Protein Hydrolysate/Leucine Co-Ingestion Reduces the Prevalence of Hyperglycemia in Type 2 Diabetic Patients

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Epidemiological surveys and preliminary intervention studies have shown that postprandial hyperglycemia is a direct and independent risk factor for the development of cardiovascular disease in type 2 diabetes (1–4). Moreover, it has been reported that postprandial spikes in blood glucose concentration are even more relevant to the onset of cardiovascular complications than merely elevated fasting blood glucose levels (5–7).

Protein hydrolysate/leucine coingestion could represent an effective nutritional intervention to stimulate postprandial insulin secretion, augment postprandial blood glucose disposal, and improve blood glucose homeostasis in type 2 diabetic patients (8–10). Though promising, the clinical relevance and applicability of such a nutritional intervention remains to be established.

In the present study, we applied continuous glucose monitoring to assess the impact of protein hydrolysate/leucine coingestion with each main meal as a nutritional intervention strategy to improve daily glycemic control in long-standing type 2 diabetic patients.

RESEARCH DESIGN AND METHODS

— Eleven long-standing type 2 diabetic patients (aged 58 ± 1 years, BMI 28 ± 1 kg/m^2, HbA_{1c} 7.4 ± 0.3%) and 11 matched healthy control subjects (aged 59 ± 2 years, BMI 28 ± 1 kg/m^2, HbA_{1c} 5.5 ± 0.1%) participated in this study. All subjects were screened for type 2 diabetes according to American Diabetes Association guidelines (11). Type 2 diabetic patients had been diagnosed for 8 ± 1 years and were using metformin with (n = 8) or without (n = 3) a sulfonylurea derivative. Blood glucose–lowering medication was continued throughout the experimental trials. Subjects maintained normal dietary and physical activity patterns but refrained from exhaustive physical labor and exercise training for 3 days before each trial.

Each subject participated in a crossover study with two trials during which blood glucose concentrations were recorded for 40 h under free-living conditions using a continuous glucose monitoring system (CGMS) (GlucoDay*S*; A. Menarini Diagnostics, Firenze, Italy) (12). Subjects received three beverages containing a protein hydrolysate/leucine mixture or a placebo beverage. Prepacked beverages were consumed directly after each main meal. All meals, snacks, and beverages were provided in preweighed packages and were ingested at predetermined time points to ensure fully standardized dietary modulation during both trials. The standardized diet provided 121 kJ·kg^{-1}·day^{-1} (64% carbohydrate, 25% fat, and 11% protein). Beverages contained 4 ml/kg water (PLA) or water containing 0.3 g/kg casein protein hydrolysate and 0.1 g/kg leucine (PRO). Both trials were performed in a randomized and double-blind manner.

The acquired data were downloaded from the CGMS onto a personal computer with GlucoDay software (version 3.0.5). Values reported by the CGMS were converted into glucose values using self-monitoring blood glucose (SMBG) values. To quantify and compare the prevalence of hyperglycemia between groups and trials, the amount of time during which glucose concentrations were >10 mmol/l was calculated. A multiway ANOVA or a Student's t test for paired or unpaired observations were applied where applicable. All data are expressed as means ± SE and significance was set at P = 0.05.

RESULTS

— Total 24-h glucose concentrations were higher in the diabetic group versus the control subjects group (10.2 ± 0.4 vs. 6.2 ± 0.6 mmol/l, respectively, $P < 0.01$). In the diabetic patients, 24-h glucose concentrations in the PRO trial were significantly lower compared with the PLA trial (9.6 ± 0.6 vs. 10.8 ± 0.5 mmol/l, respectively, $P < 0.05$) (Fig. 1). PRO ingestion resulted in a 11 ± 3% decline in the overall glucose response in the diabetic patients ($P < 0.05$). In the control subjects, differences between trials did not reach statistical significance (6.2 ± 0.4 vs. 6.3 ± 0.2 mmol/l).

Despite a healthy standardized diet and the continued use of oral blood glucose–lowering medication, hyperglycemia (>10 mmol/l) was prevalent during 55 ± 7% of the 24-h period in the diabetic patients in the PLA trial. In the control group, hyperglycemia was hardly present (2 ± 1% or 25′ ± 15′ min). In the diabetic patients, the prevalence of hyperglycemia was significantly lower in the PRO versus PLA trial (39 ± 6 vs. 55 ± 7%, respectively, $P < 0.05$). The latter represented a 26 ± 9% reduction in the prevalence of hyperglycemia from 1318′ ± 0140′ in the PLA trial to 0942′ ± 0154′ in the PRO trial ($P < 0.05$).

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Abbreviations: CGMS, continuous glucose monitoring system; SMBG, self-monitoring blood glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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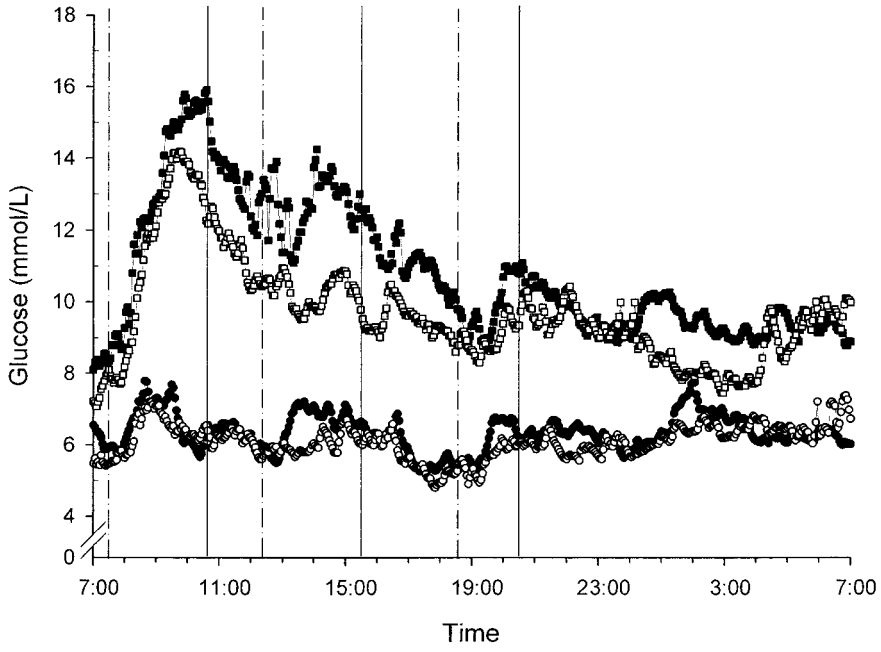

Figure 1— *Mean blood glucose patterns over a 24-h period while using a standardized diet with (open symbols) or without (filled symbols) co-ingestion of a protein hydrolysate/leucine mixture with each main meal in long-standing type 2 diabetic patients (□/■, n = 11) and healthy matched control subjects (○/●, n = 11). Vertical dashed lines indicate time of breakfast (0730), lunch (1230), and dinner (1830), respectively. Vertical solid lines indicate between-meal snacks.*

CONCLUSIONS — The prevalence of elevated postprandial glucose excursions in type 2 diabetic patients imposes a direct and independent risk for the development of cardiovascular complications (6,7,13). In accordance, both the Diabetes Control and Complications Trial (1) and the U.K. Prospective Diabetes Study (2–4) report that improving glycemic control effectively reduces the risk of developing micro- and macrovascular complications and cardiovascular disease.

The present study shows that long-standing type 2 diabetic patients who receive standard primary medical care experience hyperglycemia throughout the greater part of the day. Co-ingestion of a protein hydrolysate/leucine mixture following each main meal substantially reduces the prevalence of hyperglycemia in these patients. This is accompanied by a significant reduction in average 24-h blood glucose concentration. Although the use of continuous glucose monitoring devices in an applied setting does not allow for concomitant insulin measurements, numerous other studies (8–10,14,15) have repeatedly shown that protein hydrolysate/amino acid co-ingestion stimulates insulin secretion, resulting in improved glucose disposal and reduced postprandial glucose concentrations.

These data extend on previous findings and provide evidence that protein hydrolysate/leucine co-ingestion represents an effective dietary strategy to improve daily blood glucose homeostasis under free-living conditions in long-standing type 2 diabetic patients.

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References

1. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus: the Diabetes Control and Complications Trial Research Group. *N Engl J Med* 329:977–986, 1993
2. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33): UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352:837–853, 1998
3. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34): UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352:854–865, 1998
4. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000
5. Ceriello A: Impaired glucose tolerance and cardiovascular disease: the possible role of post-prandial hyperglycemia. *Am Heart J* 147:803–807, 2004
6. Ceriello A: Postprandial hyperglycemia and diabetes complications: is it time to treat? *Diabetes* 54:1–7, 2005
7. Heine RJ, Balkau B, Ceriello A, Del Prato S, Horton ES, Taskinen MR: What does postprandial hyperglycaemia mean? *Diabet Med* 21:208–213, 2004
8. van Loon LJC, Kruishoop M, Menheere PPCA, Wagenmakers AJM, Saris WHM, Keizer HA: Amino acid ingestion strongly enhances insulin secretion in patients with long-term type 2 diabetes. *Diabetes Care* 26:625–630, 2003
9. Manders RJ, Koopman R, Sluijsmans WE, van den Berg R, Verbeek K, Saris WH, Wagenmakers AJ, van Loon LJ: Co-ingestion of a protein hydrolysate with or without additional leucine effectively reduces postprandial blood glucose excursions in type 2 diabetic men. *J Nutr* 136:1294–1299, 2006
10. Manders RJ, Wagenmakers AJ, Koopman R, Zorenc AH, Menheere PP, Schaper NC, Saris WH, van Loon LJ: Co-ingestion of a protein hydrolysate and amino acid mixture with carbohydrate improves plasma glucose disposal in patients with type 2 diabetes. *Am J Clin Nutr* 82:76–83, 2005
11. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 26 (Suppl. 1):S5–S20, 2003
12. Maran A, Crepaldi C, Tiengo A, Grassi G, Vitali E, Pagano G, Bistoni S, Calabrese G, Santeusanio G, Leonetti F, Ribaudo M, Di Mario U, Annuzzi G, Genovese S, Riccardi G, Previti M, Cucinotta D, Giorgino F, Bellomo A, Giorgino R, Poscia A, Varalli M: Continuous subcutaneous glucose monitoring in diabetic patients: a multicenter analysis. *Diabetes Care* 25:347–352, 2002
13. Ceriello A: The possible role of postprandial hyperglycaemia in the pathogenesis of diabetic complications. *Diabetologia* 46 (Suppl. 1):M9–M16, 2003
14. Frid AH, Nilsson M, Holst JJ, Bjorck IM: Effect of whey on blood glucose and insulin responses to composite breakfast and lunch meals in type 2 diabetic subjects. *Am J Clin Nutr* 82:69–75, 2005
15. Gannon MC, Nuttall FQ: Control of blood glucose in type 2 diabetes without weight loss by modification of diet composition. *Nutr Metab (Lond)* 3:16, 2006