Metabolism
Clinical and Experimental

VOL 45, NO 6 JUNE 1996

PRELIMINARY REPORT

The Effect of Low-Glycemic Carbohydrate on Insulin and Glucose Response In Vivo and In Vitro in Patients With Coronary Heart Disease

Gary Frost, Bruce Keogh, David Smith, Karen Akinsanya, and Anthony Leeds

The insulin resistance syndrome has recently been implicated in the etiology of coronary heart disease, with a possible metabolic defect at the level of the adipocyte. We report the effects of a low- versus high-glycemic-index (LGI and HGI, respectively) diet on insulin and glucose response as assessed by oral glucose tolerance test (OGTT) and insulin-stimulated glucose uptake in isolated adipocytes in a group of 32 patients with advanced coronary heart disease. The area under the insulin curve following OGTT was significantly reduced after 4 weeks in the LGI group ($P < .03$), but not in the HGI group. Insulin-stimulated glucose uptake in isolated adipocytes harvested from a presternal fat biopsy was significantly greater following the LGI diet ($P < .05$). This study demonstrates that simple short-term dietary measures can improve insulin sensitivity in patients with coronary heart disease.
Copyright © 1996 by W.B. Saunders Company

INSULIN RESISTANCE SYNDROME has been proposed as a major risk factor for coronary heart disease.[1] It has been postulated that a metabolic defect at the level of the adipocyte may play a central role.[2,3]

Studies on the postprandial glucose response to carbohydrate-containing foods have demonstrated that low–glycemic-index (LGI) foods—especially those that retard carbohydrate absorption—decrease the insulin and glucose response as compared with high–glycemic-index (HGI) foods, suggesting an increase in insulin sensitivity in normal volunteers,[4] non–insulin-dependent diabetics,[5] and obese insulin-resistant subjects.[6] There are possibly two effects that account for these observations. First, acute small-bowel effects of delayed gastric emptying decrease the rate of amylase breakdown due to retained cell structure and high amylose starch content, and reduce glucose diffusion across the intestinal wall.[7] Second, and possibly of greater importance, there is evidence to suggest that LGI foods that contain a significant amount of slowly absorbed fermentable carbohydrate ingested the evening before an oral glucose tolerance test (OGTT) enhance the suppression of hepatic glucose production and free fatty acids (FFA), creating a more insulin-sensitive environment.[8]

The aim of this study was to assess the effect of a 4-week trial of a LGI versus HGI diet on insulin and glucose response in vivo and in vitro in a group of patients with advanced coronary heart disease. We were particularly interested in the effects of a LGI diet aside from the well-documented small-bowel effects.

SUBJECTS AND METHODS

Thirty-two patients with advanced coronary heart disease on the waiting list for coronary artery bypass surgery were enrolled in a randomized study to assess the effect of a LGI versus HGI diet on insulin and glucose response. The study was approved by the Research Ethics Committee of the Royal Postgraduate Medical School and Hammersmith Hospital. There was no significant difference in demographic characteristics of the two groups, including adipocyte cell size (Table 1).

Six weeks before surgery, all subjects completed a 7-day diary of habitual dietary intake. This was used along with estimated energy expenditure to plan isocaloric advice based on the subjects' normal energy distribution between fat, carbohydrate, and protein. Follow-

From the Department of Nutrition and Dietetics, Hammersmith Hospital, and the Department of Endocrinology and Metabolism and the Cardiothoracic Surgical Unit, Royal Postgraduate Medical School, London; and the Department of Nutrition and Dietetics, Kings College, University of London, London, UK.

Submitted June 27, 1995; accepted December 4, 1995.

Supported by British Heart Foundation Project Grant No. PG93/145. Gary Frost is in receipt of a bursary from Kelloggs UK.

Address reprint requests to Gary Frost, BSc, Nutrition and Dietetic Department, Hammersmith Hospital, London W12 OHS, UK.

Copyright © 1996 by W.B. Saunders Company

0026-0495/96/4506-0001$03.00/0

Table 1. Subject Characteristics (mean ± SEM)

Characteristic	HGI	LGI
No.	15	15
Sex		
Male	11	12
Female	4	3
Age (yr)	63.46 ± 1.97	61.80 ± 1.66
Height (m)	1.69 ± 0.02	1.71 ± 0.03
Weight (kg)		
1, week 0	83.04 ± 2.96	80.17 ± 3.55
2, week 4	83.20 ± 3.00	80.17 ± 3.45
BMI (kg/m^2)	29.32 ± 0.92	27.53 ± 0.71
Waist (cm)	104.15 ± 2.37	97.33 ± 3.00
Hips (cm)	108.69 ± 2.46	106.87 ± 1.58
Waist to hip ratio	0.96 ± 0.02	0.91 ± 0.02
Cell diameter (μm)	82.3 ± 8	88.3 ± 4.1

Abbreviation: BMI, body mass index.

ing this run-in period and an overnight fast, subjects received a 75-g OGTT. Blood samples were taken at −30, 0, 30, 60, 90, and 120 minutes. An OGTT was chosen instead of a test of the diet, since we were interested in investigating the effects of long-term low-glycemic intake other than small bowel effects. The volunteers were then randomized to one of two dietary treatments. LGI diet subjects were encouraged to change one of their major carbohydrate sources to a low-glycemic carbohydrate at each meal. HGI diet subjects were encouraged to avoid LGI foods and to eat rapidly absorbed carbohydrates. The aim of the dietary manipulation was to change only the type of carbohydrate leaving the other macronutrients unchanged. All volunteers were given an individualized dietary plan and written advice. Subjects were given financial support over the period of the study to meet the cost of the dietary change. Changes in dietary intake were monitored at week 1 and week 4.

The OGTT was repeated after 4 weeks on the diet. Analysis at all time points was performed for glucose (glucose oxidase; Boehringer), FFA (enzyme colorimetric method; Wako, Hampshire, UK), and insulin (radioimmunoassay[9]). In addition, fasting serum was analyzed for triglyceride, cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol by enzyme colorimetric assays (Boehringer).

All subjects remained on the assigned diet until the fasting period (the evening before the operation). During the operation, a 1.5-g presternal fat biopsy was taken for in vitro analysis of insulin-stimulated glucose uptake in isolated adipocytes. This technique has been described in detail elsewhere.[10,11] Adipocytes were dispersed using collagenase (1 mg/0.5 g tissue) in a 37°C vibrating water bath at 140 cycles/min for 75 minutes. Cells were then filtered, washed, and left in glucose-free oxygenated Krebs-Ringer buffer for 120 minutes in a shaking water bath at 40 cycles/min. Isolated adipocytes (25 μL concentrated cells, ~30,000) were incubated in 500 μL 1% albumin buffer in the presence or absence of 1 nmol/L insulin (bovine; Sigma, Poole, UK) for 45 minutes, and then 0.1 μCi (300 nmol/L) 2-deoxy-[U-^{14}C]-D-glucose (Amersham, Buckinghamshire, UK) was added and the adipocytes were incubated for a further 15 minutes. The incubation was terminated by centrifuging the cells through 500 μL silicone oil (Sigma). The amount of radioactivity associated with the adipocytes was determined by liquid scintillation counting.

To assess how insulin-stimulated glucose uptake in isolated adipocytes relates to underlying insulin sensitivity, we investigated the relationship between the above technique and the hyperinsulinemic glucose clamp (the gold standard) using standard methodology.[12] Sixteen volunteers with advanced coronary heart disease who underwent hyperinsulinemic glucose clamping for another study volunteered to have a presternal fat biopsy taken.

Statistical Analysis

Results are presented as the mean ± SEM. All analyses were intergroup comparison using Student's *t* test (as the data were normally distributed).

RESULTS

Figure 1 shows a direct significant relationship between hyperinsulinemic glucose-clamping and insulin-stimulated glucose uptake in isolated adipocytes ($r = .72, P < .02$). Of

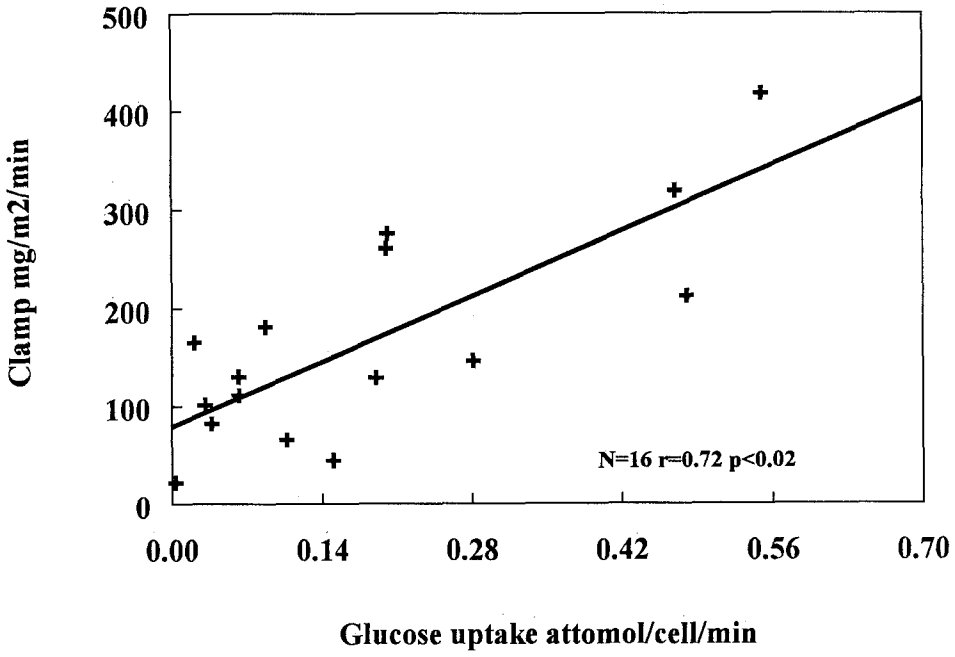

Fig 1. Relationship between the hyperinsulinemic glucose clamp and insulin-stimulated glucose uptake in isolated human adipocytes.

32 subjects recruited, one did not complete the study and one other was diagnosed with lung carcinoma 1 week after the operation, leaving 15 subjects in each group. Demographic details are presented in Table 1.

Tables 2 and 3 show the changes in dietary intake at 0, 1, and 4 weeks in both groups. The HGI group demonstrated a stable intake throughout the study (Table 2). The LGI group had a decrease in energy intake at week 1, which was corrected at that time (Table 3). There was no change in weight over the period of the study, which suggests that weight could not account for any effect on insulin resistance. The only significant change was that the glycemic index in the LGI group decreased from 86 to 76 ($P < .01$). Intergroup analysis showed no statistical difference on baseline glycemic indexes, but did show a significant difference after 4 weeks on the diet.

Biochemical results are shown in Table 4. The LGI group showed a significant decrease in incremental area under the insulin curve at 4 weeks (63 ± 10 to 44 ± 8, $P < .03$) that was not present in the HGI group (61 ± 16 to 61 ± 10), with a significant difference between the intergroup comparison of the end value ($P < .05$). There was no significant change in the glucose response in either group, nor was there a significant change in fasting insulin or glucose levels.

Of 30 patients reported herein, an additional two patients refused operation. The data presented for in vitro glucose uptake by isolated adipocytes are from 13 patients in the HGI group and 15 in the LGI group. There was a significant increase in insulin-stimulated glucose uptake in the LGI group ($P < .05$; Fig 2). No difference was observed whether the results were expressed as per cell or per cell surface area.

DISCUSSION

The immediate postprandial effects on glucose and insulin levels of LGI foods that retard carbohydrate absorption are well reported.[7] Following an overnight fast, as in this study, it is unlikely that small-bowel effects would play a role, since the transit time of similar foods is 8 to 12 hours.[13] Our study suggests that although a LGI diet over a 4-week period did not change fasting insulin and glucose levels, there was a significant decrease in the amount of insulin

Table 2. Changes in Nutrient Intake Over the Study Period in Subjects Randomized to the HGI Diet (mean ± SEM)

Intake	Week 0	Week 1	Week 4
Energy (kcal)	2,100 ± 127	2,142 ± 156	1,942 ± 116
Protein			
g	92 ± 5	87 ± 6	83 ± 6
%	18 ± 1	17 ± 1	17 ± 1
CHO			
g	263 ± 18	239 ± 16	232 ± 15
%	47 ± 2	43 ± 2	45 ± 2
Fat			
g	79 ± 6	90 ± 10	75 ± 6
%	34 ± 2	37 ± 2	35 ± 2
Alcohol			
g	5 ± 2	10 ± 4	10 ± 4
%	2 ± 1	3 ± 1	4 ± 1
P:S ratio	0.44 ± 0.06	0.54 ± 0.09	0.55 ± 0.06
Total nonstarch polysaccharides	14 ± 1	13 ± 1	13 ± 1
Glycemic index	90 ± 2	90 ± 3	91 ± 1

Abbreviations: CHO, carbohydrate; P:S, polyunsaturated to saturated.

Table 3. Changes in Nutrient Intake Over the Study Period in Subjects Randomized to the LGI Diet (mean ± SEM)

Intake	Week 0	Week 1	Week 4
Energy (kcal)	2,017 ± 140	1,708 ± 96	1,875 ± 148
Protein			
g	79 ± 6	80 ± 4	80 ± 4
%	16 ± 1	19 ± 1	18 ± 1
CHO			
g	226 ± 12	206 ± 12	220 ± 20
%	43 ± 2	46 ± 2	45 ± 3
Fat			
g	80 ± 10	62 ± 8	73 ± 11
%	35 ± 2	32 ± 3	34 ± 3
Alcohol			
g	19 ± 5	10 ± 4	16 ± 7
%	7 ± 2	4 ± 1	4 ± 2
P:S ratio	0.66 ± 0.07	0.73 ± 0.10	0.70 ± 0.06
Total nonstarch polysaccharides	14 ± 2	13 ± 1	14 ± 1
Glycemic index	86 ± 2	72 ± 2*	76 ± 1*

NOTE. Abbreviations are as in Table 2.
*$P < .05$ *v* HGI group.

Table 4. Changes in Insulin, Glucose, and Lipid Levels Over the Dietary Intervention Period (mean ± SEM)

	HGI Group		LGI Group	
Parameter	Start	End	Start	End
Fasting insulin (pmol/L)	80 ± 15	84 ± 15	76 ± 18	84 ± 16
Insulin incremental area under the OGTT curve (nmol/L/min)	61 ± 16	61 ± 16*	63 ± 10	44 ± 8*
Fasting glucose (mmol/L)	6.9 ± 0.5	6.2 ± 0.2	7.9 ± 0.8	7.3 ± 0.3
Glucose incremental area under the OGTT curve (mmol/L/min)	527 ± 104	551 ± 90	612 ± 76	451 ± 106
FFA (mmol/L)				
0 minutes	0.22 ± 0.03	0.21 ± 0.03	0.34 ± 0.1	0.31 ± 0.1
120 minutes	0.03 ± 0.01	0.04 ± 0.01	0.09 ± 0.04	0.07 ± 0.03
Total cholesterol (mmol/L)	6.54 ± 0.2	6.21 ± 0.31	6.8 ± 0.27	6.1 ± 0.28
Triglycerides (mmol/L)	1.54 ± 0.16	1.58 ± 0.28	1.81 ± 0.33	1.89 ± 0.32
LDL cholesterol (mmol/L)	4.5 ± 0.21	4.3 ± 0.33	4.9 ± 0.27	4.3 ± 0.31
HDL cholesterol (mmol/L)	1.08 ± 0.09	1.01 ± 0.07	1.07 ± 0.11	1.00 ± 0.11

Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein.
*$P < .05$.

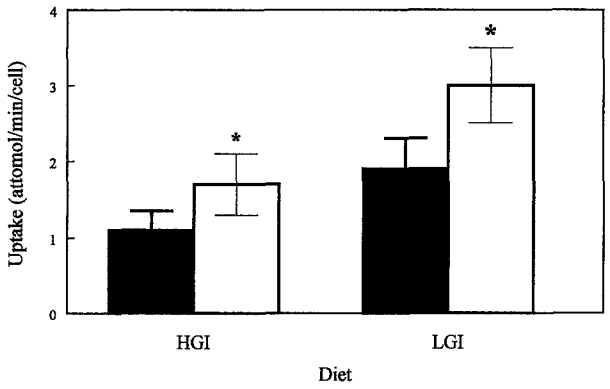

Fig 2. Insulin-stimulated in vitro glucose uptake in adipocytes following LGI or HGI diet. (■) Basal; (□) stimulated. *Intergroup significant difference, $P < .05$.

needed to handle a standard glucose load following an overnight fast in patients with severe coronary artery disease. Similar findings have been recently reported in normal individuals, using similar methodology.[4,14] It is possible that some of the metabolic effects of reduced hepatic glucose production described by Thorburn et al[8] are playing a role here.

As a method for assessing insulin sensitivity, insulin-stimulated glucose uptake in isolated adipocytes correlates with hyperinsulinemic glucose clamp results. Since adipose tissue may play a central role in insulin resistance, it is of interest to establish a direct method for assessing insulin sensitivity in this tissue.[2] Continuing investigation by our team, using insulin-stimulated glucose uptake in isolated adipocytes, has shown an uptake of 2.1 ± 0.4 amol/cell/min in a group with demonstrable coronary heart disease versus 3.1 ± 0.55 amol/cell/min in a group with normal coronary arteries undergoing valve surgery ($P < .05$, unpublished data, March 1996). Interestingly, this difference is similar to that reported herein between patients on the 4-week LGI diet (3.0 ± 0.5 amol/cell/min) and those in the HGI group (1.7 ± 0.4 amol/cell/min, $P < .05$), suggesting an improved insulin sensitivity in the adipose tissue. A recent study using adipocytes from rats after 3 weeks of a LGI diet had similar findings of increased glucose uptake.[15]

Together, the improved insulin response and increased insulin-stimulated glucose uptake in the LGI group suggest an improved insulin sensitivity in response to a glucose load. The mechanism for the observed effect of the LGI diet remains to be elucidated. Others have suggested that short-chain fatty acids from increased large-bowel fermentation may play a role.[8] We were unable to demonstrate a change in the level of FFA on the LGI diet, and therefore, if the change in insulin resistance is due to large-bowel fermentation, it may be via a direct effect of short-chain fatty acids on liver and peripheral tissue rather than via changes in FFA.

The results of this study indicate the potential for LGI diets to increase insulin sensitivity in free-living subjects with advanced coronary disease.

ACKNOWLEDGMENT

We would like to acknowledge Professor K. Taylor, Karon Masters, Professor S. Bloom, Dr D. O'Shea, and Dr K. Meeran for their support and encouragement.

REFERENCES

1. Laws A, Reaven GM: Insulin resistance and risk factors for coronary heart disease. Baillieres Clin Endocrinol Metab 7:1063-1078, 1993

2. Frayn KN, Coppack SW: Insulin resistance, adipose tissue and coronary heart disease. Clin Sci Colch 82:1-8, 1992 (editorial)

3. Reynisdottir S, Eriksson M, Angelin B, et al: Impaired activation of adipocyte lipolysis in familial combined hyperlipemia. J Clin Invest 95:2161-2169, 1995

4. Behall KM, Howe JC: Effect of long-term consumption of amylose vs amylopectin starch on metabolic variables in human subjects. Am J Clin Nutr 61:334-340, 1995

5. Wolever TM, Jenkins DJ, Vuksan V, et al: Beneficial effect of a low glycaemic index diet in type II diabetes. Diabetes Med 9:451-458, 1992

6. Slabber M, Barnard H, Kuyl J, et al: Effect of a low-insulin-response, energy restricted diet on weight loss and plasma insulin concentrations in hyperinsulinemic obese females. Am J Clin Nutr 60:48-53, 1994

7. Wolever TM: The glycemic index. World Rev Nutr Diet 62:120-185, 1990

8. Thorburn A, Muir J, Proietto J: Carbohydrate fermentation decreases hepatic glucose output in healthy subjects. Metabolism 42:780-785, 1993

9. Albane J, Ekins R, Martiz G, et al: A sensitive precise radioimmunoassay of serum insulin relying on charcoal separation of bound and free moieties. Acta Endocrinol (Copenh) 70:487-509, 1972

10. Kashiwagi A, Mott D, Bogardus C, et al: The effects of short-term overfeeding on adipocyte metabolism in Pima Indians. Metabolism 34:364-370, 1985

11. Garvey WT, Hueckstead TP, Matthaei S, et al: Role of glucose transporters in the cellular insulin resistance of type II non–insulin-dependent diabetes mellitus. J Clin Invest 81:1528-1536, 1988

12. Defronzo R, Jordan D, Reubin A: Glucose clamp technique: A method for quantifying insulin secretion and resistance. Am J Physiol 237:E214-E223, 1979

13. Englysy HN, Cummings JH: Digestion of polysaccharides of some cereal foods in the human small bowel. Am J Clin Nutr 42:778-787, 1985

14. Wolever TM, Jenkins DJ, Ocana AM, et al: Second-meal effect: Low-glycemic-index foods eaten at dinner improve subsequent breakfast glycemic response. Am J Clin Nutr 48:1041-1047, 1988

15. Kabir M, Rizkalla S, Luo J, et al: Effects of a 3 week high or low glycemic index starchy diet on adipocyte glucose metabolism in normal and diabetic rats. Diabetes 44:257A, 1995 (abstr)