The Effect of Unabsorbable Carbohydrate on Gut Hormones

Modification of Post-Prandial GIP Secretion by Guar

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Summary. Five healthy volunteers and 6 diabetics were given a mixed test meal on two occasions – once with and once without 10 g guar flour. Addition of guar caused a 47% decrease in maximum post-prandial GIP levels, a 48% decrease in blood glucose and a 48% decrease in plasma insulin in normal subjects. In diabetics, addition of guar caused a 30% reduction in maximum post-prandial GIP and 58% decrease in blood glucose. Four normal and 6 diabetic subjects were given a predominantly carbohydrate meal, again with and without 10 g guar. Addition of guar caused a 78% decrease in blood glucose and a 59% decrease in plasma insulin in normal subjects. In diabetics addition of guar caused a 71% decrease in maximum post-prandial plasma GIP and a 68% decrease in blood glucose. Lowering of post-prandial blood glucose, plasma insulin and GIP levels by guar was statistically significant in every case. Addition of guar to the predominantly carbohydrate meal caused a decrease in total plasma GLI in both normal and diabetic subjects but reached statistical significance only in the normal subjects. There was a highly significant correlation ($r = 0.83$; $p < 0.0005$) between peak post-prandial insulin levels in normal subjects and the corresponding plasma GIP concentration. The reduction in GIP or GLI secretion may, therefore, be partly responsible for the smaller rise in plasma insulin observed in normal volunteers when guar is added to meals.

Key words: Guar, GIP, glucagon-like immunoreactivity, enteroinsular axis, insulin, glucose, diabetics.

the seeds of the Indian cluster bean, *Cyamopsis tetragonoloba* [1]. Previous studies have shown that the addition of guar to a carbohydrate 'meal' decreases the post-prandial rise in blood glucose and plasma insulin in both normal subjects and diabetics [2]. It has been suggested that guar exerts its effect on post-prandial insulin secretion by forming intra-luminal gels in the small intestine thereby causing a delay in glucose absorption compared with a control meal [3]. However, several of the gastrointestinal hormones, notably gastric inhibitory polypeptide (GIP) and gut glucagon-like-immunoreactivity (GLI) are capable of stimulating insulin release [4, 5, 6]. The effect of guar on the secretion of these gastrointestinal hormones has not been reported. Both GLI and GIP release are thought to be subject to feed-back control by insulin [4, 6, 7]. We have, therefore, examined the effect on post-prandial secretion of GIP and GLI, in healthy and diabetic subjects, of adding guar to a predominantly carbohydrate 'meal' and a genuine mixed meal.

Materials and Methods

1. Mixed Meal

The study group consisted of 5 healthy volunteers (3 males and 2 females; 22.6 ± 2.1 years; mean % ideal body weight, 99.3 ± 0.5) and 6 insulin-treated diabetics receiving 28 to 80 units of insulin per day (6 males; 40.8 ± 8.1 years; mean % ideal body weight, 100.0 ± 1.1). Volunteers ate the test meal in the morning after a 12-hour overnight fast. The composition of the basic meal is shown in Table 1; the fibre-supplemented meal contained, in addition, 10 g guar (Norgine Ltd.) incorporated into the soup and bread. The diabetic subjects' diet normally included a breakfast containing 20–30 g carbohydrate; breakfast carbohydrate input for the healthy volunteers ranged from zero to approximately 30 g. The meals were taken in random order, one to two weeks apart, and were eaten over approximately 15 min.

There has recently been considerable interest in the possibility of treating diabetic subjects with the unabsorbable carbohydrate, guar, a gum produced from

Table 1. Composition of the basic mixed test meal and carbohydrate test meal

	Mixed meal	Carbohydrate meal
Components	Soup (298 ml)	Soup (298 ml)
	Egg (50 g)	–
	Bread ^a	Bread
	(control 36.3 g)	(control 38.0 g)
	(test 66.6 g)	(test 68.5 g)
	Butter (7.5 g)	
	Milk (100 ml)	–
Total carbohydrate (g)	52.1	47.3
Total fat (g)	28.1	12.5
Total protein (g)	20.2	10.6

^a The difference in weight between test and control was due to addition of water to the guar-supplemented bread, to make loaves of similar consistency

2. High Carbohydrate Meal

The study group consisted of 4 healthy male volunteers (29.3 ± 3.5 years; mean % ideal body weight, 99.6 ± 0.4) and 6 insulin-treated diabetics (5 males and 1 female; 50.0 ± 7.6 years; mean % ideal body weight, 102 ± 1.2) receiving 28 to 72 units insulin per day. The constituents of the basic meal are shown in Table 1. The fibre-supplemented meal contained 10 g guar, incorporated into the soup and bread. Meals were taken in random order, after an overnight fast, as before.

In all 4 tests the diabetic subjects received their usual morning dose of insulin 15 minutes before the meal. Venous blood samples were collected before and at frequent intervals for 180 min after the start of the meal whilst subjects were at rest. An aliquot of blood was added to perchloric acid and analysed for glucose by a hexokinase method [8]. The remainder was placed in tubes containing 100 μ mol EDTA and 5.000 KIU aprotinin/ml blood. The plasma was separated and assayed for immunoreactive insulin [9], immunoreactive GIP [8, 10], 'pancreatic specific' immunoreactive glucagon, using an antiserum directed against the C-terminal portion of porcine pancreatic glucagon [11], and 'total' glucagon-like-immunoreactivity, using an antiserum directed against the N-terminal portion of porcine pancreatic glucagon and known to cross-react with extracts from porcine small intestine [12]. The sensitivity of the assay for GIP in plasma, defined by the method of Ekins [13], was 110 ng/l and that for 'total' and 'pancreatic specific' glucagon 80 ng/l. This interassay coefficient of variation for GIP was 4.1% at 2677 pg/ml GIP and 22.5% at 138 pg/ml. For total glucagon-like immunoreactivity the interassay variation was 22% at 400 pg/ml and 15.6% at 1200 pg/ml. Intraassay coefficients of variation were 8.2% and 4.6% respectively for the glucagon assay. The results were compared using two-tailed Student's *t*-test for paired data. Informed consent was obtained from all subjects.

Results

Fig. 1 shows the mean blood glucose responses to the predominantly carbohydrate meal and the mixed meal in healthy subjects and diabetics. Results for the diabetics are plotted as an increment over the fasting

blood glucose values before insulin was given, in order to facilitate comparison with control subjects in whom fasting blood glucose levels were all very similar. The mean fasting glucose level in the diabetic subjects for all meals was 12.8 mmol/l (range 4.8–23.6 mmol/l) but in individual subjects fasting blood glucose values were within 2 mmol/l of each other on both test and control days. Addition of guar to the meals decreased the post-prandial rise in blood glucose concentration in both the healthy and diabetic subjects. The effect was greater in the diabetic than in the normal subjects.

Mean plasma insulin responses in the healthy subjects to the two types of meal with and without added guar are shown in Fig. 2. The addition of guar significantly decreased the post-prandial rise in plasma insulin after both types of meal.

Fig. 3 shows mean plasma GIP responses to both types of meal. Addition of guar to the meals significantly reduced the post-prandial rise in GIP in all cases, but was more effective in reducing post-prandial GIP levels after the predominantly carbohydrate meal than after the mixed meal. There was no significant difference between the GIP responses of the healthy subjects and the diabetics for either type of meal.

There was a highly significant correlation in the healthy subjects ($r = 0.83$, $p < 0.0005$) between their peak plasma insulin responses and the plasma GIP level at the corresponding time. This correlation was observed after both the mixed and carbohydrate meals whether taken with or without added guar (Fig. 4).

The glycaemia/insulinaemia relationship in healthy subjects, as expressed by the ratio of peak plasma insulin level over the corresponding blood glucose level was significantly altered by the addition of guar to both types of meal (mean ratio for control meals 6.01 ± 0.85 , for guar-supplemented meals 4.47 ± 0.83 ; $p < 0.05$).

Mean 'pancreatic specific' immunoreactive glucagon remained at basal levels (166 ± 16 ng/l) for the first hour after eating each of the test meals; it rose slightly, but non-significantly, in the latter half of the test, coincident with the fall in blood glucose, reaching a mean plasma level of 227 ± 29 ng/l at 120 min. There was no significant difference between any of the groups.

'Total' plasma GLI rose in response to both types of meal, in diabetics as well as in healthy subjects (Fig. 5). Although the response to meals supplemented with guar was generally smaller than after control meals, statistically significant differences were obtained only in the case of the predominantly carbohydrate meal eaten by healthy subjects in

Fig. 1. Post-prandial blood glucose levels in normal and diabetic subjects after mixed and carbohydrate test meals (●—● = control meal; ○—○ = meal + guar, mean $\pm$ SEM, * p < 0.05, ** p < 0.025, *** p < 0.01)

Fig. 2. Post-prandial plasma insulin levels in normal subjects after mixed and carbohydrate meals (●—● = control meal; ○—○ = meal + guar, mean $\pm$ SEM, * p < 0.05, ** p < 0.025, *** p < 0.01)

Fig. 3. Post-prandial plasma GIP levels in normal and diabetic subjects after mixed and carbohydrate test meals (●—● = control meal; ○—○ = meal + guar, mean $\pm$ SEM, * p < 0.05, ** p < 0.025, *** p < 0.01)

whom the incremental area under the curve was also significantly smaller ($p < 0.05$) for the guar supplemented meal. There was no significant correlation in the healthy subjects between their peak plasma insulin responses and the total plasma GLI level at the corresponding time¹.

¹ Raw data available on request to L. Morgan

Fig. 4. Correlation between the peak plasma insulin response to a test meal and the corresponding plasma GIP level (● = mixed control meal; ○ = mixed meal + guar; ■ = carbohydrate control meal; □ = carbohydrate meal + guar)

Discussion

The diminution of the post-prandial rise in blood glucose and plasma insulin observed when guar is added to either a predominantly carbohydrate or mixed meal is similar to that reported by Jenkins and co-workers [2] for carbohydrate meals.

GIP secretion is stimulated by the ingestion of either glucose or triglyceride, peak plasma levels of GIP tending to occur about 45 min after oral glucose and about 2 hours after oral fat [14]. There is evidence that the release of GIP from the gut in response to oral glucose may be regulated by the rate of absorption of glucose [15]. Because it increases the viscosity of solutions, guar gum has been widely used in the food industry as a thickener and stabiliser of fat emulsions. It has been suggested [16] that addition of guar the meals reduces the rate of diffusion of nutrients, in the gut, towards the absorptive surface although the total absorption of carbohydrates, as measured by urinary xylose excretion, is unchanged [3].

Post-prandial secretion of GIP was reduced by the addition of guar to both types of test meal, a possible mechanism being a reduction in the rate of absorption of nutrients. The effect of guar on the rise in plasma GIP levels was more pronounced when it was added to the carbohydrate meal than when added to the mixed meal. The ability of guar to reduce post-prandial GIP secretion may, therefore, be directed mainly at the secretion of GIP in response to a carbohydrate stimulus rather than to a fat stimulus.

Fig. 5. Post-prandial plasma 'total' GLI levels in normal and diabetic subjects after mixed and carbohydrate test meals (●—● = control meal; ○—○ = meal + guar, mean $\pm$ SEM, * $p < 0.05$; ** $p < 0.025$)

Both GIP and GLI are able to stimulate insulin secretion in the presence of hyperglycaemia. Therefore, it seems probable that the diminution in the insulin response to the test meals by the addition of guar is, at least in part, due to diminished gut hormone secretion, and the alteration in the insulinaemia/glycaemia relationship in healthy subjects by addition of guar to test meals supports this view. At the time of peak insulin secretion plasma GIP levels correlated significantly with plasma insulin levels but no such correlation was observed for GLI. The relative contributions of GIP and GLI in promoting insulin secretion cannot be assessed in these experiments. However, the reduction in post-prandial GIP secretion caused by guar, together with the correlation between plasma GIP and insulin levels points to GIP playing a significant role in the reduction of post-prandial insulin secretion by guar.

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References

- Jenkins, D. J. A., Hockaday, T. D. R., Howart, R., Apling, E. C., Wolever, T. M. S., Leeds, A. R., Bacon, S., Dilawari, J.: Treatment of diabetes with guar-gum: reduction of urinary glucose loss in diabetics. *Lancet* **1977** *II*, 779–780
- Jenkins, D. J. A., Leeds, A. R., Wolever, T. M. S., Goff, D. V., Alberti, K. G. M. M., Gassull, M. A., Hockaday, T. D. R.: Unabsorbable carbohydrates and diabetes: decreased post-prandial hyperglycaemia. *Lancet* **1976** *II*, 172–174
- Gassull, M. A., Goff, D. V., Haisman, P., Hockaday, T. D. R., Jenkins, D. J. A., Jones, K., Leeds, A. R., Wolever, T. M. S.: The effect of unavailable carbohydrate gelling agents in reducing the post-prandial glycaemia in normal volunteers and diabetics. *J. Physiol. (Lond)*. **259**, 52–53 (1976)
- Brown, J. C., Dryburgh, J. R., Ross, S. A., Dupré, J.: Identification and actions of gastric inhibitory polypeptide. *Recent Prog. Horm. Res.* **31**, 487–532 (1975)
- Samols, E., Marri, G., Marks, V.: Promotion of insulin secretion by glucagon. *Lancet* **1965** *II*, 415–416
- Marks, V., Turner, D. S.: The gastrointestinal hormones with particular reference to their role in the regulation of insulin secretion. *Essays Biochem.* **3**, 109–152 (1977)
- Matsuyama, T., Foà, P. P.: Effects of pancreatectomy (PX) and of enteral administration of glucose (G) on plasma insulin (IRI), total (GRI) and pancreatic (IRG) glucagon. *Diabetes* **23**, 344 (1974)
- Lloyd, B., Burrin, J., Smythe, P., Alberti, K. G. M. M.: Enzymic fluorometric continuous-flow assays for blood glucose, lactate, pyruvate, alanine, glycerol, and 3-hydroxybutyrate. *Clin. Chem.* **24**, 1724–1729 (1978)
- Soeldner, J. S., Stone, D.: Critical variables in the radioimmunoassay of serum insulin using the double antibody technic. *Diabetes* **14**, 771–779 (1965)
- Morgan, L. M., Morris, B. A., Marks, V.: Radioimmunoassay of gastric inhibitory polypeptide. *Ann. Clin. Biochem.* **15**, 172–177 (1978)
- Al-Tamer, Y. Y.: Ph. D. thesis. University of Surrey 1978
- Murphy, R. F., Conlon, J. M., Buchanan, K. D.: The use of antibodies in the characterisation of glucagon-like polypeptides. In: Gut hormones. Bloom, S. R. (Ed.), pp. 379–382. Edinburgh, London, New York: Churchill-Livingstone 1978
- Ekins, R. P.: Radioimmunoassay design. In: Radioimmunoassay in clinical biochemistry. Pasternak, C. A. (Ed.), pp. 3–13. London, Philadelphia, Rheine: Heyden 1975
- Brown, J. C., Dryburgh, J. R., Moccia, P., Pederson, R. A.: The current status of GIP. In: Gastrointestinal hormones. Thompson, J. C. (Ed.), pp. 537–547. Austin, Tx.: University of Texas Press 1975
- Ebert, R., Creutzfeldt, W.: Aspects of GIP pathology. In: Gut Hormones. Bloom, S. R. (Ed.), pp. 294–300. Edinburgh, London, New York: Churchill-Livingstone 1978
- Jenkins, D. J. A., Leeds, A. R., Gassull, M. A., Crochet, B., Alberti, K. G. M. M.: Decrease in post-prandial insulin and glucose concentrations by guar and pectin. *Ann. Intern. Med.* **86**, 20–23 (1977)

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