Macronutrients have different metabolic effects in nondiabetics and diabetics[1,2]

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ABSTRACT The glycemic and hormonal responses to protein, fat and carbohydrate alone and together were studied in normal, noninsulin-dependent (NIDD) and insulin-dependent (IDD) diabetic subjects. Fat and protein markedly reduced the glycemic response to oral carbohydrate in nondiabetics. In NIDD, the presence of protein and fat had no significant effect on the glycemic response. In IDD, while fat had no effect, protein enhanced the glycemic response. The insulin and GIP responses to the macronutrients together and individually were remarkably similar in all subject groups. Protein behaved as an insulin secretagogue in normal and NIDD while fat acted as a GIP secretagogue in normal and both diabetic groups. Protein appeared to function as a GIP secretagogue when combined with both fat and carbohydrate. It is concluded that caution is required when the glycemic responses to foods observed in nondiabetics are extended to diabetics. *Am J Clin Nutr* 1985;42:449–453.

KEY WORDS Nondiabetes, diabetes, glucose, insulin, GIP, absorbable carbohydrate, fat, protein

Introduction

In the previous study (1), we have highlighted the influence on glycemic and hormonal responses due to physical factors in a legume meal. These factors markedly modified the metabolic response in nondiabetics while the glycemic response in particular was less affected in diabetics. In nondiabetics the protein (2) and fat (3) content of the meal modify the metabolic response to dietary carbohydrate. The relative effect of these factors in diabetics (4, 5) is less well defined and is the subject of this report.

Materials and methods

Subjects

Nine nondiabetic subjects (6 female and 3 male age 31.9 ± 2.8 yr (mean ± SEM), 129.0 ± 5.9% ideal body weight (IBW—Metropolitan Life Insurance Co, 1959)) were compared against stable outpatient diabetic volunteers. The patients consisted of 11 noninsulin-dependent diabetics (NIDD—2 female, 9 male, age 61.2 ± 1.8 yr, 118.0 ± 5.7% IBW, duration of disease 6.6 ± 1.9 yr, 6 receiving sulphonylureas and 5 diet alone) and 8 insulin-dependent, ketosis-prone diabetics (IDD—1 female, 7 males, age 35.9 ± 5.5 yr, 115 ± 4.7% IBW, duration of disease 9.3 ± 2.1 yr. One patient had mild postural hypotension (an IDD), but none had symptomatic gastroparesis. The investigations were performed in accordance with the principles of the Declaration of Helsinki and were approved by the Research (Advisory and Ethics) Committee of the Hospital.

Meal tests

The uncooked flummery is based on the macronutrient content of the beans on toast meal of the earlier paper (1). The spectrum of carbohydrate types has been matched to the beans meal from published tables (6, 7, 8). The three meals studied were *1*) the uncooked flummery (51.2 g carbohydrate, principally cornstarch, 21.4 g protein, 10.5 g fat), *2*) carbohydrate (51.2 g) and fat (10.5 g), and *3*) carbohydrate (51.2 g) alone. The carbohydrate and fat and carbohydrate alone meals (2 and 3 respectively) are based on the flummery meal. Ingestion of the macronutrient components was only palatable and ac-

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ceptable if the starch was uncooked. The carbohydrate was soaked for 24 h without cooking in the pressure cooker before ingestion in a manner similar to the beans. Again, all meals were made up to the same vol (500 ml) with water.

Details of the metabolic studies, analytical methods and data analysis are provided in an accompanying paper (1).

Results

Fasting plasma glucose, insulin and GIP

The mean fasting plasma glucose for the normal subjects was 4.8 mmol/l (range 4.7–4.8 for the three meals), for NIDD was 8.4 mmol/l (8.1–8.6) and for IDD was 11.5 mmol/l (10.7–12.7). There were no significant (2-way Anova) differences within any subject groups between different meals. The mean fasting insulin level for normal subjects was 4.5 mμ/l (range 4.1–4.9) and NIDD was 9.7 mμ/l (9.2–9.9). The mean fasting GIP level for normal subjects was 421 pg/ml (range 329–533), for NIDD was 515 pg/ml (501–533) and for IDD was 877 pg/ml (748–1002). Again, no consistent significant differences were found within any subject group between different meals.

Meal responses

*Plasma glucose (**Fig 1**).* The nondiabetic glycemic response to the carbohydrate and fat meal is significantly greater than that of the uncooked flummery (2-way Anova, $p < 0.05$). The responses differed at one time point (120 min, Student's paired t test, $p < 0.05$), but did not differ significantly in the peak responses. Likewise the overall glycemic response to carbohydrate alone was significantly greater than to the carbohydrate and fat meal (2-way Anova, $p < 0.05$). These responses also differed significantly between 15 and 45 min (Student's paired t test, $p < 0.05$ and $p < 0.01$) and in peak values ($p < 0.01$).

For NIDD the glycemic responses of the three meals did not differ significantly (2-way Anova). In contrast for IDDM, while the glycemic responses of the carbohydrate alone and carbohydrate and fat meals did not differ significantly (2-way Anova), both were significantly less ($p < 0.01$) than that for the uncooked flummery. The glycemic responses for both the carbohydrate alone and carbohydrate and fat meals were significantly less than for uncooked flummery be-

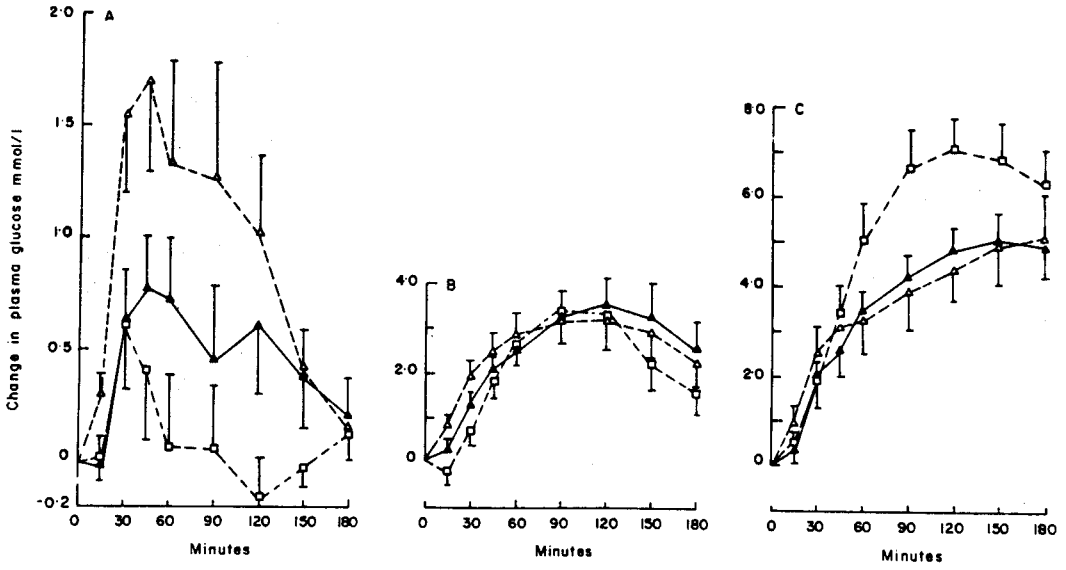

FIG 1. Plasma glucose response to the three meals tested in all subject groups: *A*, Nondiabetic; *B*, Noninsulin dependent diabetic; *C*, Insulin dependent diabetic. □---□ uncooked flummery, ▲——▲ carbohydrate and fat meal, △---△ carbohydrate alone meal. (Mean ± SEM). NB: Scale on ordinate different for diabetics in Figures 2 and 3.

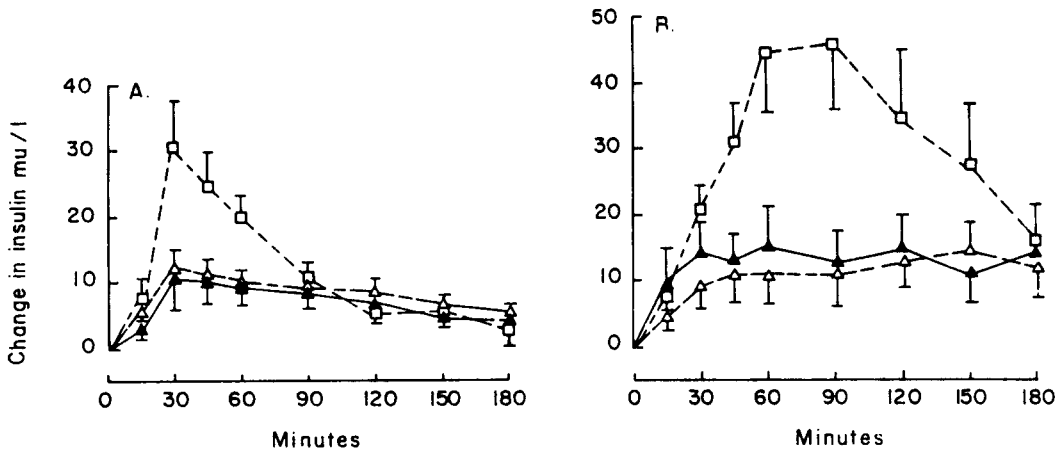

FIG 2. Insulin responses to the three meals tested in the nondiabetic (*A*) and NIDD (*B*). Symbols as in Figure 1.

tween 60 and 120 min (Student's paired *t* test, $p < 0.05$ and $p < 0.01$) and in the peak levels ($p < 0.01$).

There was a strong correlation (Spearman Rank, $\rho = 0.55$, $n = 28$, $p < 0.01$) between the fasting plasma glucose and the incremental response in plasma glucose to the uncooked flummery when all data were pooled.

Insulin (Fig 2). The overall insulin response for the uncooked flummery is significantly greater in nondiabetics (2-way Anova, $p < 0.05$) and NIDD ($p < 0.01$) than that for the carbohydrate and fat meal. For the nondiabetic subjects these two responses differed significantly between 30 and 60 min (Student's paired *t* test, $p < 0.05$ to $p < 0.01$) and in peak levels ($p < 0.01$). For the NIDD, the 2 responses differed significantly between 45 and 120 min ($p < 0.05$ to $p < 0.01$) and in peak levels ($p < 0.01$).

The insulin responses to the carbohydrate and fat and carbohydrate alone meals do not differ significantly for either nondiabetic or NIDD subjects.

GIP (Fig 3). The GIP response to the flummery was significantly greater (2-way

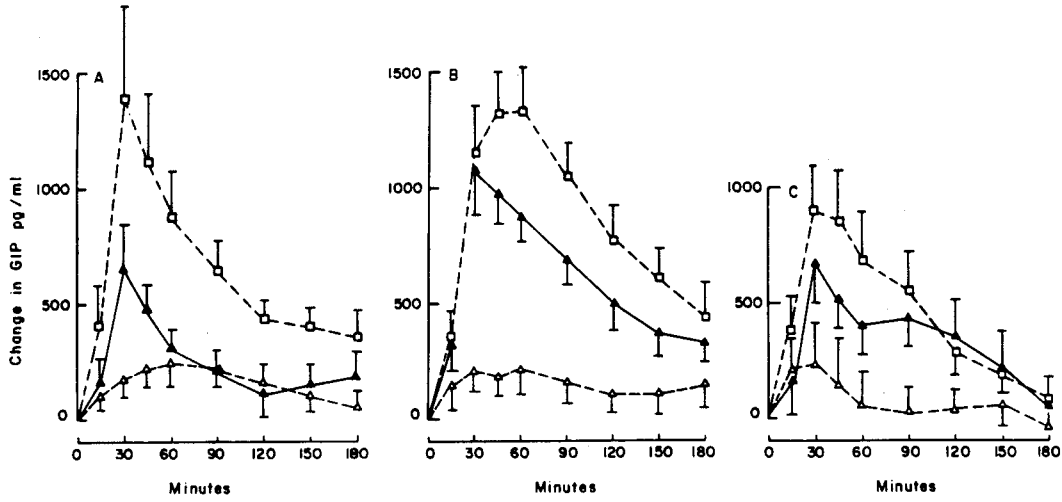

FIG 3. GIP responses to the three meals tested in all subject groups. *A*, Nondiabetic; *B*, Noninsulin dependent diabetic; *C*, Insulin dependent diabetic. Symbols as in Figure 1.

Anova, $p < 0.01$) than that for carbohydrate and fat for nondiabetics. The two responses also differed at time points 45 to 120 min (Student's paired t test, $p < 0.05$ to $p < 0.02$). Likewise, the GIP response in NIDD to the flummery was greater when compared with the carbohydrate and fat meal (2-way Anova, $p < 0.05$; time points 60–90 min, Student's paired t test, $p < 0.05$). There was a similar trend for these two meals in IDD but the differences did not reach statistical significance.

The GIP responses in nondiabetics to the carbohydrate and fat meals tended to be greater than that for carbohydrate alone although the difference did not reach statistical significance. For both diabetic groups the response to the carbohydrate and fat meal was significantly above that for the carbohydrate alone meal (2-way Anova, NIDD $p < 0.01$, IDD $p < 0.05$). The peak responses for these two meals also differed significantly in NIDD (Student's paired t test, $p < 0.01$). For both diabetic groups the two responses also differed significantly at different time points (Student's paired t test, NIDD 30–150 min, $p < 0.05$ to $p < 0.01$; IDD 60–120 min, $p < 0.05$ to $p < 0.01$).

Discussion

We have previously confirmed that physical food factors may substantially modify the glycemic responses to a meal in nondiabetics. In contrast, we have shown that these factors in diabetics have a reduced or even different impact on the glycemic response. In the current study we have confirmed the marked individual effects of the macronutrients fat and protein on reducing the plasma glucose response to a meal in nondiabetics. Again, in contrast for diabetics, these macronutrients did not reduce the glycemic response to the carbohydrate in the meal and for IDD, protein actually increased the magnitude of the response. Limited earlier studies have reported that fat and protein potentially modify the postprandial plasma glucose level in poorly defined or very mild (4, 5, 9, 10) diabetics in a manner similar to that observed in normal subjects. However, this study has shown that in well-defined diabetic groups (NIDD and IDD) neither of these macronutrients significantly reduce the glycemic response. It is of interest that earlier workers (11) did recognize the contribution to the postprandial plasma glucose response due to protein in insulin-deficient subjects.

Fat reduces the rate of gastric emptying (12) which is the presumed mechanism for the reduced glycemic response in nondiabetics. The absence of an effect in both diabetic groups may reflect the presence of mild gastric stasis due to unrecognized autonomic neuropathy.

The hormonal responses to the macronutrients are largely similar in all subject groups. Protein is a recognized insulin secretagogue (2) and in both nondiabetic and NIDD subjects the insulin response to the meal was reduced by the withdrawal of protein. In contrast, fat does not affect insulin secretion and in neither subject group was an effect on the insulin response observed when fat was withheld.

Fat is an important GIP secretagogue and alone does not raise insulin levels (13) and this is consistent with the differences observed in the hormonal responses between the carbohydrate and fat and carbohydrate alone meals seen in both diabetic groups. The same trend, although not too statistically significant, was observed for the nondiabetics. Mixed amino acids (14) alone stimulate GIP secretion and this is again consistent with the significantly enhanced GIP response to the meal containing protein observed in this study in both normal subjects and NIDD with a similar trend found in IDD.

As highlighted in the accompanying paper (1), there is a correlation between the fasting plasma glucose and the response to a mixed meal. Although this could indicate that the fasting plasma glucose level influences the amplitude of the meal response, this is not necessarily so and has not been widely observed in the past.

There is a significant age difference between the NIDD and the other two subject groups. However, this is unlikely to account for the differences observed between the groups as the responses of the NIDD in general fall between those observed for IDD and normals.

In conclusion, we have again shown that there are major differences between diabetic and nondiabetic subjects in the influences of

different food factors on the glycemic responses. This further reinforces the need for studies designed to optimize the reduction in the postprandial plasma glucose responses in diabetics to be performed in subjects with diabetes. In contrast, the hormonal responses for nondiabetics and diabetics to the interacting macronutrients are remarkably similar. It is interesting that these studies have again observed an apparent separation of food factor induced changes in the glycemic and hormonal responses in NIDD (15). The pathophysiologic significance of this observation is uncertain.

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