

Effect of whey on blood glucose and insulin responses to composite breakfast and lunch meals in type 2 diabetic subjects¹⁻³

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ABSTRACT

Background: Whey proteins have insulinotropic effects and reduce the postprandial glycemia in healthy subjects. The mechanism is not known, but insulinogenic amino acids and the incretin hormones seem to be involved.

Objective: The aim was to evaluate whether supplementation of meals with a high glycemic index (GI) with whey proteins may increase insulin secretion and improve blood glucose control in type 2 diabetic subjects.

Design: Fourteen diet-treated subjects with type 2 diabetes were served a high-GI breakfast (white bread) and subsequent high-GI lunch (mashed potatoes with meatballs). The breakfast and lunch meals were supplemented with whey on one day; whey was exchanged for lean ham and lactose on another day. Venous blood samples were drawn before and during 4 h after breakfast and 3 h after lunch for the measurement of blood glucose, serum insulin, glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide 1 (GLP-1).

Results: The insulin responses were higher after both breakfast (31%) and lunch (57%) when whey was included in the meal than when whey was not included. After lunch, the blood glucose response was significantly reduced [-21% ; 120 min area under the curve (AUC)] after whey ingestion. Postprandial GIP responses were higher after whey ingestion, whereas no differences were found in GLP-1 between the reference and test meals.

Conclusions: It can be concluded that the addition of whey to meals with rapidly digested and absorbed carbohydrates stimulates insulin release and reduces postprandial blood glucose excursion after a lunch meal consisting of mashed potatoes and meatballs in type 2 diabetic subjects. *Am J Clin Nutr* 2005;82:69–75.

KEY WORDS Milk, whey, type 2 diabetes, blood glucose, serum insulin, incretin hormones

INTRODUCTION

In recent years, the awareness of the insulinotropic effects of milk has been growing (1). It seems that milk proteins, in particular the whey fraction, have a stimulating effect on insulin secretion in healthy subjects (2).

The key mechanism is not known, but elevated concentrations of specific insulinogenic amino acids as well as bioactive peptides, either originally present in whey or formed during digestion, are possible. Also, the incretin hormones seem to be involved. Particularly, glucose-dependent insulinotropic polypeptide (GIP) has been reported to increase significantly in blood

plasma after whey ingestion (2). In addition to GIP, glucagon-like peptide 1 (GLP-1) is known to have insulinotropic properties during normal plasma glucose concentrations (3).

Previously, skim milk was reported to have insulinotropic effects in untreated type 2 diabetic subjects (4). It is known that proteins vary with respect to their effect on glucose metabolism in type 2 diabetic subjects and may stimulate insulin release and attenuate blood glucose response (5, 6). Food proteins are also capable of stimulating insulin response in the absence of carbohydrates (7, 8), and coingestion of dietary protein and glucose may have synergistic effects on insulin response (7).

The potential health aspects of the insulinotropic effects of milk remain unclear. Hyperinsulinemia, mediated from hyperglycemia, seems to be a risk factor for diseases within the metabolic syndrome. DelPrato et al (9) showed that experimental induction of hyperinsulinemia experimentally over a 48–72-h period at normoglycemic conditions decreased insulin sensitivity in healthy subjects. In contrast, epidemiologic evidence suggests that overweight subjects with a high intake of milk and dairy products are at lower risk of developing diseases related to the insulin resistance syndrome (10).

Clinically, fasting blood glucose rather than postprandial responses has been regarded as important as an indicator of the metabolic control of diabetes. However, the postprandial response is increasingly being recognized as a highly relevant determinant of glycated hemoglobin (Hb A_{1c}) (11). Several insulin secretagogues are available on the market such as sulfonylureas and glinides for medical treatment of type 2 diabetes (12). It could be hypothesized that the insulinotropic effect of whey might be used similarly to those pharmaceuticals for the purpose of facilitating normoglycemia in diabetic subjects.

The aim of the present study was to investigate whether the insulinotropic effect of milk proteins, which was previously

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TABLE 1
Nutrient composition of the test meal and the reference meal¹

	Carbohydrate	Protein
<i>g</i>		
Reference meal		
Breakfast		
Bread	44.7	11.6
Ham	—	18.2
Lactose	5.3	—
Total	50.0	29.8
Lunch		
Mashed potatoes	35.6	3.9 ¹
Meatballs	5.0 ¹	6.5 ¹
Ham	—	18.2
Lactose	5.3	—
Total	45.9	28.6
Whey meal		
Breakfast		
Bread	44.7	11.6
Whey	5.3	18.2
Total	50.0	29.8
Lunch		
Mashed potatoes	35.6	3.9 ¹
Meatballs	5.0 ¹	6.5 ¹
Whey	5.3	18.2
Total	45.9	28.6

¹ According to the manufacturer.

observed in healthy subjects, could be detected in type 2 diabetic patients. More specifically, we hypothesized that the insulinotropic effect of whey when used as a supplement to a breakfast and a subsequent lunch meal would lower the postprandial blood glucose response when compared with matched meals with no whey added. In addition, the responses of serum insulin, GIP, and GLP-1 were measured.

SUBJECTS AND METHODS

Test meals

White wheat bread (WWB) was baked at a commercial bakery (Koch's Bageri, Klippan, Sweden) according to the recipe described by Liljeberg and Björck (13). After baking, the loaves were frozen and stored until use. In the afternoon before each test day, the bread was placed at ambient temperature for thawing overnight. On the morning of the test day, the crust was removed and the bread was sliced in pieces to provide 4 slices per portion.

Whey powder was obtained from Arla Foods (Stockholm, Sweden). Instant potato powder (Basmos; Procordia Food, Es-löv, Sweden) and meatballs (ICA Handlarna, Solna, Sweden) were bought at a local market.

The study included 2 separate test days, in random order ≥ 1 wk apart, for each person. On both occasions breakfast and lunch 4 h later were served, with or without the addition of whey. The breakfast consisted of 102 g WWB (corresponding to 44.7 g available carbohydrates; **Table 1**) and 300 g water. For lunch 52.2 g instant potato powder stirred in 270 g boiling water and 50 g meatballs were served. Also, 300 g water was included in the lunch meal.

On one of the test days, 27.6 g whey powder was dissolved in the water for breakfast and lunch. On the other test day, whey was exchanged for 5.3 g lactose dissolved in water and 96 g lean ham.

Both protein and lactose content in the reference meals were equal to the quantities in the test meals. The amount of liquid was the same in all meals.

Chemical analysis

Lactose content in the whey powder was determined by using β -galactosidase to hydrolyze lactose enzymatically into galactose and glucose as earlier described by Nilsson et al (2). Glucose oxidase and peroxidase reagent (Glox-Novum; Kabi-Diagnostica, Stockholm, Sweden) dissolved in 0.5 mol/L tris-phosphate buffer pH 7 (5.6 g/100 mL) was used to analyze the liberated amount of glucose.

The protein contents in whey powder, ham, and bread were determined by Kjeldahl analysis (Kjeltec Auto 1030 Analyser; Tecator, Höganäs, Sweden). WWB and potato powder were analyzed for starch content according to Holm et al (14). The nutritional composition of each meal is shown in Table 1.

Study design

Fourteen diet-treated subjects with type 2 diabetes, 6 women and 8 men, aged 27–69 y, with a mean (\pm SD) body mass index (in kg/m²) of 26.2 \pm 3.1 were included in the study. Hb A_{1c} ranged from 4.3% to 7.7% ($\bar{x} \pm$ SEM: 5.4 \pm 0.2%; upper normal limit: 5.3%), and the mean (\pm SEM) fasting plasma glucose was 6.3 \pm 1.2 mmol/L. The patients were recruited by advertising in local newspapers. Of those who responded, the first 14 to fulfill the inclusion criteria were chosen for the study. Medical records were obtained from the patient's health care provider. The diagnosis was based on ≥ 2 fasting plasma glucose or postprandial plasma glucose measurements. Fasting plasma glucose > 6.9 mmol/L or postprandial (or postglucose load) plasma glucose > 12.1 mmol/L and absence of ketonemia and autoantibodies were considered diagnostic for diabetes type 2. None of the subjects had any known problems with lactose malabsorption.

The participants in the study were told to eat a few slices of WWB as a late meal in the evenings (between 2100 and 2200) before each test day. The subjects reported to the laboratory at 0745. A peripheral venous catheter was inserted into an antecubital vein, and a fasting blood sample was drawn. The breakfast was served, and the subjects ate steadily over a 12-min period. Black coffee or tea (150 mL) was served immediately after the breakfast. Each subject chose either coffee or tea at the first occasion and was then confined to the same drink throughout the study. Blood samples were drawn before breakfast (time 0) and at 10, 20, 30, 40, 60, 120, 180, and 240 min after breakfast commenced. Immediately after the 240-min sample, the subjects started eating lunch. Consequently, the 240-min value after breakfast was identical with the time 0 sample for lunch. Blood samples were also drawn at 10, 20, 30, 40, 60, 120, and 180 min after lunch. The lunch meal was eaten steadily during 12 min, and 150 mL coffee or tea was served afterward.

All meals were well tolerated, and the subjects had no problem finishing the meal within the 12-min period. All subjects were aware that they could withdraw from the study at any time. The study was conducted by an independent research organization, and the Ethics Committee of the Faculty of Medicine at Lund University approved the study.

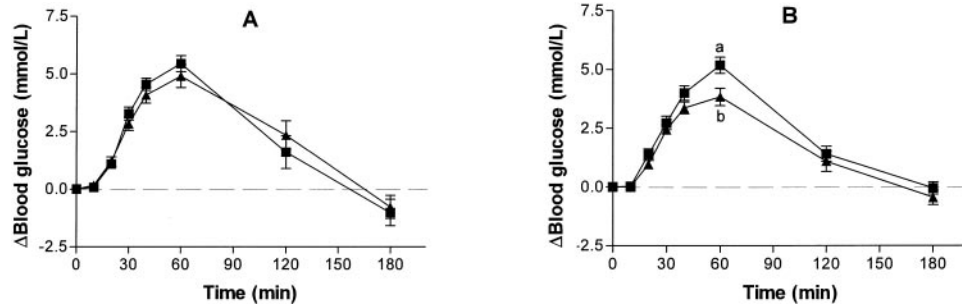


FIGURE 1. Mean (\pm SEM) incremental changes (Δ) in blood glucose in response to equal amounts of carbohydrate from a reference meal (\blacksquare) and a test meal of whey (\blacktriangle) served as breakfast (A) and lunch (B) in 14 diabetic subjects. At breakfast, no significant treatment effect ($P = 0.975$) or treatment \times time interaction ($P = 0.262$) was found. After lunch, no significant treatment effect ($P = 0.057$) was found, but a significant treatment \times time interaction ($P = 0.022$) was found. Values with different lowercase letters are significantly different, $P < 0.05$ (Tukey's test).

Blood analysis

At all time points, blood glucose was measured in blood drawn from tubes containing EDTA with the use of a B-Glucose Analyzer (Hemocue AB, Ängelholm, Sweden). Plasma GIP and GLP-1 and serum insulin were also analyzed at all time points. Insulin determination was performed on an integrated immunoassay analyzer, CODA Open Microplate System (Bio-Rad Laboratories, Hercules, CA) with the use of an enzyme immunoassay kit [Mercodia Insulin ELISA (enzyme-linked immunosorbent assay); Mercodia AB, Uppsala, Sweden].

For GIP and GLP-1 measurements we extracted plasma with 70% ethanol (by vol, final concentration). The C-terminally directed antiserum R65, which cross-reacts fully with human GIP but not with the so-called GIP 8000, whose chemical nature and relation to GIP secretion is uncertain, was used for the GIP radioimmunoassay (15). For standard and tracers we used human GIP and ^{125}I human GIP (70 MBq/nmol).

For measurement of plasma GLP-1 (16) we used standards of synthetic GLP-1 7–36 amide and antiserum code no. 89390, which is specific for the amidated C-terminus of GLP-1 and, therefore, does not react with GLP-1-containing peptides from the pancreas. The rate of secretion of GLP-1 is accurately reflected because the assay measures the sum of intact GLP-1 and the primary metabolite, GLP-1 9–36 amide, into which GLP-1 is rapidly converted (17). For both assays sensitivity was < 1 pmol/L, intraassay CV $< 6\%$ at 20 pmol/L, and recovery of standard, added to plasma before extraction, $\approx 100\%$ when corrected for losses inherent in the plasma extraction procedure.

Calculations and statistical methods

The incremental areas under the curve (AUCs) for glucose, insulin, GIP, and GLP-1 were calculated for each subject and each meal by using GRAPH PAD PRISM (version 3.02; GraphPad Software Inc, San Diego, CA). All AUCs below the baseline were excluded from the calculations. The AUCs were expressed as means \pm SEMs.

Significant differences among the AUCs were assessed with a general linear model (analysis of variance) followed by Tukey's multiple comparisons test (MINITAB, release 13.32; Minitab Inc, State College, PA). Differences resulting in P values < 0.05 were considered significant.

The differences between the products at different time points were analyzed by using a mixed model (PROC MIXED in SAS

release 8.01; SAS Institute Inc, Cary, NC) with repeated measures and an autoregressive covariance structure. When significant interactions between treatment and time were found, Tukey's multiple comparisons test was performed for each time point (MINITAB, release 13.32; Minitab Inc).

RESULTS

Breakfast meal

The fasting blood glucose and serum insulin concentrations did not differ significantly between the days of the reference and the whey breakfasts. The postprandial blood glucose concentrations are shown in **Figure 1**. The blood glucose response after breakfast was not significantly different after the whey meal than with the reference meal when evaluating AUCs (0–60 min, 0–120 min, and 0–180 min; **Table 2**).

TABLE 2

Postprandial areas under the curve (AUCs) for blood glucose, serum insulin glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide 1 (GLP-1) after the reference and whey breakfasts, in diet-treated type 2 diabetic subjects¹

	Reference	Whey	Change ²
Glucose AUC (mmol \cdot min/L)			%
0–60 min	168 \pm 10.2 ³	152 \pm 12.9	–9
0–120 min	382 \pm 32.0	370 \pm 42.8	–3
0–180 min	450 \pm 54.2	449 \pm 65.8	0
Insulin AUC (nmol \cdot min/L)			
0–60 min	7.3 \pm 1	12.3 \pm 1.7 ⁴	68
0–120 min	25.5 \pm 3.7	33.5 \pm 4.3 ⁴	31
0–180 min	37.5 \pm 5.7	44.3 \pm 6.1 ⁴	18
GIP AUC (pmol \cdot min/L)			
0–60 min	3231 \pm 592	4605 \pm 771 ⁴	43
0–120 min	7562 \pm 1319	9802 \pm 1549 ⁴	30
0–180 min	9565 \pm 1631	11464 \pm 1746	20
GLP-1 AUC (pmol \cdot min/L)			
0–60 min	1356 \pm 335	1343 \pm 136	–1
0–120 min	2520 \pm 507	2598 \pm 276	3
0–180 min	2845 \pm 563	3088 \pm 343	9

¹ $n = 14$.

² Change in postprandial response as a percentage of the reference meal.

³ $\bar{x} \pm$ SEM (all such values).

⁴ Significantly different from reference, $P < 0.05$ (ANOVA followed by Tukey's test).

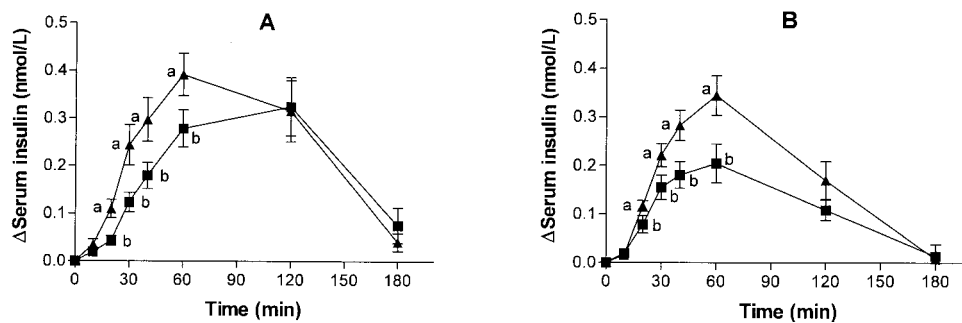


FIGURE 2. Mean (\pm SEM) incremental changes (Δ) in serum insulin in response to equal amounts of carbohydrate from a reference meal (■) and a test meal of whey (▲) served as breakfast (A) and lunch (B) in 14 diabetic subjects. At breakfast, no significant treatment effect ($P = 0.144$) was found, but a significant treatment \times time interaction ($P = 0.046$) was found. After lunch, a significant treatment effect ($P = 0.011$) and treatment \times time interaction ($P = 0.005$) were found at a given time. Values with different lowercase letters are significantly different, $P < 0.05$ (Tukey's test).

The postprandial insulin concentrations are shown in **Figure 2**. The insulin AUCs corresponding to the whey breakfast were significantly higher than the reference meal in the intervals 0–60, 0–120, and 0–180 min ($P < 0.05$; Table 2).

The GIP concentrations after the reference and whey meals are illustrated in **Figure 3**. The postprandial GIP response to the whey meal elicited higher responses than did the reference meal ($P < 0.05$) when examining the AUCs for the intervals 0–60, 0–120, and 0–180 min (Table 2).

GLP-1 concentrations are summarized in **Figure 4**. No significant differences in AUC for GLP-1 were found between the reference and whey meals (Table 2).

Lunch meal

The differences in blood glucose and serum insulin concentrations immediately before lunch (ie, 240 min after breakfast) were not statistically significant between the 2 test days. Significantly lower postprandial blood glucose responses (AUCs 0–60, 0–120, and 0–180 min) were observed when whey was included in the lunch than with the reference meal ($P < 0.05$; **Table 3**). The concomitant serum insulin response was elevated significantly after the whey meal than after the reference meal ($P < 0.05$). In accordance with the results after breakfast, the GIP responses after lunch (AUCs 0–60, 0–120, and 0–180 min) were significantly higher after the whey meal ($P < 0.05$; Table 3). Contrary to GIP, no significant difference was observed between the GLP-1 responses after whey compared with the reference meal when examining the AUCs.

DISCUSSION

Milk is known to have an insulinotropic effect (1), and it was recently shown that this property most probably is related to the whey protein fraction of milk (2). The results from the present study are in agreement with those earlier findings in healthy subjects whereby whey was found to elicit significantly higher insulin concentrations than WWB. Thus, from the present study it is evident that whey exhibits insulinotropic effects also in diet-treated diabetic subjects.

After breakfast no significant difference was observed between the whey meal and the reference meal containing ham when examining blood glucose. However, the glycemia was significantly decreased after lunch, most probably related to the higher insulin response, when whey was included in the meal. The cause for the less-pronounced insulinotropic effect of whey after breakfast is not known. Although the insulin response tended to be higher after the breakfast meal supplemented with whey, the differences in insulin response between the meal with whey added and the reference meal was smaller after breakfast (AUC 0–120 min differing 31%) than after lunch (AUC 0–120 min differing 57%). The lesser insulinotropic effect of whey after breakfast, in combination with the fact that the insulin resistance may be higher in the morning after the overnight fast (18), may explain the inability of whey to reduce the blood glucose increment after breakfast. In addition, the amounts of carbohydrates were slightly lower in the lunch meals than in the breakfast meals.

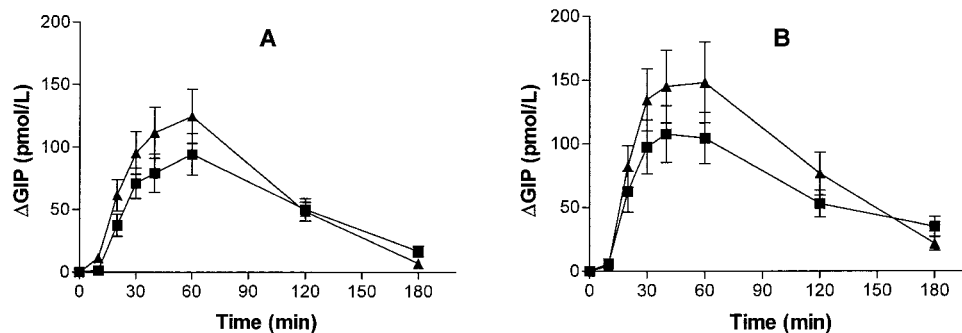


FIGURE 3. Mean (\pm SEM) incremental changes (Δ) in glucose-dependent insulintropic polypeptide (GIP) in response to equal amounts of carbohydrate from a reference meal (■) and a test meal of whey (▲) served as breakfast (A) and lunch (B) in 14 diabetic subjects. After breakfast, no significant treatment effect ($P = 0.072$) or treatment \times time interaction ($P = 0.273$) was found. After lunch, no significant treatment ($P = 0.051$) or treatment \times time interaction ($P = 0.307$) was found.

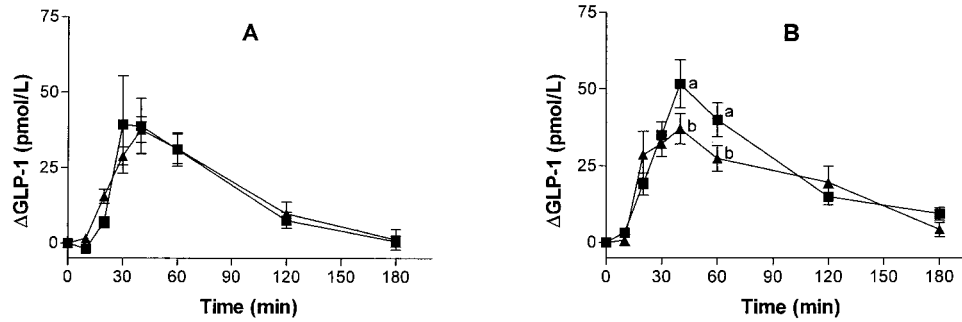


FIGURE 4. Mean (\pm SEM) incremental changes (Δ) in glucagon-like peptide 1 (GLP-1) in response to equal amounts of carbohydrate from a reference meal (■) and a test meal of whey (▲) served as breakfast (A) and lunch (B) in 14 diabetic subjects. At breakfast, no significant treatment effect ($P = 0.844$) or treatment \times time interaction ($P = 0.597$) was found. After lunch, no significant treatment effect ($P = 0.198$) was found, but a significant treatment \times time interaction ($P = 0.020$) was found. Values with different lowercase letters are significantly different, $P < 0.05$ (Tukey's test).

The key mechanism for the insulinotropic effects of milk proteins is not known. Certain amino acids may be involved (2), and a possible explanation of the differences in insulinotropic effects between various food proteins may be differences in their physical form. A liquid protein (whey) exits the stomach faster and is digested and absorbed more rapidly than a solid protein (19), resulting in a more pronounced postprandial plasma amino acid response.

Another possible pathway is through the activation of the incretin system. In parallel with insulin, the GIP concentrations were elevated in the blood shortly after ingestion when whey was included in the meal. This finding is in agreement with the earlier study in healthy subjects whereby whey was a much stronger GIP secretagogue than other food proteins such as cod, gluten, and cheese (2). The GIP response is possibly one key factor to the higher insulin response and the subsequent lowering of blood glucose seen after whey ingestion, at least in healthy subjects. In

patients with type 2 diabetes, the insulinotropic effect of GIP is more uncertain because the incretin effect appears to be impaired as a consequence of deteriorated secretion of GLP-1 and loss of insulinotropic activity of GIP (20). Likely, the defective response to GIP may depend on the metabolic disturbances of diabetes (21).

GIP response is known to be mediated by carbohydrate and fat ingestion (22), whereas the effect of dietary protein is more uncertain, although stimulating effects have been reported (23, 24). In contrast, Nordt et al (25) registered no effect of GIP response in type 2 diabetic subjects after a protein-rich meal. Earlier, whey was found to stimulate the GIP and GLP-1 response compared with casein in healthy subjects but without a subsequent effect on insulin response (26).

Although the glucose-induced insulin secretion is impaired in type 2 diabetic patients, the insulin secretion of other nutrients may remain unaffected (27). Van Loon et al (27) reported a substantially higher insulin response (189%) when an amino acid and protein mixture (wheat protein) was coingested with carbohydrates in type 2 diabetic patients but failed to show an attenuated glucose response. The insulinotropic effect of milk proteins, in particular the whey proteins, could be a valuable tool in the management of type 2 diabetes. Today sulfonylurea agents are commonly used to stimulate insulin secretion and to attenuate postprandial blood glucose. Occasionally, such treatment may cause hypoglycemia. This does not seem to be the case with GIP and GLP-1, and there have been no reports of whey causing hypoglycemia. Nuttall and Gannon (28) claimed that ingested protein in general is an efficient insulin secretagogue in type 2 diabetic subjects. It has been proposed that increasing insulin secretion may lead to early β -cell failure, the so-called " β -cell exhaustion hypothesis." The validity of the hypothesis has, however, been hard to prove. One early landmark study from 1980 showed that treatment with sulfonylurea in patients with impaired glucose tolerance significantly decreased the clinical progression to overt diabetes mellitus rather than the contrary (29). In the United Kingdom Prospective Diabetes Study (30), patients with newly diagnosed type 2 diabetes were randomly assigned to either intensive or conventional treatment. It was found that the patients treated with insulin had the same rate of decline in Hb A_{1c} and fasting blood glucose than did patients treated with sulfonylurea. Consequently, the results from the United Kingdom Prospective Diabetes Study do not support the β -cell exhaustion hypothesis.

TABLE 3

Postprandial areas under the curve (AUCs) for blood glucose, serum insulin, glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide 1 (GLP-1) after the reference and whey lunches, in diet-treated type 2 diabetic subjects¹

	Reference	Whey	Change ²
Glucose AUC (mmol \cdot min/L)			%
0–60 min	155 \pm 12.3 ³	124 \pm 9.5 ⁴	–20
0–120 min	353 \pm 25.6	277 \pm 26.8 ⁴	–21
0–180 min	403 \pm 35.0	320 \pm 35.5 ⁴	–21
Insulin AUC (nmol \cdot min/L)			
0–60 min	7.3 \pm 1.2	11.2 \pm 1.1 ⁴	53
0–120 min	17.0 \pm 2.7	26.7 \pm 3.1 ⁴	57
0–180 min	21.5 \pm 3.3	32.1 \pm 4.2 ⁴	49
GIP AUC (pmol \cdot min/L)			
0–60 min	4323 \pm 872	5872 \pm 1041 ⁴	36
0–120 min	9052 \pm 1735	12658 \pm 2442 ⁴	40
0–180 min	11692 \pm 2239	15656 \pm 2889 ⁴	34
GLP-1 AUC (pmol \cdot min/L)			
0–60 min	1752 \pm 230	1461 \pm 197	–17
0–120 min	3404 \pm 429	2907 \pm 425	–14
0–180 min	4162 \pm 511	3687 \pm 593	–11

¹ $n = 14$.

² Change in postprandial response as a percentage of the reference meal.


³ $\bar{x} \pm$ SEM (all such values).

⁴ Significantly different from reference, $P < 0.05$ (ANOVA followed by Tukey's test).

The present work is an acute study, and further studies are needed to determine possible longer-term effects of whey on blood glucose control. However, recent data suggest that dietary protein might be useful to facilitate blood glucose control in subjects with type 2 diabetes by lowering both the 24-h glucose response and Hb A_{1c} (31). Further studies are also needed to address the long-term metabolic effects of protein-induced hyperinsulinemia. Hoppe et al (32) recently showed that 1 wk with high milk intake increased insulin resistance and fasting serum insulin concentration. In contrast, epidemiologic data suggest that overweight subjects with a high intake of dairy products are at a lower risk of developing diseases related to the insulin resistance syndrome (10).

It has been proposed that reducing postprandial glycemia is a more expedient approach in diabetes treatment than lowering fasting blood glucose (11, 33). Conversely, others claim that in diabetic patients with fasting glucose > 7.8 mmol/L, the postprandial glucose response plays a much smaller role in determining the overall glycemic control (34). However, in both type 1 (35) and type 2 (36, 37) diabetic patients, postprandial glycemia was a better predictor for Hb A_{1c} concentrations compared with fasting blood glucose. Increasing the endogenous insulin response by ingestion of an insulinotropic protein, or amino acid mixture, might improve glucose homeostasis in type 2 diabetic patients and could possibly postpone the introduction of medical treatment.

In the present study, the 180-min AUC was decreased by 21% when whey was included in the lunch meal than in the reference meal containing ham. This decline was in the same range as reported by Gribble et al (38) who registered a reduction of the plasma glucose increment during a 180-min period by 1.1–1.9 mmol/L and an 18% reduction in total postprandial (180 min) glucose exposure after different doses of nateglinide, a novel rapid-acting nonsulfonylurea insulin secretagogue. Kitabchi et al (39) reported a reduction of 2-h blood glucose AUC response with 12–24% after a standardized meal (Sustacal), after sulfonylurea therapy (glipizide and glyburide) during 6–15 mo.

In conclusion, the insulinotropic effect of whey proteins may potentially attenuate the postprandial blood glucose excursions over the day. The ability to amplify insulin secretion by specifically tailored amino acid mixtures is under investigation, and this approach may have fewer adverse effects than the commonly used therapeutic agents. 

AHF recruited the subjects, collected the blood samples, was responsible for the analysis of blood glucose, and was involved in the design of the study and evaluation of the data. MN was involved in the design of the study, the statistical analysis, and the evaluation and was responsible for the insulin analysis. JJH was responsible for the incretin analysis and was involved in the evaluation. IMEB was responsible for securing the funding and was involved in the design and the evaluation. All authors contributed to the writing of the paper. None of the authors had a conflict of interest.

REFERENCES

- Östman EM, Elmståhl HGML, Björck IME. Inconsistency between glycemic and insulinemic responses to regular and fermented milk products. *Am J Clin Nutr* 2001;74:96–100.
- Nilsson M, Stenberg M, Frid AH, Holst JJ, Björck IME. Glycemia and insulinemia in healthy subjects after lactose equivalent meals of milk and other food proteins: the role of plasma amino acids and incretins. *Am J Clin Nutr* 2004;80:1246–53.
- Viltsboll T, Krarup T, Madsbad S, Holst JJ. Both GLP-1 and GIP are insulinotropic at basal and postprandial glucose levels and contribute nearly equally to the incretin effect of a meal in healthy subjects. *Regul Pept* 2003;114:115–21.
- Gannon MC, Nuttall FQ, Krezowski PA, Billington CJ, Parker S. The serum insulin and plasma glucose responses to milk and fruit products in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 1986;29:784–91.
- Nuttall FQ, Mooradian AD, Gannon MC, Billington C, Krezowski P. Effect of protein ingestion on the glucose and insulin response to a standardized oral glucose load. *Diabetes Care* 1984;7:465–70.
- Gannon MC, Nuttall FQ, Neil BJ, Westphal SA. The insulin and glucose responses to meals of glucose plus various proteins in type II diabetic subjects. *Metabolism* 1988;37:1081–8.
- Gannon MC, Nuttall FQ, Lane JT, Burmeister LA. Metabolic response to cottage cheese or egg white protein, with or without glucose, in type II diabetic subjects. *Metabolism* 1992;41:1137–45.
- Saeed A, Jones SA, Nuttall FQ, Gannon MC. A fasting-induced decrease in plasma glucose concentration does not affect the insulin response to ingested protein in people with type 2 diabetes. *Metabolism* 2002;51:1027–33.
- DelPrato S, Leonetti F, Simonson DC, Sheehan P, Matsuda M, DeFronzo RA. Effect of sustained physiologic hyperinsulinaemia and hyperglycaemia on insulin secretion and insulin sensitivity in man. *Diabetologia* 1994;37:1025–35.
- Pereira MA, Jacobs DR Jr, Van Horn L, Slattery ML, Kartashov AI, Ludwig DS. Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA Study. *JAMA* 2002;287:2081–9.
- Fonseca V. Clinical significance of targeting postprandial and fasting hyperglycemia in managing type 2 diabetes mellitus. *Curr Med Res Opin* 2003;19:635–41.
- Doyle ME, Egan JM. Pharmacological agents that directly modulate insulin secretion. *Pharmacol Rev* 2003;55:105–31.
- Liljeberg HGM, Björck IME. Bioavailability of starch in bread products. Postprandial glucose and insulin responses in healthy subjects and in vitro resistant starch content. *Eur J Clin Nutr* 1994;48:151–63.
- Holm J, Björck IME, Drews A, Asp N-G. A rapid method for the analysis of starch. *Starch/Stärke* 1986;38:224–6.
- Krarup T, Madsbad S, Moody AJ, et al. Diminished immunoreactive gastric inhibitory polypeptide response to a meal in newly diagnosed type I (insulin-dependent) diabetics. *J Clin Endocrinol Metab* 1983;56:1306–12.
- Orskov C, Rabenholz L, Wettergren A, Kofod H, Holst JJ. Tissue and plasma concentrations of amidated and glycine-extended glucagon-like peptide I in humans. *Diabetes* 1994;43:535–9.
- Deacon CF, Fridal L, Klarasov L, Olesen M, Holst JJ. Glucagon-like peptide I undergoes differential tissue-specific metabolism in the anesthetized pig. *Am J Physiol* 1996;271:E458–64.
- Plat L, Byrne MM, Sturis J, et al. Effects of morning cortisol elevation on insulin secretion and glucose regulation in humans. *Am J Physiol* 1996;270:E36–42.
- Boirie Y, Dangin M, Gachon P, Vasson M-P, Maubois J-L, Beaufrère B. Slow and fast dietary proteins differently modulate postprandial protein accretion. *Proc Natl Acad Sci U S A* 1997;94:14930–5.
- Holst JJ. Gastric inhibitory polypeptide analogues: do they have a therapeutic role in diabetes mellitus similar to that of glucagon-like Peptide-1? *BioDrugs* 2002;16:175–81.
- Viltsboll T, Knop FK, Krarup T, et al. The pathophysiology of diabetes involves a defective amplification of the late-phase insulin response to glucose by glucose-dependent insulinotropic polypeptide-regardless of etiology and phenotype. *J Clin Endocrinol Metab* 2003;88:4897–903.
- Elliott RM, Morgan LM, Tredger JA, Deacon S, Wright J, Marks V. Glucagon-like peptide-1 (7–36)amide and glucose-dependent insulinotropic polypeptide secretion in response to nutrient ingestion in man: acute post-prandial and 24-h secretion patterns. *J Endocrinol* 1993;138:159–66.
- Calbet JA, Holst JJ. Gastric emptying, gastric secretion and enterogastrone response after administration of milk proteins or their peptide hydrolysates in humans. *Eur J Nutr* 2004;43:127–39.
- Simpson RW, McDonald J, Wahlqvist ML, Atley L, Outch K. Macronutrients have different metabolic effects in nondiabetics and diabetics. *Am J Clin Nutr* 1985;42:449–53.
- Nordt TK, Besenthal I, Eggstein M, Jakober B. Influence of breakfasts with different nutrient contents on glucose, C peptide, insulin, glucagon, triglycerides, and GIP in non-insulin-dependent diabetics. *Am J Clin Nutr* 1991;53:155–60.



26. Hall WL, Millward DJ, Long SJ, Morgan LM. Casein and whey exert different effects on plasma amino acid profiles, gastrointestinal hormone secretion and appetite. *Br J Nutr* 2003;89:239–48.
27. Van Loon LJ, Kruijshoop M, Menheere PP, Wagenmakers AJ, Saris WH, Keizer HA. Amino acid ingestion strongly enhances insulin secretion in patients with long-term type 2 diabetes. *Diabetes Care* 2003;26:625–30.
28. Nuttall FQ, Gannon MC. Plasma glucose and insulin response to macronutrients in nondiabetic and NIDDM subjects. *Diabetes Care* 1991;14:824–38.
29. Sartor G, Schersten B, Carlstrom S, Melander A, Norden A, Persson G. Ten-year follow-up of subjects with impaired glucose tolerance: prevention of diabetes by tolbutamide and diet regulation. *Diabetes* 1980;29:41–9.
30. UKPDS. United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *Br Med J* 1995;310:83–8.
31. Gannon MC, Nuttall FQ, Saeed A, Jordan K, Hoover H. An increase in dietary protein improves the blood glucose response in persons with type 2 diabetes. *Am J Clin Nutr* 2003;78:734–41.
32. Hoppe C, Molgaard C, Vaag A, Barkholt V, Michaelsen KF. High intakes of milk, but not meat, increase serum IFG-1 and IGFBP-3 in eight-year-old boys. *Eur J Clin Nutr* 2004;58:1211–6.
33. Ratner RE. Controlling postprandial hyperglycemia. *Am J Cardiol* 2001;88:26H–31H.
34. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 1999;131:281–303.
35. Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. *Diabetes Care* 2002;25:275–8.
36. Avignon A, Radauceanu A, Monnier L. Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. *Diabetes Care* 1997;20:1822–6.
37. Bastyr EJ III, Stuart CA, Brodows RG, et al. Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA 1c. IOEZ Study Group. *Diabetes Care* 2000;23:1236–41.
38. Gribble FM, Manley SE, Levy JC. Randomized dose ranging study of the reduction of fasting and postprandial glucose in type 2 diabetes by nateglinide (A-4166). *Diabetes Care* 2001;24:1221–5.
39. Kitabchi AE, Kaminska E, Fisher JN, et al. Comparative efficacy and potency of long-term therapy with glipizide or glyburide in patients with type 2 diabetes mellitus. *Am J Med Sci* 2000;319:143–8.

