Acute Effect of Low and High Glycemic Index Meals on Post-prandial Glycemia and Insulin Responses in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: Post-prandial hyperglycemia is an important independent risk factor in the development of cardiovascular disease in diabetes. This randomised cross-over study was conducted to compare the post-prandial glycemic and insulin responses to both high and low glycemic index (GI) meals in patients with type 2 diabetes (T2DM). **Methods:** A total of 41 patients with established T2DM (16 males, 25 females, Age= 55 $\pm$ 10 years and BMI= 27 $\pm$ 4 kg/m^2) were randomly given either a High GI or a Low GI meal in a cross-over manner. Both test meals were separated by one week washout periods. The meals contained almost the same amount of energy and macronutrients with the exception of the GI values (High GI=70 vs Low GI= 36). Venous blood was taken through an indwelling catheter periodically at 0, 30, 60, 90, 120, 150 and 180 minutes respectively. The incremental area under the curve (iAUC) was used to calculate the post-prandial glycemia and insulin excursion over the 3-hour period. **Results**: The low GI meal induced lower glycemic responses at times 30, 60, 90 and 120 minutes (mean$\pm$SE; low GI=8.1$\pm$0.4, 9.1$\pm$0.4, 8.9$\pm$0.4 and 8.5$\pm$0.4 mmol/l vs high GI= 9.1$\pm$0.4, 10.7$\pm$0.4, 11.0$\pm$0.5 and 9.7$\pm$0.5 mmol/l) and reduced the insulin levels at time 60, 90, 120 and 150 minutes (mean$\pm$SE; low GI= 17.1$\pm$1.7, 21.1$\pm$2.0, 20.4$\pm$1.7, 18.5$\pm$1.8 vs high GI= 25.0$\pm$2.5, 31.2$\pm$2.9, 29.8$\pm$3.0 and 23.0$\pm$2.3 μIU/ml) ($p<0.05$). The area under the glycemic (mean$\pm$SE; low GI= 215.93 $\pm$ 15.9 mmol.L/minute vs high GI= 419.52 $\pm$ 32.7 mmol.L/minute) and insulin (mean$\pm$SE; low GI= 1439.76 $\pm$ 226 vs high GI= 2372.76 $\pm$ 317μIU.ml/min) curves were lower after the low GI than high GI meal respectively ($p<0.05$). **Conclusion**: The low GI meal has the ability to reduce the post-prandial hyperglycemia as well insulin responses in type 2 diabetes patients.

Keywords: **Glycemic index, insulin concentration, post-prandial hyperglycemia, type 2 diabetes**

INTRODUCTION

Cardiovascular disease (CVD) is the major cause of morbidity in patients with type 2 diabetes. There is now accumulating evidence to show that increased post-prandial glycemia is among the strong risk factors for CVD development. [1]

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Post-prandial hyperglycemia is a very frequent phenomenon in patients with type 2 diabetes and it can occur even when overall glycemic control appears to be adequate.[2] Pharmacologic therapies targeting post-prandial hyperglycemia are evolving.[3] For example, treatment with Acarbose, a á-glucosidase inhibitor that delays the breakdown of carbohydrate into glucose in the small intestines leading to a reduction in post-prandial hyperglycemia.[4]

Post-prandial glycemia is influenced by both the amount and type of dietary carbohydrate in food. Despite equal amounts of total available carbohydrate consumed, their impact may vary depending on the types of carbohydrate used.[5] The type of the carbohydrate is best described by the glycemic index (GI).[5] The GI values of carbohydrate food are grouped into three categories[5] : low GI (<55), intermediate GI (56-69) and high GI food (>70). In general, most starch and carbohydrate rich food have a high GI while non starch vegetables, fruits and legumes tend to be classified as low GI food. [11]

Nevertheless, the GI concept has not been universally adopted in routine clinical practices in diabetes management.[5,6] Until recently, the amount of carbohydrate (expressed as carbohydrate exchanges) was a predominant focus of dietary management in diabetes.[6] However, this strategy of management would seem to have little merit in describing the very different effects that different types of carbohydrates have on post-prandial glycemia. [5] This study was conducted to compare the impact of two meals with similar amounts of carbohydrates but having a different GI value on post-prandial glycemia and insulin concentrations in patients with type 2 diabetes mellitus.

METHODS

Study Design and Subject Selection

This randomised, 2-period cross-over comparative study was part of the dietary intervention trial, designed to compare the effect of low GI (GI) against the conventional carbohydrate exchange (CCE) dietary advice on glycemic control and metabolic parameters over a 12-week period in patients with type 2 diabetes.[7] The rationale of this study was to validate whether the advice given to subjects during the intervention trial reflected the true impact of low and high GI meals on post-prandial responses.

A sub-group of subjects from the intervention study was recruited from the Endocrine Clinic of the UKM Medical Centre. Participation was on a voluntary basis and the recruitment was based on the following criteria: 1) diagnosis of type 2 diabetes for > 3 months prior to the study; 2) fasting blood glucose and HbA1c level < 15mmol/L and 12% respectively; and 3) treated with diet or with a stable dose of Metformin ($\leq$ 1700 mg/day), sulfonylurea ($\leq$ 15mg/day) or both, provided that these medications had been kept constant for at least 3 months before the study. The purpose and protocol of the study were explained to the subjects and their written consent was obtained prior to the initiation of the study. The study was approved by the Clinical Research Ethics Committee of UKM Medical Centre (Project Code: FF-138-2005).

Table 1. Nutrient composition of the low and high glycemic index (GI) breakfast meal

	Weight	Energy (kcal)	CHO (g)	Protein (g)	Fat (g)	Fibre (g)	Diet GI	Diet GL
Low GI meal								
Bread, whole grain	105g	180.6	20.6	14.0	3.2	18.4	21	8
Margarine	6.1g	45			5			
Apple, red delicious	115g	65.7	15.1	0.2	0.5	2.3	16	6
Plain water	250ml							
TOTAL	224.8	283.3	35.6 (53%)	14.2 (21%)	7.7 (26%)	20.7	37	13
High GI meal								
Bread, whole meal	60g	128	21.3	6.5	1.3	4.5	47	18
Margarine	6.1g	45			5			
Banana, *brangan*	62g	64.5	15.0	0.6	0.2	0.3	23	9
Plain water	250ml							
TOTAL	128.0	237.7	36.3 (63%)	7.2 (12%)	6.5 (25%)	4.8	70	27

Test Meals

The study composed of two test meals which were the low and high GI meals as shown in Table 1. These low and high GI meals reflect the diet composition (either GI or CCE) that they had to follow during the intervention study.[7] For that purpose, wholemeal and whole grain breads had been chosen as test food because both types of bread were recommended throughout the study.

Both test meals had been planned to have identical amounts of energy, macronutrients and dietary fibre (Table 1). The differences were in the type of carbohydrate and meal GI. Nevertheless, despite good meal planning, the low GI meal had a higher protein and dietary fibre than the high GI meal. This was because of the whole grain bread used for this test. At the moment, this is the only available low GI bread in the market and (incidentally) happens to have a higher content of protein and fibre than the ordinary wholemeal bread.[8]

Macronutrient composition was calculated using the Malaysian Food Composition Table [9] and the nutrient analysis of the bread was provided by the bread company. The GI of the whole meal and whole grain bread were determined prior to this study and it has been published elsewhere.[10] The GI value of the fruits (apple and banana) was obtained from published data.[11-12] The GI for both test meals was calculated based on the method described by FAO/WHO [13] and is as follows:

$$\text{Meal GI} = \sum_{i=1}^{n} \text{GI}_i \times \text{CHO}_i / \sum_{i=1}^{n} \text{CHO}_i$$

where GI_i is the GI for food i, CHO_i is the carbohydrate content in food i (grams) and n is the number of carbohydrate food items in the meal.[5]

Study Procedure

The subjects were told to maintain their diet and other living habits prior to the test. The subjects were weighed at each visit and their energy intake was checked from their food intake records before each test day. Heavy exercise and the consumption of unusually large portions of food were forbidden on the day before each test, as was the consumption of alcohol for 2 days before and smoking on the morning of the test. Subjects were asked to arrive at the Endocrine Laboratory by car or by bus if possible to avoid extra physical stress. All subjects consumed both high and low GI test meals, each separated by one week washout period in a cross-over manner. On the day of the study, subjects reported to the laboratory at 0830 after an overnight fast of at least 10 hours. Upon arrival, a canula was inserted into the antecubital vein by the medical lab assistant. After a fasting blood sample was taken, subjects took their usual dose of medication (if any), 5 to 10 minutes before consuming the test meal. The test meal (either low or high GI meal) was consumed within 15 minutes at a comfortable pace. Subsequent blood samples were taken at 30, 60, 90, 120, 150 and 180 minutes after the meal began. Subjects remained on sedentary activity such as reading or watching television during the 3-hour study period.

Blood Analysis

Blood samples (1.5 ml at each minute) were collected in a tube containing fluoride oxalate and serum separator plain tubes for the measurements of plasma glucose and serum insulin respectively. Plasma was separated by centrifugation at 2800 rpm for 10 minutes within 30 minutes of collection and stored at -20°C until assayed.

Plasma glucose was analysed by the hexokinase enzymatic reference method using the COBAS Integra® 800 automated analyser (Roche Diagnostic, Basel Switzerland) and serum insulin was analysed by a solid phase, two-site chemiluminescent enzyme labeled immune-metric assay (Immulite® 1000 Analyser, Diagnostic Company Procedure, NY, USA).

Data Analysis

The blood glucose and insulin response for every tested point of time over 3 hours was used to calculate the incremental area under curve (iAUC) for each test meal according to standardised criteria, ignoring the area beneath the baseline.[13]

The results were expressed as mean ± SE. The differences in glycemic and insulin responses as well as the iAUC were assessed by a paired T-Test. Differences for all tests were considered significant if two-tailed of the P values were < 0.05. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software version 11.5 (SPSS Inc. Chicago, USA).

RESULTS

From the 104 subjects recruited for the intervention study [7], 41 subjects agreed to participate in this study. Table 2 shows the characteristics of the study subjects. They comprised 16

Table 2. Clinical characteristics of the study subjects (n=41)

	Mean $\pm$ SD	95% CI
Age (years)	55.0 $\pm$ 9.9	51.9, 58.3
Clinical diagnosis of diabetes (years)	6.0 $\pm$ 4.7	4.51, 7.54
Body mass index (kg/m^2)	26.9 $\pm$ 4.6	25.2, 28.2
Waist circumference (cm)		
Men	91.7 $\pm$ 2.2	87.0, 96.0
Women	87.6 $\pm$ 1.9	83.7, 91.6
Fasting blood glucose (mmol/L)	7.07 $\pm$ 2.3	6.33, 7.78
HbA$_{1c}$ (%)	7.8 $\pm$ 1.3	7.33, 8.19

men and 25 women and most of them were treated with medications (26 subjects were on a combination of Metformin and Sulfonylurea). All medications remained unchanged throughout the study period.

The baseline fasting blood glucose (mmol/L $\pm$ SE; 7.1 $\pm$ 0.4 and 7.0 $\pm$ 0.3) and insulin response (8.7 $\pm$ 0.9 and 9.5 $\pm$ 0.9 $u$mol/L) before consuming the low GI and the high GI breakfast meal did not differ significantly (Figures 1 & 2).

As shown in Figure 1, there was a significant increase in post-prandial blood glucose after ingestion of both test meals (p<0.001). Blood glucose level reached a peak at 60 minutes after the low GI and at 90 minutes after the high GI meal. The blood glucose response after consuming the low GI was significantly lower at time 30, 60, 90 and 120 minutes than after the high GI meal (Mean $\pm$ SE: low GI = 8.1$\pm$0.4, 9.1$\pm$0.4, 8.9$\pm$0.4 and 8.5$\pm$0.4 mmol/l vs high GI meal = 9.1$\pm$0.4, 10.7$\pm$0.4, 11.0$\pm$0.5 and 9.7$\pm$0.5 mmol/L; p< 0.001 respectively). At 180 minutes, the post-prandial blood glucose dropped to levels similar to the basal values for both test meals (Figure 1).

Plasma insulin responses followed the glucose responses (Figure 2). There was a significant increase in post-prandial insulin concentration after the ingestion of both test meals (p < 0.001). The level of insulin peaked at 90 minutes for both test meals. The low GI meal reduced the insulin levels at times 60, 90, 120 and 150 minutes significantly (mean $\pm$ SE: low GI = 17.1$\pm$1.7, 21.1$\pm$2.0, 20.4$\pm$1.7, 18.5$\pm$1.8 vs high GI = 25.0$\pm$2.5, 31.2$\pm$2.9, 29.8$\pm$3.0 and 23.0$\pm$2.3 $u$mol/L respectively; p<0.01). At 180 minutes, the insulin responses dropped but were still significantly higher than the baseline levels for low GI and high GI meals (p<0.001).

The incremental area under the curve (iAUC) which reflects the changes occurring in blood glucose and insulin response over the 3 hours after consuming both test meals was calculated (Figures 3 and 4). The area under the glucose (mean$\pm$SE; low GI = 215.93 $\pm$ 15.9 mmol.L/min vs high GI = 419.52 $\pm$ 32.7 mmol.L/min) and insulin curves (mean $\pm$ SE; low GI = 1439.76 $\pm$ 226 vs high GI = 2372.76 $\pm$ 317 $u$mol.L/min) were significantly lower for the low GI than for the high GI meal (p<0.001).
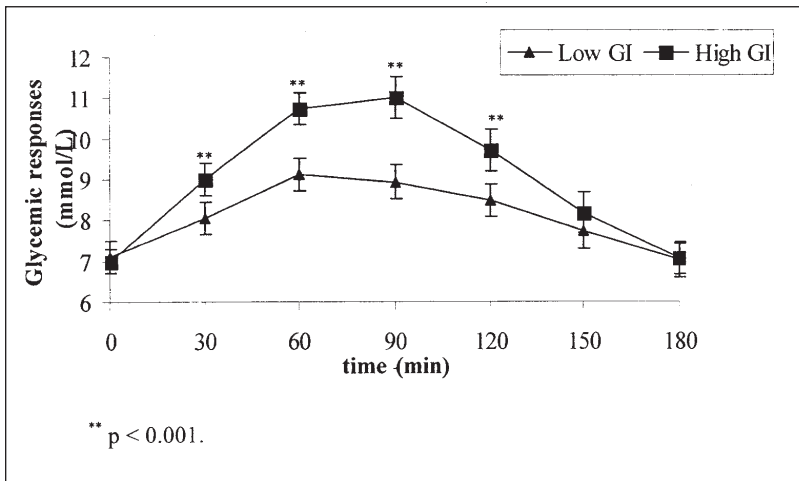
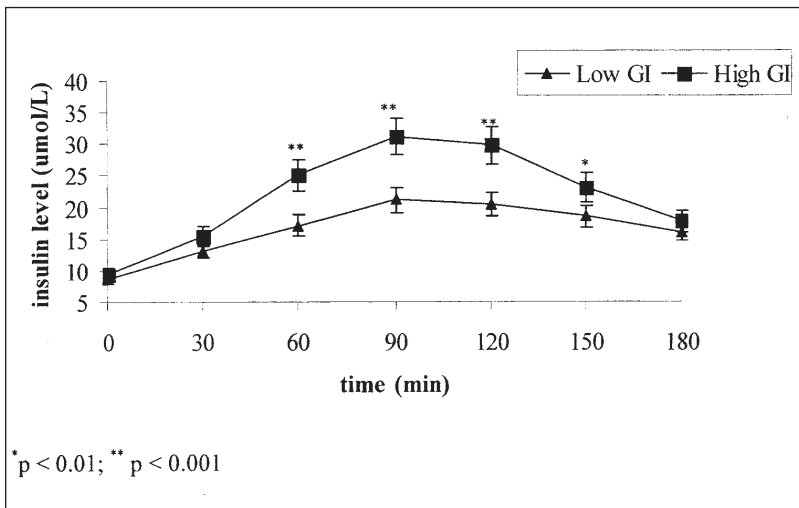**Figure 1.** Glycemic responses following low GI and high GI meals

Figure 2. Insulin concentration following low GI and high GI meals

DISCUSSION

This study has confirmed the validity of the low GI meal in reducing the post-prandial glycemic and insulin response in patients with type 2 diabetes. The high GI meal increased the post-prandial glycemia and insulin responses significantly by 39% and 26% compared to the low GI meal. This finding was comparable to the short-term study carried out among
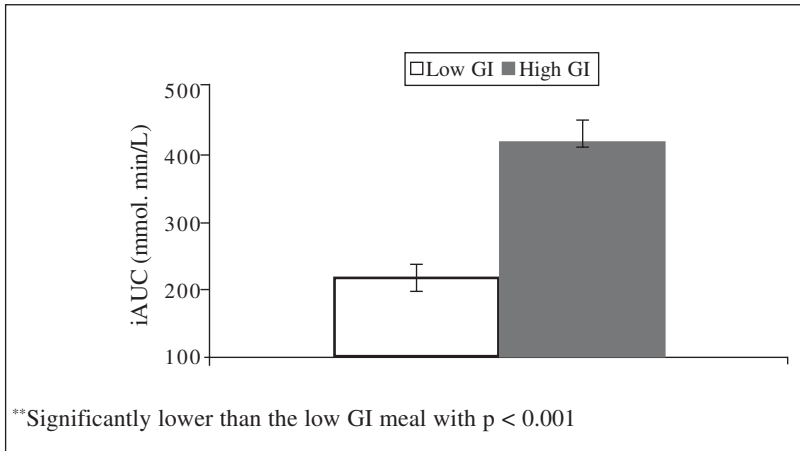
Figure 3. Mean blood glucose excursion over a 3-hour study period following low GI and high GI meals
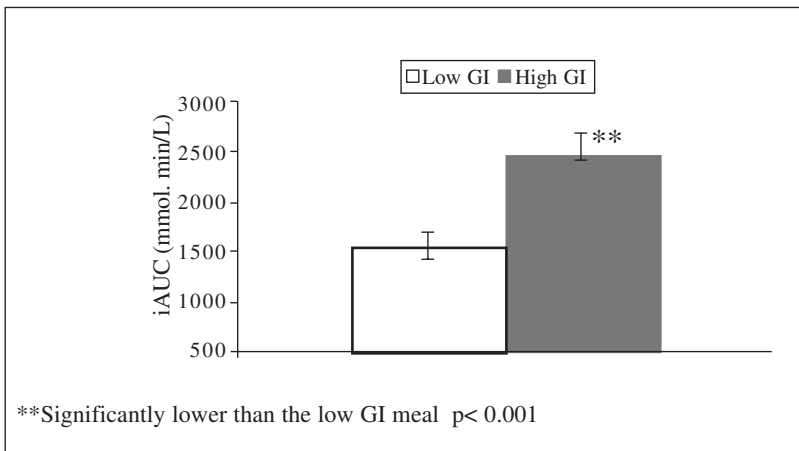

Figure 4. Mean insulin excursion over 3-hour study period following low GI and high GI meals

Canadians with type 2 diabetes[14], in which the differences between the glycemic effects of low GI and high GI meals were quantitatively predicted by the differences in meal GI.

Nevertheless, in order to maximise the differences in meal GI of the meals, the macronutrient composition was not properly controlled. Both test meals had identical amounts of energy and macronutrients but when expressed as a percentage of energy, the low GI meal had a lower carbohydrate percentage (53 vs 63%) and a higher protein percentage (21 vs 12%) than the high GI meal. Thus the question arises as to whether any difference in the macronutrients composition could have explained the study's primary findings. It is important

to note that not only the dietary sources of carbohydrate but food components (such as dietary fibre) or co-ingested macronutrients (such as protein or fat) can also affect the magnitude of reduction in post-prandial glycemic response to carbohydrate ingestion.[15]

Protein has been shown to have a marked effect in reducing glycemic responses by enhancing insulin secretion.[16]   In contrast, in this study, the decrease in post-prandial hyperglycemia after the low GI meal was in tandem with the reduction in insulin concentration. This suggests that the higher protein content in a low GI meal compared to a high GI meal was not a large enough factor to cause the observed differences in glycemic and insulin responses. Indeed, it has been reported that the amount and type of carbohydrate accounted for about 90% of the total variability in blood glucose responses, whereas protein in mixed meals scarcely contributed to the variation in blood glucose and insulin responses.[17]

Efforts were made to keep constant the dietary fibre content in both test meals as dietary fibre, specifically in a soluble form, has been shown to reduce post-prandial glycemia. [18]   However, it was not possible to maintain the dietary fibre constancy in this study because the whole grain bread used was the only low GI bread available in this country and it has been formulated with higher fibre content than the wholemeal bread. One could argue that the reduction in post-prandial glycemic and insulin responses after consuming the low GI meal could be confounded by the dietary fibre rather than due to any effect of GI. However, many of the high fibre foods especially from wheat products have had little impact on blood glucose responses.[5]   This finding was in agreement with our previous study which showed that the GI value of the rice and bread tested were not influenced by the content of total dietary fibre.[10,19]

Nonetheless, it is important in this type of study to match the macronutrient content to reduce the possibility of confounding variables. Failure to do this had made it difficult to compare the results and this must be recognised as a limitation of this study. However, the reduction in post-prandial glycemia and insulin concentration after this type of meals is particularly important in the present context because acute hyperglycemia post-prandially is an independent risk factor for the development of CVD.[20] It has been proposed that post-prandial hyperglycemia induced oxidative stress that is associated with a heightened LDL-cholesterol oxidation, an augmentation of pro-coagulation factors and adhesion molecules.[21]   All of these events are believed to be involved in the pathogenesis of atherosclerosis and CVD.[22]

Pharmacologic management by acarbose, an α-glucosidase inhibitor, had been shown to induce a significant decrease in the post-prandial rise in blood glucose and insulin concentration compared to the placebo.[23] Acarbose inhibits a á-glucosidase enzyme, which competitively blocks the enzyme's capacity to digest the carbohydrate [24], hence, reducing the rate of carbohydrate absorption. This mechanism of action of Acarbose mimics the action of low GI food.[25] This study has provided direct evidence that if   type 2 diabetics patients take this type of meal for a long period, they would achieve the same end result.[26]

In conclusion, the low GI meal reduced post-prandial glycemia and insulin concentration compared to the high GI meal. Future studies that determine the magnitude of reduction by dietary fibre and protein incorporated in carbohydrate rich meals should be undertaken in a dose-response manner.

ACKNOWLEDGEMENTS

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