in glycemic index versus high monounsaturated fat diets: effects on glucose and lipid metabolism in NIDDM. Eur J Clin Nutr 1999;53:473-78.

80.   Crapo PA, Reaven G, Olevsky J. Postprandial plasma-glucose and – insulin responses to different complex carbohydrates. Diabetes 1977;26:1178-83.

81.   Wolever TMS. The glycemic index. World Rev Nutr Diet 1990;62:120-85.

82.   Wolever TMS. Glycemic index: flogging a dead horse? Diabetes Care 20:452-56.

83.   Wolever TMS, Jenkins DJA,Collier GR, Lee R, Wong GS, Josse RG. Metabolic response to test meals containing different carbohydrate foods: 1. Relationship between rate of digestion and plasma insulin response. Nutr Res 1988;8:573-81.

84.   Jenkins DJA, Ghafari H, Wolever TMS, Taylor RH, Jenkins AL, Barker HM, Fielden H. Relationship between rate of digestion of foods and post-prandial glycaemia. Diabetologia 1982;22:450-55.

85. Jenkins DJA, Wolever TMS, Thorne MJ, Jenkins AL, Wong GS, Josse RG Csima A. The relationship between glycemic response, digestibility, and factors influencing the dietary habits of diabetics. Am J Clin Nutr 1984;1175-91.

86. Jenkins DJA, Jenkins AL, Wolever TMS, Vuksan V, Rao AV, Thompson LU, Josse RG. Low glycemic index: lente carbohydrates and physiological effects of altered food frequency. Am J Clin Nutr 1994;59(suppl):S706-S09.

87. Salmeron J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ et al. Dietary fiber, glycemic load, and risk of NIDDM in men. Diabetes Care 1997;20:545-50.

88. Brand-Miller J. Foster-Powell K. Diets with a low glycemic index: from theory to practice. Nutr Today 1999;34:64-71.

89. Frost G, Wilding J, Beecham J. Dietary advice based on the glycaemic index improves dietary profile and metabolic control in type 2 Diabetic patients. Diabetic Medicine 1994;11:397-401.

90. Jenkins DJA, Wolever TMS, Buckley G, Lam KY, Giudici S, Kalmusky J, et al. Low-glycemic-index starchy foods in the diabetic diet. Am J Clin Nutr 1988;48:248-54.

91. Brand JC, Colagiuri S, Crossman S, Allen A, Roberts DCK, Truswell AS. Low-glycemic index foods improve long-term glycemic control in NIDDM. DiabetesCare 1991;14:95-101.

92.   Fontvieille AM, Acousta M, Rizkalla SW, Bornet F, David P, Letanoux, M,

      et al. A moderate switch from high to low glycaemic-index foods for 3

      weeks improves the metabolic control of type 1 (IDDM) diabetic subjects.

      Diab Nutr Metab 1988;1:139-43.

93.   Wolever TMS, Jenkins DJA, Buckley GC, Wong, GS, Josse RG.

      Beneficial effect of a low glycaemic diet in type 2 diabetics. Diabetic

      Medicine 1992;9:451-58.

94.   Fontvieille AM, Rizkalla SW, Penfornis A, Acosta M, Bornet FRJ, Slama

      G. The use of low glycaemic index foods improves metabolic control of

      diabetic patients over fibre weeks. Diabetic Medicine 1992;9:444-50.

95.   Wolever TMS, Jenkins DJA, Vuksan V, Jenkins AL, Wong GS, Josse RG.

      Beneficial effects of low-glycemic index diet in overweight NIDDM

      subjects. Diabetes Care 1992;15:562-64.

96.   Calle-Pascual AL, Gomez V, Leon E, Bordiu E. Foods with a low glycemic

      index do not improve glycemic control of both type 1 and type 2 diabetic

      patients after one month of therapy. Diabete & Metaoblisme 1988;14:629-

      33.

97.   Jenkins DJA, Wolever TMS, Kalmusky J, Giudici S, Giordano C, Wong GS

      et al. Low glycemic index carbohydrate foods in the management of

      hyperlipidemia. Am J Clin Nutr 1985;42:604-617.

98.   Jenkins DJA, Wolever TMS, Collier G, Ocana A, Rao AV, Buckley G et al.

      Metabolic effects of a low-glycemic-index diet. Am J Clin Nutr

      1987;46:968-75.

99.   Lee BM, Wolever TMS. Effect of glucose, sucrose and fructose on plasma glucose and insulin responses in normal humans: comparison with white bread. Eur J Clin Nutr 1998;52:924-28.

100. Wolever TMS, Vuksan V, Katzman Relle L, Jenkins AL, Josse RG, Wong GS, Jenkins DJA. Glycaemic index of fruits and fruit products in patients with diabetes. Inter J Fd Sc Nutr 1993;43:205-12.

101. Jenkins DJA, Wolever TMS, Taylor RH, Griffiths JC, Krzeminska K, Lawrie JA, et al. Slow release carbohydrate improves second meal tolerance. Am J Clin Nutr 1982;35:1339-46.

102. Frost G, Keogh B, Smith D, Akinsnya K Leeds A. The effect of low-glycemic carbohydrate on insulin and glucose response in vivo and in vitro in patients with coronary heart disease. Metabolism 1996;45:669-72.

103. Frost G, Leeds A, Trew G, Margara R, Dornhorst A. Insulin sensitivity in women at risk of coronary heart disease and the effect of a low glycemic diet. Metabolism 1998;47:1245-51.

104. Beebe C. Diets with a low glycemic index: not ready for practice yet! Nutr Today 1999;34:82-86.

105. Franz MJ. In defense of the American Diabetes Association's recommendations on the glycemic index. Nutr Today 1999;34:78-81.

106. Wolever TMS, Spadafora P, Eshuis H. Interaction between colonic acetate and propionate in humans. Am J Clin Nutr 1991;53:681-87.

107. Thorburn A, Muir J, Proietto J. Carbohydrate fermentation decreases hepatic glucose output in healthy subjects. Metabolism 1993;42:780-85.

108. Jenkins DJA, Wolever TMS, Ocana AM, Vuskan V, Cunnane SC, Jenkins M et al. Metabolic effects of reducing rate of glucose ingestion by single bolus versus continuous sipping. Diabetes 1990;39:775-81.

109. Jenkins DJA, Ocana AM, Jenkins AL, Wolever TMS, Vuskan V, Katzman L, et al. Metabolic advantages of spreading the nutrient load: effects of increased meal frequency in non-insulin-dependent diabetes. Am J Clin Nutr 1992;55:461-67.

110. Jenkins DJA, Wolever TMS, Vuskan V, Brighenti F, Cunnane SC, Rao AV, et al. Nibbling versus gorging: metabolic advantage of increased meal frequency. N Eng J Med 1989;321:929-34.

111. U.S. department of health and human services. The lipid research clinics population studies data book. Volume 11. The prevalence study—nutrient intake. September 1982. NIH Pulbication No. 82-2014.

112. US agricultural research service. Composition of foods. Agriculture handbook no. 8. Washington, DC: US Department of Agriculture, 1992.

113. Wolever TMS, Nguyen P-M, Chiasson J-L, et al. Determinants of diet glycemic index calculated retrospectively from diet records of 342 individuals with non-insulin-dependent diabetes mellitus. Am J Clin Nutr 1994;59:1265-69.

114. Finegood DT, Hramiak IM, Duprè J. A modified protocol for estimation of insulin sensitivity with the minimal model of glucose kinetics in patients with insulin-dependent diabetes. J Clin Endo Metab 1990;70:1538-49.

115. Pacini G, Bergman RN. MINMOD: A computer program to calculate insulin sensitivity an dpacreatic responsivity from the frequently sampled intravenous glucose tolerance test. Comp Meht Prog Biomed 1986;23:113-22.

116. Snedecor GW, Cochran WG. Statistical Mehtods. 7th Edition. The Iowa State Unviersity Press, 1980:274-79.

117. Ferrari P, et al. Reproducibility of insulin sensitivity measured by the minimal model method. Diabetologia 1991;34:527-30.

118. Daly ME, Vale C, Walker M, Alberti KGMM, Mathers JC. Dietary carbohydrates and insulin sensitivity: a review of the evidence and clinical implications. Am J Clin Nutr 1997;66:1072-85.

119. Borkman M, Campbell LV, Chisholm DJ, Storlien LH. Comparison of the effects on insulin sensitivity of high carbohydrate and high fat diets in normal subjects. J Clin Endocrinol Metab 1991;72:432-37.

120. Reaven GM. Do high carbohydrate diets prevent the development or attenuate the manifestations (or both) or syndrome X? A view point strongly against. Current Opinion in Lipidology 1997;8:23-7.

121. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward K, Beard JC, Palmer JP, Porte Jr D. Quantification of the relationship between insulin sensitivity and β-cell function in human subjects. Diabetes 1993;42:1663-72.

122. Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man. Measurement of insulin sensitivity

and β-cell glucose sensitivity from the response to intravenous glucose. J Clin Invest 1981;68:1456-67.

123.   Hollenbeck C, Reaven GM. Variations in insulin-stimulated glucose uptake in healthy individuals with normal glucose tolerance. J Clin Endocrinol Metab 1987;64:1169-73.

124.   Lind L, Lithell H, Pollare P, Ljunghall S. On the diversity of insulin secretion and sensitivity in subjects with impaired glucose tolerance. Exp Clin Endocrinol 1993;101:311-14.

125.   Kiens B, Richter EA. Types of carbohydrate in an ordinary diet affect insulin action and muscle substrates in humans. Am J Clin Nutr 1996;63:47-53.

126.   Hughes VA, Fiatarone MA, Fielding RA, Ferrara CM, Elahi D, Evans WJ. Long-term effects of a high-carbohydrate diet and exercise on insulin action in older subjects with impaired glucose tolerance. Am J Clin Nutr 1995;62:426-33.

127.   Bonanome A, Visona A, Lusiani L, Beltramello G, Confortin L, Biffanti S et al. Carbohydrate and lipid metabolism in patients with non-insulin-dependent diabetes mellitus: effects of a low-fat, high-carbohydrate diet vs a diet high in monounsaturated fatty acids. Am J Clin Nutr 1991;54:586-90.

128.   Del Prato S, Leonetti F, Simonson DC, Sheehan P, Matsuda M, DeFronzo RA. Effect of sustained physiologic hyperinsulinaemia and

hyperglyceaemia on insulin secretion and insulin sensitivity in man.
Diabetolgia 1994;37:1025-35.

129. Tsihlias EB. Comparison of low and high fibre breakfast cereals and a high monounsaturated fat diet without breakfast cereals in the dietary management of Type 2 Diabetes. Department of Nutritional Sciences University of Toronto. MSc Thesis 1999. Page 61.

130. Wolever TMS, Bolongnesi C. Source and amount of carbohydrate affect postprandial glucose and insulin in normal subjects. J Nutr 1996;126:2798-806.

131. Wolever TMS, Jenkins DJA, Vuksan V, Katzman L, Jenkins AL, Josse RG. Variation in meal fat does not affect the relative blodd glucose response of spaghetti in subjects with type 2 diabetes. Diab Nutr Metab 1992;5:191-97.

132. Zhou Y-P, Grill VE. Long-term exposure of rat pancreatic islets to fatty acids inhibits glucose-induced insulin secretion and biosynthesis through a glucose fatty acid cycle. J Clin Invest 1994;93:870-76.

133. Jenkins DJA, Cuff D, Wolver TMS, Knowland D, Thompson LU, Cohen Z, Prokipchuk E. Digestibility of carbohydrate foods in an ileostomate: relationship to dietary fiber, in vitro digestibility, and glycemic response. Am J Gastroenterol 1987;82:709-17.

134. Depres JP, Lamarche B. Low-intensity endurance exercise training, plasma lipoproteins and the risk of coronary heart disease. J Int Med 1994;236:7-22.

135. Lissner L, Lindroos AK. Is dietary underreporting macronutrient-specific? Eur J Clin Nutr 1994;48:453-54.

136 Macdiarmid JI, Blundell JE. Dietary under-reporting: what people say about recording their food intake. Eur J Clin Nutr 1997;51:310-03.

137. Heymsfield SB, Darby PC, Muhlheim LS, Gallagher D, Wolper C, Allison DB. The calorie: myth, measurement, and reality. Am J Clin Nutr 1995; 62(suppl):1034S-41S.

138. Lichtman SW, Pisarska K, Berman ER, Pestone M, Dowling H, Offenbacher E, et al. Discrepancy between self-reported and actual cloric intake and exercise in obese subjects. N Engl J Med 1992;327:1893-98.

139. Weyer C, Bogardus C, Pratley RE. Metabolic characteristics of individuals with impaired fasting glucose and/or impaired glucose tolerance. Diabetes 1999;48:2197-2203.

Appendix A

Consent Form

Consent Form

Effect of high and low glycemic index versus high monounsaturate fat diet on insulin sensitivity in subjects with impaired glucose tolerance.

Investigators:	Thomas MS Wolever, MD, PhD	978-5556 or 867-7473
	David JA Jenkins MD. DSc	867-7477
	Robert G Jesse, MD	864-5293
	Lawrence A Leiter, MD	864-6068
	Vladimir Vuksan, PhD	867-7475

INTRODUCTION

Impaired glucose tolerance (IGT) is when the blood sugar response after eating is greater than normal, but not high enough to be in the diabetic range. People with IGT usually need more insulin than normal to control blood sugar levels, which is known as insulin resistance. If the pancreas is unable to keep making the excess amounts of insulin needed, diabetes can develop. We believe that reducing insulin resistance will prevent diabetes from developing in people with IGT. Insulin resistance may be able to be improved by altering the amount and type of fat and carbohydrate in the diet. Recent studies suggest that diets high in monounsaturated fat, such as is found in olive oil and canola oil, may have a beneficial effect on blood cholesterol, but the effect on insulin resistance is not known. Also, different carbohydrate foods have different effects on blood glucose and insulin responses after meals, and the responses of foods have been classified using the glycemic index. We believe that the use of low glycemic index foods will reduce blood insulin levels and improve insulin resistance. The purpose of this study is to compare the effects of a diets containing high and low glycemic index foods versus a diet rich in monounsaturated fat on blood sugar and insulin responses in people with IGT. and to see if these diets will reduce insulin resistance, which may help prevent diabetes.

PROCEDURES

Before entering the study, I will have a medical history, a physical exam, electrocardigram, and blood and urine tests.

If I accept to participate in this project, I will be asked to follow one of 3 different diets for a period of 4 months. My diet will be either high in monounsaturated fat (eg. olive oil. canola margarine); or contain high glycemic index foods (such as bread, rice. mashed potatoes and certain breakfast cereals); or contain low gycemic index foods (spaghetti, barley, beans and certain breakfast cereals). I agree to follow the diet plan prescribed to me by the study dietitian as closely as I can for 4 months. The diet plan will be based on what I normally eat and will take into account my likes and dislikes. As

118

part of the study, I will be given specific foods to eat and I will use these as instructed. These foods may include margarine, oils, breads, grains and cereals. I will obtain the other foods in my diet myself. To help plan my diet, before starting the study I will record all the foods I eat for 7 days. I understand that I will be assigned by random chance to one of the three study diets.

If I accept to participate in this project, I am also agreeing to participate in day profile and insulin sensitivity tests at the Clinical Nutrition and Risk Factor Modification Center, St. Michael's Hospital. These tests will require me to spend 1½ days at the Nutrition Center before the start of the study diet and 1½ days during the last 2 weeks of the study diet.

Day profile: I will come to the Nutrition Center at 7:30am after a 10-12h overnight fast and will stay until the test is over at about 8:00pm. A small plastic tube will be placed in a vein in my arm for taking blood samples, and this tube will be kept open by injecting a small amount (3-5ml or ½ to 1 teaspoon) of saline (salt solution). After a fasting blood sample is taken, I will be served a normal breakfast test meal at about 8:00am, lunch at 1:00pm and dinner at 5:00pm, similar the diet I have been prescribed. A total of 15 further blood samples (5ml or one teaspoon each) will be taken at intervals after eating breakfast, lunch and dinner. I will collect all the urine I pass during the day into a plastic bottle according to the instructions I will given. After the final blood sample, I will empty my bladder into the urine collection bottle and will be free to go home. The total amount of blood taken for each day profile test is 70ml (1/3 cup).

Insulin sensitivity test: I will come to the Nutrition Center at 7:30am after a 10-12h overnight fast and will stay until the test is over at about 1:00pm. A small plastic tube will be placed into a vein in one arm for taking blood samples, and this tube will be kept open by injecting a small amount of saline (salt solution). Another small tube will be placed into a vein in my other arm for injecting glucose (blood sugar) and insulin. Three blood samples (3ml or half a teaspoon each) will be taken over a 20min period. At time 0min a small amount of glucose solution will be injected into a vein in my arm and 10 more blood samples taken over the next 20min. Then a small amount of insulin will be injected into my vein and 19 more blood samples taken over the next 2h and 40min. After this test is over, I will be given a lunch meal and then will be free to leave. The total amount of blood to be taken over the day will be 100ml (2/5 of a cup).

If I accept to participate in this project, I will have 7 additional short visits to the Nutrition Centre in the morning after a 10-12h overnight fast to be weighed, have a blood sample (20ml or 4 teaspoons) taken and have my blood pressure measured. At each visit I will bring with me a 3-day food record, will see the dietitian and pick up study foods.

Effect of high and low glycemic index versus high monounsaturate fat diet on insulin sensitivity in subjects with impaired glucose tolerance.

RISKS

There are no known risks from the dietary treatments. The only thing I might notice is an increase in flatulence or an increase in the bulk of the stools.

The insulin sensitivity test is a standard procedure. The insulin injected is identical to human insulin and should not produce any adverse reaction. The glucose solution injected may cause some discomfort in my arm or shoulder due to irritation of the vein lining. The most serious consequence of this would be continued minor discomfort for a few weeks due to thrombosis of the vein (blood clot). However, this is unlikely and the chances of it happening will be reduced by warming my arm during the injection, and flushing my vein with about ½ cup (125ml) normal saline to wash away the glucose.

There may be some discomfort from taking the blood samples and blood may leak under the skin causing bruising and swelling. The chance of this is reduced by not bumping or moving the tube in my arm and by keeping pressure on the site of the blood sample for 2-3 minutes after the needle or tube is removed. If bruising does occur, it will go away in 2 to 3 days.

BENEFITS

I may expect to benefit from the study in the following ways: my blood sugar, blood lipids and blood pressure may improve. I will receive the benefits of evaluation of symptoms and general health discussions with the doctor and help in finding additional treatment if needed. I will receive advice from a registered dietitian regarding a healthy diet. Finally, I will have the chance to contribute to a study which may be of benefit to people with IGT in the future.

CONFIDENTIALITY

The results from the study will be confidential. My results will not be shown to anyone, unless required by law, without my written permission. My results will be sent to my physician if I wish.

PAYMENTS

I will not have to pay for any of the medical examinations or laboratory tests that are required for the study. I will be compensated for all expenses that I have to incur because of my participation (eg. travel expenses). I will also be compensated for time lost from work. I will be expected to buy the foods in my diet from a store of my choice except for the foods given to me to use during the study which will be provided free.

STOPPING THE STUDY

I understand that the study physician may stop my being in the study at any time without my consent. My participation may be discontinued if the study doctor judges that it is in my best interests or if I fail to comply to study procedures.

QUALIFICATIONS

I understand that I can not be in this study if I abuse alcohol or drugs, or if I have a serious illness which is not under control. I am above the age of 18 years.

CONSENT

I have read this consent form, have had all my questions about the study answered, and believe I know what will happen to me if I agree to be part of the study.

I freely volunteer to participate in this study. I may quit at any time. If I decide not to participate or quit, I will not be penalized and will not give up any benefits or which I had before entering the study. If I decide not to participate, or quit, I will notify the study physician. I have received a copy of this consent form.

Volunteers name:..

Volunteer's signature:...Date:..........................

Physician's signature:...Date:..........................

Witness' signature:...Date:..........................

Appendix B

Nutrition Education Handout for

High GI High Carbohydrate Diet Group

Dietary Guidelines

Outlined below is a list of recommended starchy foods that should be included into your diet on daily basis or as often as possible for the duration of the study.

For Breakfast include at least one serving of the following starchy foods:

Breakfast Cereals
        cornflakes,   puffed wheat
        rice krispies   muesli
        branflakes   shredded wheat

                                        1 serving = 3/4 cup

Bread
        white or whole wheat bread
        bagels
        pita bread
        white, or whole wheat rolls rolls
        pancakes   1 serving = 1 slice

Include at least one serving of the following items at both your Lunch and Dinner:

Grains
        instant or polished rice
        instant mashed potatoes(from a box, homemade)
        sliced potatoes (scalloped)
        buckwheat   1 serving = 1/2 cup
        millet

Breads
        white or whole wheat bread
        bagels
        pita bread
        white, or whole wheat rolls rolls   1 serving = 1 slice

There are no restrictions on the following types of foods:

        fruit
        vegetables
        meat, fish, polutry, lamb
        milk or milk products
        snacks (sweet and savory) only in moderation

Suggested Meal Plan

Breakfast

1 cup Cornflakes
1 cup Milk
1/2 Bagel
1 tbsp Peanut Butter
1 tsp Jam
1 Banana

Mid morning Snack

1 Fruit Yogurt (1% MF)

Lunch

1 PC Cous Cous Soup
1 Pita Bread
1 Slice (30 g) Cheddar Cheese (22% MF)
1 Bunch Grapes
Cucumber and Tomato Slices

Snack

2 Cookies

Dinner

¾-1 1/2 cup Instant Mashed Potatoes (Homemade or Instant)
3-5 oz Lean Chicken, Beef, Pork, Lamb
1/4 cup Lean Gravy (defatted)
1 cup Green Beans and Carrots
1 -1 1/2 cup Mixed Salad
1 tbsp Lite Dressing (2 tsp vinegar + 1 tsp oil)
1 cup Mixed Fruit

Evening Snack

1 cup Pretzels

Appendix C

Nutrition Education Handout for

Low GI High Carbohydrate Diet Group

Dietary Guidelines:

Outlined below is a list of the recommended starchy foods that should be included into your diet on a daily basis or as often as possible for the duration of the study.

For Breakfast include at least one serving of the following starchy foods:

Breakfast Cereals: 1 serving = ¾ cup
    Oatbran
    Oatmeal
    Read River Cereal
    Bran Buds with Psyllium
    Barley (cracked, pearled, rolled
    Buckwheat Grain (not flakes)

Whole Grain Bread: 1 serving = 1 slice
    Pumpernickel (Dimpfelmyer, Holtzheuser)
    Linseed (Rudolf)
    Rye (Dimpfelmyer)
    High Fibre Crispbread (Ryvita)

Include at least one of the following items at **both** you Lunch and Dinner:

Whole Grain Bread: 1 serving = 1 slice
    Pumpernickel (Dimpfelmyer, Holtzheuser)
    Linseed (Rudolf)
    Rye (Dimpfelmyer)
    High Fibre Crispbread (Ryvita)

Legumes: 1 serving = ½ cup cooked
    Dried Beans (black, kidney, white, navy, pinto, soy, broad, etc.)
    Dried Peas (chick, split, green, blackeyed)
    Dried Lentils (green, red, brown)

Grains: 1 serving = ¾ cup
    Pasta (al dente) (wheat, whole wheat)
    Parboiled Rice
    Bean Noodles
    Buckwheat Noodles

Starchy Fruits and Vegetables
    Corn
    Green Peas
    Yams, Sweet Potatoes, Potatoes (non Mashed)
    Unripe Bananas

There are no restrictions on the following types of foods:
    Fruit
    Vegetables
    Meat, fish, poultry
    Milk or milk products
    Snack (sweet or savory) only in moderation

Menu Plan

Breakfast

¾ cup Red River Cereal
1 cup milk
1 orange
1 slice pumpernickel bread
1 tsp margarine
2 tsp jam

Morning Snack

1 fruit yogurt (1% MF)

Lunch

1 ½ cup pasta and bean salad
2 oz lean ground beef
1 cup tomato sauce
1 ½ cup mixed salad
1 tbsp dressing (2 tsp vinegar, 1 tsp oil)
¾ cup green beans
1 cup fruit salad
4 oz wine

Evening Snack

1 cup pretzels

Appendix D

Nutrition Education Handout for

High MUFA Low Carbohydrate Diet Group

IGT STUDY INFORMATION

Dietary Recommendations:

Please consume the following foods or combination of foods over the day.

1. Consume _____ tablespoons of olive oil

2. Use _____ teaspoons of margarine

Make your own salad dressing, or add the olive oil to pasta or rice. Dip bread into plain or flavoured olive oil. Add basil or other herbs and spices to the oil to add flavour.

Add the margarine to bread or vegetables or into any starch dish.

Divide the quantity into 3, having a little bit at each meal.

Other excellent sources of monounsaturated rich foods are: peanut butter (unprocessed), avocados, almonds, walnuts and hazelnuts.

In addition to adding the following servings of high monounsaturated sources of fat in your diet, please follow the following guidelines. Following these recommendation will increase the fibre and vegetable protein and lower the animal fat (saturated fat) and total fat in your diet. Please follow the guidelines as closely as possible to optimize your diet. Try new combinations of foods and recipes to expand the variety of food and your taste experience.

1. Include starches at each meal. For breakfast have a slice of bread or bagel. Unsugared breakfast cereals are also a healthy alternative. Choose higher fibre breakfast cereals to increase the fibre intake in the diet. Hot or cold, breakfast cereals are low in fat. For the other meals include at least one serving of starch. For example low fat starches include: rice, bread, pasta, cous cous, potatoes, etc. By choosing a higher fibre cereal, your feeling of satiety will be increased. Try to include at least 6 servings of starch in your diet on a daily basis.

3. Be sure to include lots of fresh fruits and vegetables in your daily diet. Eat the skin whenever possible, as it is an excellent source of vitamins, minerals and fiber. Try to include a minimum of 5 servings of fruit and vegetables per day.

7. Choose lower fat milk, yogurt (<2% fat) and other dairy products. Try lower fat cheeses such as skim milk cheddar or mozzarella (<7%), ricotta (<5%), cottage cheese (<2%) or quark. Instead of regular ice cream, enjoy a 1% icecream or icemilk, low-fat sherbet, frozen yogurt or other low fat non-dairy frozen desserts.

8. Choose *smaller portions* (i.e. 3 oz) and *leaner cuts* of meats, fish or poultry. Pick meats with a minimum amount of marbling. Lean cuts of beef, veal, pork, lamb

include the following: "loin", "eye", and "round". White chicken and turkey meat is leaner than dark meat.

9. Halibut, sole, haddock, cod, white fish are good low fat choices. If eating fatty fish such as mackerel, tuna, salmon, herring or sardines choose smaller portions and fish packed in water. Although these deep sea fishes are higher in fat, the fish oils they contain may be beneficial. Prepare fish with as little added fat as possible (see point 7).

10. Avoid prepared meats such as bologna and salami for sandwiches. Choose sheer cuts of meats such as roast beef, ham or turkey or chicken. Remember that if you can make out the muscle fibre of the meat it is likely less processed and lower in fat. Choosing lean cuts of meats at fast food deli counters may provide a lower fat sandwich than asking for a tuna or salmon salad sandwich. Remember portion control is key. Try not to exceed the one ounce mark for lunch sandwiches. Some deli sandwiches can have up to five ounces of meat.

Rule of Thumb: Try to limit animal product intake to three ounces per day. Do not exceed 4-6 ounces per day.

11. Trim and remove all fat before cooking. Skim excess fat off soups or stews after cooking. Bake, broil, BBQ, stir fry, boil or microwave with little or no added fat. Avoid frying or deep frying. Avoid breaded fried foods since they absorb a lot of fat.

12. When available, choose the "light" varieties with less fat. While at a restaurant, ask for the dressing and gravy on the side. This is an excellent way to control the amount you eat. Be on the look out for high fat dishes with names like: au gratin, hollandaise, pesto.

13. Season foods with lemon juice, vinegar, garlic, onion, mustard, herbs, spices, low fat yogurt, salsa, relish, cranberry sauce, jam, jellies, soy sauce, chilies, sesame seeds, etc. Add these ingredients to the olive oil to increase the variety and different tastes.

14. Watch out for "invisible fat". Many commercially baked goods (cookies, pastries, cakes, etc.), snack foods (chips, nachos, crackers), and sauces are high in fat. In addition, many of these products are often high in hydrogenated fat and tropical oils which should be avoided. Try bagels, soda crackers, pretzels, pita puffs, rice cakes or other low fat crackers, arrowroot or sultana cookies, fruits or vegetables.

GOOD RULE OF THUMB: the softer or more liquid a fat product is at room temperature, the more likely it is to be high in unsaturated "good" fat. Good margarines include Becel, Olivina and Fleishman's.

Appendix E

Study Visit Monitoring Form

Diet Information

Food Recording Form (Include Week(s))

Collected _____   Reviewed _____

Satiety   Ravenous   .Too full
                 -3   -2   -1   0   1   2   3

Adherence to prescribed diet / Difficulties encountered / Counseling provided

Metabolic Diet Quantity : _____

Metabolic Diet Quality : _____

_____

_____

_____

_____

_____

Activity / Stress / Symptom problems

_____

_____

_____

Metabolic diet modifications

Omit : _____

Reduce : _____

Add : _____

Increase : _____

Metabolic Study
Medical Note

Name : _____ ID # : ____ Date : _____

Phase : 1   2   3   Week : -2   0   1   2   3   4

Anthropometry and General Information :

Weight (kg) : _____ Wt▲ (from wk0) : _____ kg Height (cm) : _____

Body fat (%) : _____ Waist to Hip : _____

Blood Pressure : (L or R) : _____ Repeat : _____

Last Bowel Movement : _____ Last Urination : _____

Smoke :   Y   N   If yes, number per day : _____

Alcohol Use : Y   N   If yes, drinks per week : _____

Medical Information (change from last visit) :

Medication _____

Unusual events _____

Exercise _____

Bowel _____

Chart Note

_____

_____

_____

_____

_____

_____

_____

134

Appendix F

8 Hour Metabolic Day Profile Menus

Start: All Participants

End: High GI High Carbohydrate

End: Low GI High Carbohydrate

End: High MUFA Low Carbohydrate

8 hour Metabolic Day Profile Menus

<u>**Baseline**</u>

Breakfast

      Orange juice

      Cheerio's with 1% milk

      White bread with Becel margarine and jam

      Tea or coffee

Lunch

      White Bread with Becel margarine

      Ham/Turkey or Peanut butter and jam

      Arrowroot cookie

      Cucumber and tomato

      Banana

      1% fruit flavoured yoghurt

      tea or coffee with milk

8 hour Metabolic Day Profile Menu

End

High GI

The same as the Start Menu- week 0

Low GI

Breakfast

       Orange juice

       Oatmeal or Bran Buds with Psyllium with 1% milk

       Sugar

       Pumpernickel Bread and/or White Bread

       Becel Margarine and jam

       Tea or coffee

Lunch

       White bread and or Dimpfelmyer Pumpernickel Bread

       Ham/Turkey or Peanut butter and jam

       Brown Beans in tomato sauce

       Arrowroot cookie

       Cucumber and tomato

       Banana

       1% fruit flavoured yoghurt

       Tea or coffee with milk

MUFA

Breakfast

Olive Oil

Orange juice

Cheerio's with 1% milk

White bread with Olivena margarine and jam

Lunch

Olive Oil

White Bread with Olivena margarine

Ham/Turkey or Peanut butter and jam

Arrowroot cookie

Cucumber and tomato

Banana

1% fruit flavoured yoghurt

Tea or coffee with milk