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Glutamine Reduces Postprandial Glycemia and Augments the Glucagon-Like Peptide-1 Response in Type 2 Diabetes Patients[1–3]

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Abstract

Impaired glucagon-like peptide (GLP-1) secretion or response may contribute to ineffective insulin release in type 2 diabetes. The conditionally essential amino acid glutamine stimulates GLP-1 secretion in vitro and in vivo. In a randomized, crossover study, we evaluated the effect of oral glutamine, with or without sitagliptin (SIT), on postprandial glycemia and GLP-1 concentration in 15 type 2 diabetes patients (glycated hemoglobin 6.5 ± 0.6%). Participants ingested a low-fat meal (5% fat) after receiving either water (control), 30 g L-glutamine (Gln-30), 15 g L-glutamine (Gln-15), 100 mg SIT, or 100 mg SIT and 15 g L-glutamine (SIT+Gln-15). Studies were conducted 1–2 wk apart. Blood was collected at baseline and postprandially for 180 min for measurement of circulating glucose, insulin, C-peptide, glucagon, and total and active GLP-1. Gln-30 and SIT+Gln-15 reduced the early (t = 0–60 min) postprandial glycemic response compared with control. All Gln treatments enhanced the postprandial insulin response from t = 60–180 min but had no effect on the C-peptide response compared with control. The postprandial glucagon concentration was increased by Gln-30 and Gln-15 compared with control, but the insulin:glucagon ratio was not affected by any treatment. In contrast to Gln-30, which tended to increase the total GLP-1 AUC, SIT tended to decrease the total GLP-1 AUC relative to control (both $P = 0.03$). Gln-30 and SIT increased the active GLP-1 AUC compared with control ($P = 0.008$ and $P = 0.01$, respectively). In summary, Gln-30 decreased the early postprandial glucose response, enhanced late postprandial insulinemia, and augmented postprandial active GLP-1 responses compared with control. These findings suggest that glutamine may be a novel agent for stimulating GLP-1 concentration and limiting postprandial glycemia in type 2 diabetes. J. Nutr. 141: 1233–1238, 2011.

Introduction

Defective insulin secretion is a key abnormality contributing to hyperglycemia and type 2 diabetes (1,2). Incretin hormones, such as glucagon-like peptide-1 (GLP-1)[9] and glucose-dependent insulinotropic polypeptide, play a major role in mediating physiological insulin release following a meal (3,4). Although controversial (5,6), some evidence suggests that GLP-1 secretion is defective in type 2 diabetes (2,7–9), developing as a consequence, rather than cause, of the hyperglycemic state (2,6,7). Insulin release from the β-cell in response to endogenous GLP-1 is preserved in well-controlled type 2 diabetes (10). However, the potency of GLP-1 to enhance insulin secretion may be decreased in more advanced disease (11). In contrast, gl ucose-dependent insulinotropic polypeptide secretion is intact in diabetes, although the insulinotropic response to this incretin hormone is impaired (12). Interestingly, the blunted insulin response to incretins in poorly controlled type 2 diabetes may be restored when glycemic control is improved (11).

There has been much recent interest in developing methods by which GLP-1 action can be enhanced in diabetes. An alternative approach to the use of GLP-1 receptor agonists and inhibitors of dipeptidyl peptidase-IV (DPP-IV) is the direct stimulation of GLP-1 secretion from intestinal L-cells. This approach has the additional benefit of stimulating other entero-endocrine pep-

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[3] This trial was registered at clinicaltrials.gov as NCT-00673894.
[9] Abbreviations used: DPP-IV, dipeptidyl peptidase-IV; GLP, glucagon-like peptide; Gln-15, L-glutamine 15 g; Gln-30, L-glutamine 30 g; SIT, sitagliptin; SIT +Gln-15, sitagliptin + 15 g L-glutamine.
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tides, including peptide YY and oxyntomodulin, which suppress appetite and reduce food intake (13,14), and GLP-2, which stimulates regeneration and repair of intestinal epithelium (15). Moreover, stimulation of L-cell secretion will increase the GLP-1 9–36 concentration, the cleaved product of DPP-IV, which is a weak insulinotropic agonist that suppresses hepatic glucose production and possibly exerts antioxidant actions in the heart and vasculature (16).

We have previously demonstrated that oral glutamine increases the GLP-1 concentration in lean, insulin-resistant obese and diabetic individuals, an effect associated with an increased circulating insulin concentration (17). Glutamine is one of the most abundant free amino acid in humans, comprising 20% of the amino acid pool in plasma and 50% in human skeletal muscle (18). Interestingly, the circulating glutamine concentration is reduced in well-controlled type 2 diabetes of short duration (19). Oral glutamine doses of 0.35–0.65 $g \cdot kg^{-1}$ result in peak concentrations at 30–60 min (17,20), with similar concentrations attained in individuals with and without diabetes (17). An oral glutamine intake of up to 0.5 $g \cdot kg^{-1}$ is relatively palatable (20) and has been shown to be safe over 14 d with no adverse effects on liver and renal function in middle-aged and elderly individuals (18).

Whether oral glutamine reduces postprandial glycemia when consumed with a meal in patients with type 2 diabetes remains unknown. The aims of this study were to determine whether glutamine attenuates postprandial glycemia in patients with type 2 diabetes when consumed with a meal and whether glutamine enhances postprandial circulating insulin, C-peptide, and GLP-1 concentrations.

Materials and Methods

Type 2 diabetes patients were recruited through advertisements at the St. Vincent's Hospital precinct, Sydney, and in local newspapers. Exclusion criteria included treatment with oral hypoglycemic agents other than metformin, ethanol intake of 40 g/d or more, liver or kidney disease, weight change of >2 kg in the preceding 6 mo, use of weight loss medications, previous bowel surgery, and documented malabsorption. The study was a randomized crossover design and was approved by the Human Research and Ethics Committee at St. Vincent's Hospital. All participants gave written informed consent.

Study design. Participants attended the Clinical Research Facility at the Garvan Institute of Medical Research on 5 separate occasions, fasted from 2200 h the previous night, and received, in a random order: water (control); 30 g of L-glutamine (Gln-30); 15 g L-glutamine (Gln-15); 100 mg sitagliptin (SIT); and 100 mg SIT plus Gln-15 (SIT + Gln-15). Following these treatments, participants consumed a meal comprising 33 g Wheat-Bix and 250 mL low fat milk, providing 963 kJ (37 g carbohydrate, 1.3 g fat, and 16 g protein). SIT was administered 25 min prior to the meal (t = −25) with 50 mL of water. L-Glutamine powder (Cambridge Commodities) was consumed in 300 mL of ice-cold water, to avoid its transformation to pyroglutamic acid (21), over 2 min immediately prior to the meal, which was consumed over 10 min (t = −10–0 min). Because glutamine at high concentration does not dissolve completely in water, we used the swish and swallow technique, as previously described (20). Participants were instructed to complete the meal, which was monitored by the study nurse. t = 0 corresponds to the end of meal ingestion.

Study visits were generally separated by 1–2 wk. Participants taking metformin omitted this medication on study days. A large-bore i.v. indwelling cannula was inserted into a large antecubital vein on each visit for blood sampling. At the first visit, weight and height were measured with the participant wearing light street clothing and BMI was calculated (weight in kilograms divided by the square of the height in meters, $kg \cdot m^{-2}$). On each study day, 2 fasting baseline blood samples were collected at t = −35 and −25 min (prior to SIT administration). After consumption of the meal, blood samples were collected at t = 15, 30, 45, 60, 90, 120, 150, and 180 min for blood glucose, serum insulin and C-peptide, and plasma glucagon and GLP-1 (total and active). Satiety was assessed fasting, immediately after meal ingestion (t = 0) and half-hourly for 180 min using a visual analogue scale.

Analytical methods. Blood for glucose was collected in a fluoride oxalate tube and assayed immediately after collection, by the glucose oxidase electrode (Yellow Springs Instrument Company, YSI; Life Sciences). Glycated hemoglobin was analyzed by cation-exchange HPLC using the Variant II analyzer (Bio-Rad Laboratories). All other assays were performed on plasma and serum samples stored at −80°C. Insulin, C-peptide, and glucagon were quantified by RIA (Linco Research). Blood for total and active GLP-1 was collected into chilled EDTA-coated tubes (with DPP-IV inhibitor and trasylol in the active GLP-1 testing tube to prevent DPP-IV and protease activity, respectively), which were immediately centrifuged for 7 min at 4100 × *g*, snap-frozen, and stored at −80°C until analysis. Total GLP-1 concentrations were measured by RIA after extraction of plasma with 70% ethanol (v:v, final concentration). Carboxy-terminal GLP-1 immunoreactivity was determined using antiserum 89390, which has an absolute requirement for the intact amidated carboxyl terminus of GLP-1 7–36 amide and cross-reacts <0.01% with carboxy-terminally truncated fragments and 89% with GLP-1 9–36 amide, the primary metabolite of DPP-IV–mediated degradation. The sum of the 2 components (total GLP-1 concentration) reflects the rate of secretion of the L-cell (22). Active GLP-1 was analyzed at t = −35, −25, 15, 30, 60, 120, and 180 min (limited number to ensure all samples from the same participant were analyzed on the same plate) using an ELISA on unextracted plasma, as previously reported (23). For both assays, sensitivity was <1 pmol/L and intra-assay CV < 6%.

Statistical analysis. Baseline characteristics of the cohort are presented as mean ± SD. Fasting baseline glucose, insulin, C-peptide, glucagon, and GLP-1 data were calculated as the mean of the t = −35 and −25 results of all 5 visits. Insulin data were not normally distributed and were $\log_{10}$-transformed prior to statistical analysis. Because there were no differences in baseline concentrations among treatments for glucose, insulin, C-peptide, glucagon, or total and active GLP-1 by 1-way ANOVA, AUC are presented. AUC were calculated using the trapezoidal rule. When calculating the AUC, t = −35 and −25 time points were averaged to serve as the baseline value. Consistent with our previously reported biphasic GLP-1 response to glutamine and glucose (17), first (0–60 min) and second (60–180 min) phase AUC are also reported. The treatments were compared with the control using paired *t* tests. Significance was calculated using the Dunn-Bonferroni correction (24) for the 4 control vs. treatment pairs at an overall significance threshold of 0.05. Thus, an individual paired *t* test of $P < 0.0125$ (0.05/4) was deemed significant. Data were analyzed using SPSS version 15. Comparisons between treatments were not performed. There was no effect of gender on the data and thus data for the whole cohort are presented. There were 13 different combinations for the order of treatments in the present study; thus, the effect of treatment order on the results could not be tested. In any case, treatments were separated by at least 1 wk; thus, the order of the treatments was not expected to affect the results.

Results

Cohort characteristics. Fifteen participants (9 males and 6 females) were studied. Mean age was 63.6 ± 5.2 y and BMI 29.7 ± 4.4 $kg \cdot m^{-2}$. Type 2 diabetes was of a short duration (2.4 ± 1.2 y). Participants were treated with lifestyle alone (n = 4) and/or metformin therapy (n = 11) and glycemia was well controlled (glycated hemoglobin 6.5 ± 0.6%). Averaged across the 5 visits, fasting results were as follows: blood glucose, 6.2 ± 0.8 mmol/L; serum insulin, 146 ± 90 pmol/L; serum C-peptide, 3.3 ± 1.4 μg/L;

plasma glucagon, 77.1 ± 27.7 ng/L; plasma total GLP-1 23.1 ± 7.9 pmol/L; and plasma active, GLP-1, 4.4 ± 3.4 pmol/L.

Circulating metabolites. Gln-30 and SIT+Gln-15 reduced the postprandial glucose response compared with control, an effect limited to the first phase (t = 0–60 min) (**Fig. 1**; **Table 1**). Gln-15 tended to decrease the first phase glucose response from t = 0–60 min ($P = 0.016$). SIT did not affect postprandial glycemia during either phase (Table 1).

Gln-30 and Gln-15 increased and SIT+Gln-15 tended to increase ($P = 0.017$) the postprandial insulin response compared with control, an effect primarily due to the t = 60–180 min period (Table 1). SIT did not increase the insulin concentration in either phase (Table 1). The effect of the treatments on insulin should be viewed relative to the prevailing glucose level; therefore, the insulin:glucose ratio was calculated and the results were similar (Fig. 1; Table 1).

Different from its effect on insulin, glutamine did not enhance the postprandial C-peptide response (Table 1). However, Gln-15 increased the C-peptide:glucose ratio at t = 0–60 min. SIT increased ratio when taken alone or in combination with 15 g glutamine (Fig. 1; Table 1).

The postprandial glucagon concentration was increased by Gln-30 and Gln-15 (Table 1) and tended to be increased by SIT +Gln-15 ($P = 0.018$). The ratio of insulin:glucagon was also calculated (Fig. 1). Gln-30 decreased this ratio at t = 0–60 min. Otherwise, due to parallel increases in insulin and glucagon concentrations, the ratio was not different from control for all treatments (Table 1).

Gln-30 tended to increase the total GLP-1 AUC ($P = 0.03$) compared with control. In contrast, SIT+Gln-15 and SIT alone both tended to decrease the t = 0–180 AUC compared with control ($P = 0.013$ and $P = 0.03$) and significantly decreased the total GLP-1 AUC at t = 0–60 min (Table 1) relative to control. Active GLP-1 AUC was enhanced by both Gln-30 and SIT compared with control, an effect driven by the t = 0–60 min period (Table 1).

Adverse effects and satiety. Glutamine was generally well tolerated, with no patient experiencing diarrhea or vomiting. One participant felt nauseated after taking the Gln-15 and Gln-30 and another after taking Gln-30 only. Headache was reported by 1 participant after all 3 glutamine treatments, by another after Gln-30 only, and in a 3rd patient after Gln-15 only. None

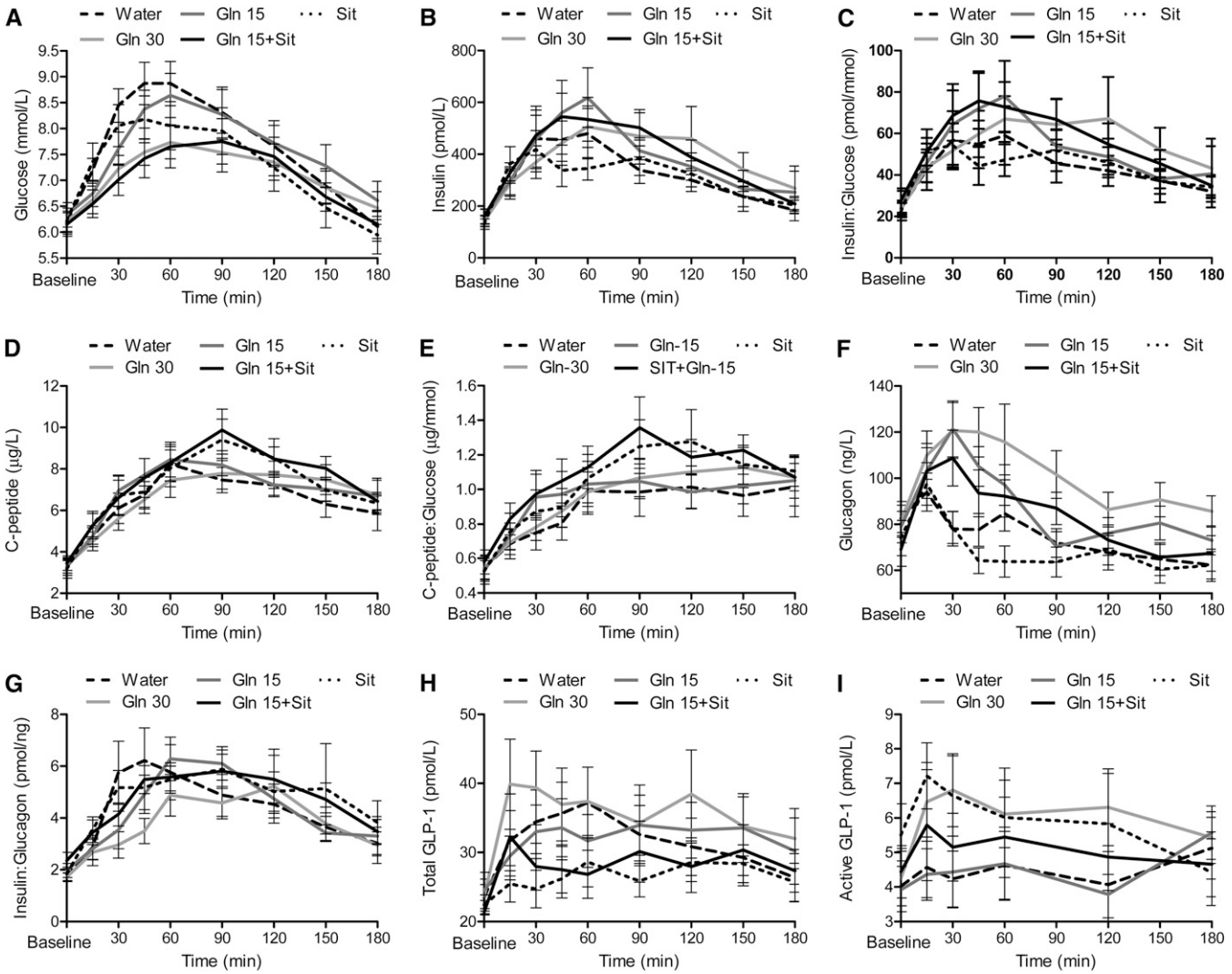

FIGURE 1 Circulating glucose (*A*), insulin (*B*), the insulin:glucose ratio (*C*), C-peptide (*D*), the C-peptide:glucose ratio (*E*), glucagon (*F*), the insulin:glucagon ratio (*G*), total GLP-1 (*H*), and active GLP-1 (*I*) concentrations in individuals with type 2 diabetes in response to a high-carbohydrate, low-fat meal following ingestion of water, Gln-30, Gln-15, SIT+Gln-15, or SIT. Values are means ± SEM, $n = 15$.

TABLE 1 Circulating glucose, insulin, insulin:glucose ratio, C-peptide, C-peptide:glucose ratio, glucagon, insulin:glucagon ratio, total, and active GLP-1 AUC following ingestion of a high-carbohydrate, low-fat meal with water, Gln-30, Gln-15, SIT+Gln-15, or SIT[1]

		Water	Gln-30	Gln-15	SIT+Gln-15	SIT
Glucose[2]	$AUC_{t\ =\ 0–180\ min}$, *mmol/L·180 min*	13.9 ± 0.62	12.9 ± 0.48*	13.8 ± 0.65	12.8 ± 0.56**	13.2 ± 0.72
	$AUC_{t\ =\ 0–60\ min}$, *mmol/L·60 min*	4.80 ± 0.18	4.25 ± 0.15**	4.53 ± 0.18	4.18 ± 0.18**	4.61 ± 0.23
	$AUC_{t\ =\ 60–180\ min}$, *mmol/L·120 min*	9.12 ± 0.45	8.65 ± 0.37	9.27 ± 0.48	8.64 ± 0.40	8.60 ± 0.50
Insulin[2,4]	$AUC_{t\ =\ 0–180\ min}$, *Log_{10}pmol/L·180 min*	4.32 ± 0.12	4.46 ± 0.12*	4.47 ± 0.10**	4.52 ± 0.10	4.33 ± 0.10
	$AUC_{t\ =\ 0–60\ min}$, *Log_{10}pmol/L·60 min*	1.46 ± 0.05	1.46 ± 0.04	1.49 ± 0.05	1.51 ± 0.04	1.45 ± 0.04
	$AUC_{t\ =\ 60–180\ min}$, *Log10pmol/L·120 min*	2.86 ± 0.07	2.99 ± 0.08*	2.98 ± 0.06*	3.01 ± 0.07*	2.88 ± 0.07
Insulin:glucose ratio[2,4]	$AUC_{t\ =\ 0–180\ min}$, *Log_{10}pmol/mmol·180 min*	2.74 ± 0.14	2.93 ± 0.13*	2.89 ± 0.12**	3.00 ± 0.11*	2.79 ± 0.12
	$AUC_{t\ =\ 0–60\ min}$, *Log_{10}pmol/mmol·60 min*	0.93 ± 0.05	0.95 ± 0.04	0.97 ± 0.05*	1.01 ± 0.04*	0.92 ± 0.05
	$AUC_{t\ =\ 60–180\ min}$, *Log_{10}pmol/mmol·120 min*	1.81 ± 0.09	1.98 ± 0.09*	1.92 ± 0.07*	1.99 ± 0.07*	1.87 ± 0.07
C-peptide[2]	$AUC_{t\ =\ 0–180\ min}$, *μg/L·180 min*	12.0 ± 1.15	12.6 ± 1.07	12.8 ± 0.81	13.9 ± 1.12	13.3 ± 1.10
	$AUC_{t\ =\ 0–60\ min}$, *μg/L·60 min*	3.62 ± 0.40	3.39 ± 0.31	3.82 ± 0.35	3.91 ± 0.45	3.80 ± 0.42
	$AUC_{t\ =\ 60–180\ min}$, *μg/L·120 min*	8.35 ± 0.77	9.17 ± 0.78	8.95 ± 0.53	9.99 ± 0.69	9.67 ± 0.77**
C-peptide:glucose ratio[2]	$AUC_{t\ =\ 0–180\ min}$, *μg/mmol·180 min*	1.64 ± 0.21	1.76 ± 0.17	1.74 ± 0.17	2.02 ± 0.19*	1.92 ± 0.21*
	$AUC_{t\ =\ 0–60\ min}$, *μg/mmol·60 min*	0.45 ± 0.06	0.47 ± 0.05	0.52 ± 0.06*	0.56 ± 0.06*	0.50 ± 0.06
	$AUC_{t\ =\ 60–180\ min}$, *μg/mmol·120 min*	1.19 ± 0.16	1.30 ± 0.13	1.23 ± 0.12	1.46 ± 0.13	1.42 ± 0.15**
Glucagon[3]	$AUC_{t\ =\ 0–180\ min}$, *ng/L·180 min*	13.3 ± 1.22	18.1 ± 1.64**	15.7 ± 1.32**	14.9 ± 1.34	12.3 ± 1.15
	$AUC_{t\ =\ 0–60\ min}$, *ng/L·60 min*	4.99 ± 0.43	6.90 ± 0.67**	6.20 ± 0.53**	5.79 ± 0.62	4.64 ± 0.42
	$AUC_{t\ =\ 60–180\ min}$, *ng/L·120 min*	8.33 ± 0.80	11.4 ± 1.02**	9.44 ± 0.82	9.16 ± 0.75	7.68 ± 0.74
Insulin:glucagon ratio[2,4]	$AUC_{t\ =\ 0–180\ min}$, *Log_{10}pmol/ng·180 min*	1.01 ± 0.09	0.91 ± 0.09	1.03 ± 0.07	1.13 ± 0.07	1.09 ± 0.08
	$AUC_{t\ =\ 0–60\ min}$, *Log_{10}pmol/ng·60 min*	0.33 ± 0.04	0.24 ± 0.03*	0.30 ± 0.03	0.34 ± 0.03	0.34 ± 0.03
	$AUC_{t\ =\ 60–180\ min}$, *Log_{10}pmol/ng·120 min*	0.69 ± 0.06	0.67 ± 0.06	0.74 ± 0.05	0.79 ± 0.05	0.75 ± 0.06
Total GLP-1[3]	$AUC_{t\ =\ 0–180\ min}$, *pmol/L·180 min*	5.72 ± 0.72	6.44 ± 0.85	5.81 ± 0.68	5.14 ± 0.64	4.90 ± 0.44
	$AUC_{t\ =\ 0–60\ min}$, *pmol/L·60 min*	1.98 ± 0.24	2.20 ± 0.32	1.86 ± 0.21	1.68 ± 0.23*	1.54 ± 0.15*
	$AUC_{t\ =\ 60–180\ min}$, *pmol/L·120 min*	3.73 ± 0.49	4.27 ± 0.60	3.95 ± 0.54	3.47 ± 0.46	3.36 ± 0.31
Active GLP-1[3]	$AUC_{t\ =\ 0–180\ min}$, *pmol/L·180 min*	0.80 ± 0.14	1.10 ± 0.14*	0.80 ± 0.15	0.90 ± 0.15	1.04 ± 0.17*
	$AUC_{t\ =\ 0–60\ min}$, *pmol/L·60 min*	0.27 ± 0.04	0.37 ± 0.05*	0.26 ± 0.06	0.32 ± 0.05	0.38 ± 0.05*
	$AUC_{t\ =\ 60–180\ min}$, *pmol/L·120 min*	0.54 ± 0.11	0.73 ± 0.10	0.54 ± 0.11	0.59 ± 0.10	0.66 ± 0.12

[1] Data are mean ± SEM, $n = 15$. Asterisks indicate different from water (control): $*P < 0.0125$, $**P < 0.001$.
[2] AUC/100.
[3] AUC/1000.
[4] Data were $\log_{10}$-transformed for statistical analysis.

of the treatments affected satiety, as evaluated by visual analogue scale (data not shown).

Discussion

In this randomized crossover study, we demonstrated that a single dose of 30 g of glutamine or 15 g glutamine in combination with SIT, reduced postprandial glycemia in patients with type 2 diabetes relative to control. Both treatments also augmented the postprandial insulin response, particularly when considered relative to the reduced glycemia.

We have previously shown that oral glutamine increases the circulating GLP-1 concentration when consumed without a meal in lean, obese nondiabetic, and obese diabetic individuals (17). In the present study, when given with a meal to type 2 diabetes patients, 30 g of glutamine tended to increase total GLP-1 and increased the active GLP-1 concentration relative to the control, suggesting increased GLP-1 secretion from intestinal L-cells. Similar to previous findings in humans in response to a meal (9), glucose (17,25), or glutamine (17), the total GLP-1 response in the present study was biphasic, with an early peak at ~15 min and a second peak from 90 to 120 min. Our current and previous results are consistent with in vitro studies demonstrating that glutamine stimulates the release of GLP-1 from the GLP-1–secreting cell line GLUTag (26). Specifically, at concentrations that mimic the postprandial phase, glutamine stimulated GLP-1 secretion from GLUTag cells shortly after its application (26). Furthermore, glutamine was a more potent GLP-1 secretagogue than glucose or other amino acids (26). In vitro, glutamine triggered membrane depolarization and initiated action potential and calcium entry to the cells but also had an independent effect on GLP-1 secretion (26). However, it remains unclear whether the mechanisms characterized in cell lines are preserved in vivo (27).

The current study suggests that the glucose-lowering effect of glutamine is due at least in part to increased GLP-1 concentrations. A critical question is whether glutamine-induced increases in GLP-1 reduce glycemia by increasing insulin secretion or slowing of gastric emptying, or both. Our data suggest that the latter is likely to be more important. First, we observed that the reduction in postprandial glycemia preceded any increase in insulinemia. Second, although we found that glutamine increased the postprandial insulin response, there was no corresponding increase in C-peptide, suggesting that glutamine may affect insulin clearance rather than secretion. These data indicate that the effect of glutamine on glycemia is predominantly mediated through slowing of gastric emptying. Indeed, in healthy humans, a glutamine and carbohydrate mixed solution prolonged gastric emptying compared with carbohydrate alone (28). Slowed gastric emptying in response to glutamine in the present study may be due to the increase in GLP-1 (29) or the increased energy with glutamine consumption.

Amino acids have previously been reported to be strong stimulants of glucagon release in dogs (30), as we have recently shown for glutamine in humans (17). Consistently, glutamine increased the postprandial glucagon concentration in the present study. This may be expected to counteract a potential benefit of glutamine on glycemia via enhanced hepatic glucose production (31). In the fasting state, glucagon maintains a normal blood glucose concentration and is maximally active when glucose and insulin concentrations are low. In the present study, the postprandial increase in glucagon following glutamine consumption was paralleled by an increase in insulin concentration and thus would not be expected to affect hepatic glucose production, which is relevant in the fasting state.

SIT led to a relatively lower total GLP-1 concentration but a higher active GLP-1 concentration compared with control, consistent with the known mechanism of action of DPP-IV inhibitors (32). The lower total GLP-1 concentration is likely to be a response to negative feedback by active GLP-1 (32,33). When SIT was given in combination with glutamine, total GLP-1 secretion decreased, which was likely due to SIT.

Adverse effects of glutamine were uncommon in the current study. Glutamine was well tolerated and led to minor gastrointestinal symptoms in only 2 participants. In a recent study that examined the safety of glutamine given at a dose of 0.5 $g \cdot kg^{-1}$ body $weight \cdot d^{-1}$ for 14 d in a similar age and weight group, glutamine was well tolerated without adverse effects noted on clinical and laboratory measures, including renal and liver function, and lactate and ammonia concentrations (18).

Our study has some limitations. We limited recruitment to individuals with diabetes of <5-y duration and therefore are unable to comment as to whether glutamine has equally beneficial effects on glycemia in patients with type 2 diabetes of longer duration. The relatively intact β-cell function in individuals with a shorter duration of diabetes may limit the beneficial effects of glutamine to such participants. Moreover, in patients with well-controlled type 2 diabetes, the action of GLP-1 on insulin secretion is preserved (10); thus, glutamine is more likely to be effective in this group of participants. A second limitation is the lack of an amino acid comparator, which would help determine whether the effect on GLP-1 is glutamine specific or a generalized amino acid effect. However, our recent observations in humans (17) and in vitro (26) suggest that the GLP-1 response is specific to glutamine. Third, we cannot exclude the possibility that the greater energy intake with glutamine supplementation accounted for some of the effects observed in the present study.

In summary, we demonstrate that the consumption of 30 g of glutamine or 15 g of glutamine plus SIT markedly reduced postprandial glycemia in patients with well-controlled type 2 diabetes of short duration. These effects are likely to be mediated through GLP-1–induced slowing of gastric emptying. Our results suggest that glutamine may represent a novel approach to increasing the GLP-1 concentration and reducing postprandial glycemia in type 2 diabetes, a state of relative glutamine deficiency (19). With poor adherence to the multiple medications required to treat type 2 diabetes, nutritional supplementation with an amino acid may prove beneficial. The longer-term effects of such treatment require further investigation, particularly in light of recommendations regarding dietary protein intake in patients with type 2 diabetes (34).

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