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

Dorit Samocha-Bonet,4 Olivia Wong,4 Emma-Leigh Synnott,4 Naomi Piyaratna,4 Ashley Douglas,4 Fiona M. Gribble,5 Jens J. Holst,6 Donald J. Chisholm,4,7 and Jerry R. Greenfield4,7,8*

4Diabetes and Obesity Research Program, Garvan Institute of Medical Research, Sydney 2010, Australia; 5The Cambridge Institute of Medical Research and Department of Clinical Biochemistry, University of Cambridge, Cambridge CB2 0XY, UK; 6Department of Medical Physiology, University of Copenhagen, the Panum Institute, Copenhagen DK-2200, Denmark; 7Faculty of Medicine, University of New South Wales, Sydney 2032, Australia; and 8Department of Endocrinology and Diabetes Center, St. Vincent’s Hospital, Sydney 2010, Australia

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 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) and glucose-dependent insulinitropic 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, glucose-dependent insulinitropic polypeptide secretion is intact in diabetes, although the insulinitropic 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-
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 · 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 · 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 t-glutamine (Gln-30); 15 g t-glutamine (Gln-15); 100 mg statin (ST); 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 30 mL of water. t-Glutamine powder (Cambridge Commodities) was consumed in 300 mL of ice-cold water, to avoid its transformation to pyroglutamic acid (21), over 2 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 · 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). Glycerated 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 tryosyl 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 log₁₀-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 · 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).

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.
Glucagon AUCt = 0–180 min, Insulin:glucose ratio AUCt = 0–180 min, Insulin AUCt = 0–180 min, C-peptide AUCt = 0–180 min, glutamine stimulates the release of GLP-1 from the GLP-1–
results are consistent with in vitro studies demonstrating that
Active GLP-1 AUCt = 0–180 min, 1236 Samocha-Bonet et al.
the present study was biphasic, with an early peak at
increased the active GLP-1 concentration relative to the control,
In the present study, when given with a meal to type 2 diabetes
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
doze of 30 g of glutamine or 15 g glutamine in combination with
SIT, reduced postprandial glycaemia in patients with type 2 diabetes relative to control. Both treatments also augmented the
postprandial insulin response, particularly when considered relative to the reduced glycaemia.
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 concentra-
tions. A critical question is whether glutamine-induced increases
in GLP-1 reduce glycaemia 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 glycaemia preceded any increase in
C-peptide, suggesting that glutamine may affect insulin
clearance rather than secretion. These data indicate that the effect
of glutamine on glycaemia is predominantly mediated through
slowing of gastric emptying. Indeed, in healthy humans, a glut-
amine and carbohydrate mixed solution prolonged gastric empty-
ing 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.

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Water</th>
<th>Glu-30</th>
<th>Glu-15</th>
<th>SIT+Glu-15</th>
<th>SIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCt = 0–180 min, mmol/L</td>
<td>13.9 ± 0.62</td>
<td>12.9 ± 0.48*</td>
<td>13.8 ± 0.65</td>
<td>12.8 ± 0.56**</td>
<td>13.2 ± 0.72</td>
</tr>
<tr>
<td>AUCt = 0–60 min, mmol/L</td>
<td>4.80 ± 0.18</td>
<td>4.25 ± 0.15**</td>
<td>4.53 ± 0.18</td>
<td>4.18 ± 0.18**</td>
<td>4.61 ± 0.23</td>
</tr>
<tr>
<td>C-peptide AUCt = 0–180 min, pmol/L</td>
<td>9.12 ± 0.45</td>
<td>8.65 ± 0.37</td>
<td>9.27 ± 0.48</td>
<td>8.64 ± 0.40</td>
<td>8.60 ± 0.50</td>
</tr>
<tr>
<td>C-peptide:glucose ratio AUCt = 0–180 min, pmol/mmol</td>
<td>4.32 ± 0.12</td>
<td>4.46 ± 0.12*</td>
<td>4.47 ± 0.10**</td>
<td>4.52 ± 0.10</td>
<td>4.33 ± 0.10</td>
</tr>
<tr>
<td>C-peptide:glucose ratio AUCt = 0–60 min, pmol/mmol</td>
<td>1.46 ± 0.05</td>
<td>1.46 ± 0.04</td>
<td>1.49 ± 0.05</td>
<td>1.51 ± 0.04</td>
<td>1.45 ± 0.04</td>
</tr>
<tr>
<td>Glucagon AUCt = 0–60 min, pmol/L</td>
<td>2.86 ± 0.07</td>
<td>2.99 ± 0.08*</td>
<td>2.98 ± 0.06*</td>
<td>3.01 ± 0.07*</td>
<td>2.88 ± 0.07</td>
</tr>
<tr>
<td>Glucagon:glucose ratio AUCt = 0–60 min, pmol/mmol</td>
<td>0.72 ± 0.06</td>
<td>0.79 ± 0.07*</td>
<td>0.87 ± 0.07*</td>
<td>0.92 ± 0.07</td>
<td>0.97 ± 0.07**</td>
</tr>
<tr>
<td>Glu-15</td>
<td>Water</td>
<td>Glu-30</td>
<td>Glu-15</td>
<td>SIT+Glu-15</td>
<td>SIT</td>
</tr>
<tr>
<td>AUCt = 60–180 min, pmol/L</td>
<td>12.0 ± 1.15</td>
<td>12.6 ± 1.07</td>
<td>12.8 ± 0.81</td>
<td>13.9 ± 1.12</td>
<td>13.3 ± 1.10</td>
</tr>
<tr>
<td>AUCt = 0–60 min, pmol/L</td>
<td>3.62 ± 0.40</td>
<td>3.39 ± 0.31</td>
<td>3.82 ± 0.35</td>
<td>3.91 ± 0.45</td>
<td>3.80 ± 0.42</td>
</tr>
<tr>
<td>C-peptide AUCt = 60–180 min, pmol/L</td>
<td>8.35 ± 0.77</td>
<td>9.17 ± 0.78</td>
<td>8.95 ± 0.53</td>
<td>9.99 ± 0.69</td>
<td>9.67 ± 0.77**</td>
</tr>
<tr>
<td>C-peptide:glucose ratio AUCt = 60–180 min, pmol/mmol</td>
<td>1.64 ± 0.21</td>
<td>1.76 ± 0.17</td>
<td>1.74 ± 0.17</td>
<td>2.02 ± 0.19*</td>
<td>1.92 ± 0.21*</td>
</tr>
<tr>
<td>C-peptide:glucose ratio AUCt = 60–180 min, pmol/mmol</td>
<td>0.45 ± 0.06</td>
<td>0.47 ± 0.05</td>
<td>0.52 ± 0.06*</td>
<td>0.56 ± 0.06*</td>
<td>0.50 ± 0.06</td>
</tr>
<tr>
<td>Glucagon AUCt = 60–180 min, pmol/L</td>
<td>13.3 ± 1.22</td>
<td>18.1 ± 1.64**</td>
<td>15.7 ± 1.32**</td>
<td>14.9 ± 1.34</td>
<td>12.3 ± 1.15</td>
</tr>
<tr>
<td>Glucagon:glucose ratio AUCt = 60–180 min, pmol/mmol</td>
<td>4.99 ± 0.43</td>
<td>6.90 ± 0.67**</td>
<td>6.20 ± 0.53**</td>
<td>5.79 ± 0.62</td>
<td>4.64 ± 0.42</td>
</tr>
<tr>
<td>Glu-15</td>
<td>Water</td>
<td>Glu-30</td>
<td>Glu-15</td>
<td>SIT+Glu-15</td>
<td>SIT</td>
</tr>
<tr>
<td>AUCt = 60–180 min, pmol/L</td>
<td>8.33 ± 0.80</td>
<td>11.4 ± 1.02**</td>
<td>9.44 ± 0.82</td>
<td>9.16 ± 0.75</td>
<td>7.68 ± 0.74</td>
</tr>
<tr>
<td>AUCt = 0–60 min, pmol/L</td>
<td>1.01 ± 0.09</td>
<td>0.91 ± 0.09</td>
<td>1.03 ± 0.07</td>
<td>1.13 ± 0.07</td>
<td>1.09 ± 0.08</td>
</tr>
<tr>
<td>Total GLP-1 AUCt = 60–180 min, pmol/L</td>
<td>0.05 ± 0.06</td>
<td>0.67 ± 0.07</td>
<td>0.74 ± 0.05</td>
<td>0.79 ± 0.05</td>
<td>0.75 ± 0.06</td>
</tr>
<tr>
<td>Total GLP-1 AUCt = 0–180 min, pmol/L</td>
<td>5.72 ± 0.72</td>
<td>6.44 ± 0.85</td>
<td>5.81 ± 0.68</td>
<td>5.14 ± 0.64</td>
<td>4.90 ± 0.44</td>
</tr>
<tr>
<td>Active GLP-1 AUCt = 0–180 min, pmol/L</td>
<td>1.98 ± 0.24</td>
<td>2.20 ± 0.32</td>
<td>1.86 ± 0.21</td>
<td>1.68 ± 0.23*</td>
<td>1.54 ± 0.15*</td>
</tr>
<tr>
<td>Active GLP-1 AUCt = 0–60 min, pmol/L</td>
<td>3.73 ± 0.49</td>
<td>4.27 ± 0.60</td>
<td>3.95 ± 0.54</td>
<td>3.47 ± 0.46</td>
<td>3.36 ± 0.31</td>
</tr>
</tbody>
</table>

1 Data are mean ± SEM, n = 15. Asterisks indicate different from water (control): *P < 0.0125, **P < 0.001.
2 AUC100.
3 AUC1000.
4 Data were log10-transformed for statistical analysis.
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·kg⁻¹ body weight·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 increase in glucagon-like peptide-1 and gastrin in type 2 diabetic patients. 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.

Acknowledgments
We thank Lene Brus Albaek and Signe Jorgensen for performing the GLP-1 assays, Louise Purcell for technical advice, and Adelle Coster for statistical advice. J.R.G. designed research, conducted research, and had primary responsibility for final content; O.W., E.L.S., N.P., A.D., J.J.H. conducted research; D.S-B. analyzed data and wrote the paper; And E.M.G. and D.J.C. designed research. All authors read and approved the final manuscript.

Literature Cited


