PUBLISHED VERSION

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Diabetes Care, 2013; 36(8):2262-2265

Originally published at:
http://doi.org/10.2337/dc12-1663

http://hdl.handle.net/2440/82155

Effects of Intraduodenal Glutamine on Incretin Hormone and Insulin Release, the Glycemic Response to an Intraduodenal Glucose Infusion, and Antropyloroduodenal Motility in Health and Type 2 Diabetes

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OBJECTIVE—Glutamine reduces postprandial glycemia when given before oral glucose. We evaluated whether this is mediated by stimulation of insulin and/or slowing of gastric emptying.

RESEARCH DESIGN AND METHODS—Ten healthy subjects were studied during intraduodenal (ID) infusion of glutamine (7.5 or 15 g) or saline over 30 min, followed by glucose (75 g over 100 min), while recording antropyloroduodenal pressures. Ten patients with type 2 diabetes mellitus (T2DM) were also studied with 15 g glutamine or saline.

RESULTS—ID glutamine stimulated glucagon-like peptide 1 (GLP-1; healthy: $P < 0.05$; T2DM: $P < 0.05$), glucose-dependent insulinotropic polypeptide (GIP; $P = 0.098$; $P < 0.05$), glucagon ($P < 0.01$; $P < 0.001$), insulin ($P = 0.05$; $P < 0.01$), and phasic pyloric pressures ($P < 0.05$; $P < 0.05$), but did not lower blood glucose ($P = 0.077$; $P = 0.5$).

CONCLUSIONS—Glutamine does not lower glycemia after ID glucose, despite stimulating GLP-1, GIP, and insulin, probably due to increased glucagon. Its capacity for pyloric stimulation suggests that delayed gastric emptying is a major mechanism for lowering glycemia when glutamine is given before oral glucose.

Postprandial glycemic control represents a major focus of type 2 diabetes mellitus (T2DM) management (1). The rate of gastric emptying and the release of "incretin" hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are both important determinants of postprandial glycemic excursions (2). Glucose empties from the stomach in health in the range of 1–4 kcal/min, regulated by inhibitory small-intestinal feedback via stimulation of pyloric motility and suppression of antral and duodenal contractions (3). Differences in gastric emptying account for about one-third of the variation in postprandial blood glucose levels after oral glucose (4).

Glutamine reduces glucose excursions when given before oral glucose in T2DM (5), potentially by stimulating GLP-1 secretion (6) and/or slowing gastric emptying (7). The purpose of the current study was to determine whether glutamine retains its capacity to lower glycemia when glucose is delivered directly into the duodenum, thereby removing any influence of gastric emptying, while measuring antropyloroduodenal motility, gut hormones, and insulin.

RESEARCH DESIGN AND METHODS—Ten healthy men (29.5 ± 3.8 years, BMI 22.6 ± 0.7 kg/m^2) and 10 patients (5 men) with diet-controlled T2DM (68 ± 1.1 years, BMI 28.9 ± 1.1 kg/m^2, HbA$_{1c}$ 6.7 ± 0.2% [49.7 ± 1.5 mmol/mol]) gave written, informed consent. The protocol was approved by the Royal Adelaide Hospital Research Ethics Committee.

After an overnight fast, a multilumen manometry catheter (Dentsleeve International, Mississauga, ON, Canada) was inserted transnasally and positioned with a sleeve sensor across the pylorus. Healthy subjects received an intraduodenal (ID) infusion containing 15 or 7.5 g glutamine in 350 mL aqueous solution, or 350 mL of 0.9% saline control, over 30 min ($t = 0–30$ min) in randomized, single-blinded order. This was followed by an ID glucose infusion at 3 kcal/min over 100 min ($t = 30–130$ min) with frequent blood sampling. Patients with T2DM were studied only twice (15 g glutamine or saline).

Blood glucose was analyzed using a Medisense Precision glucometer (Abbott Laboratories, Bedford, MA), and serum insulin, total GLP-1 and GIP, and glucagon were measured using established assays (8). Manometric pressures were analyzed using custom-designed software (9) to count isolated pyloric pressure waves (IPPWs) and the total number of waves in all antral and duodenal channels, respectively.

Data were analyzed over two periods—glutamine/saline infusion ($t = 0–30$ min) and glucose infusion ($t = 30–130$ min). Incremental areas under the curves (iAUC)
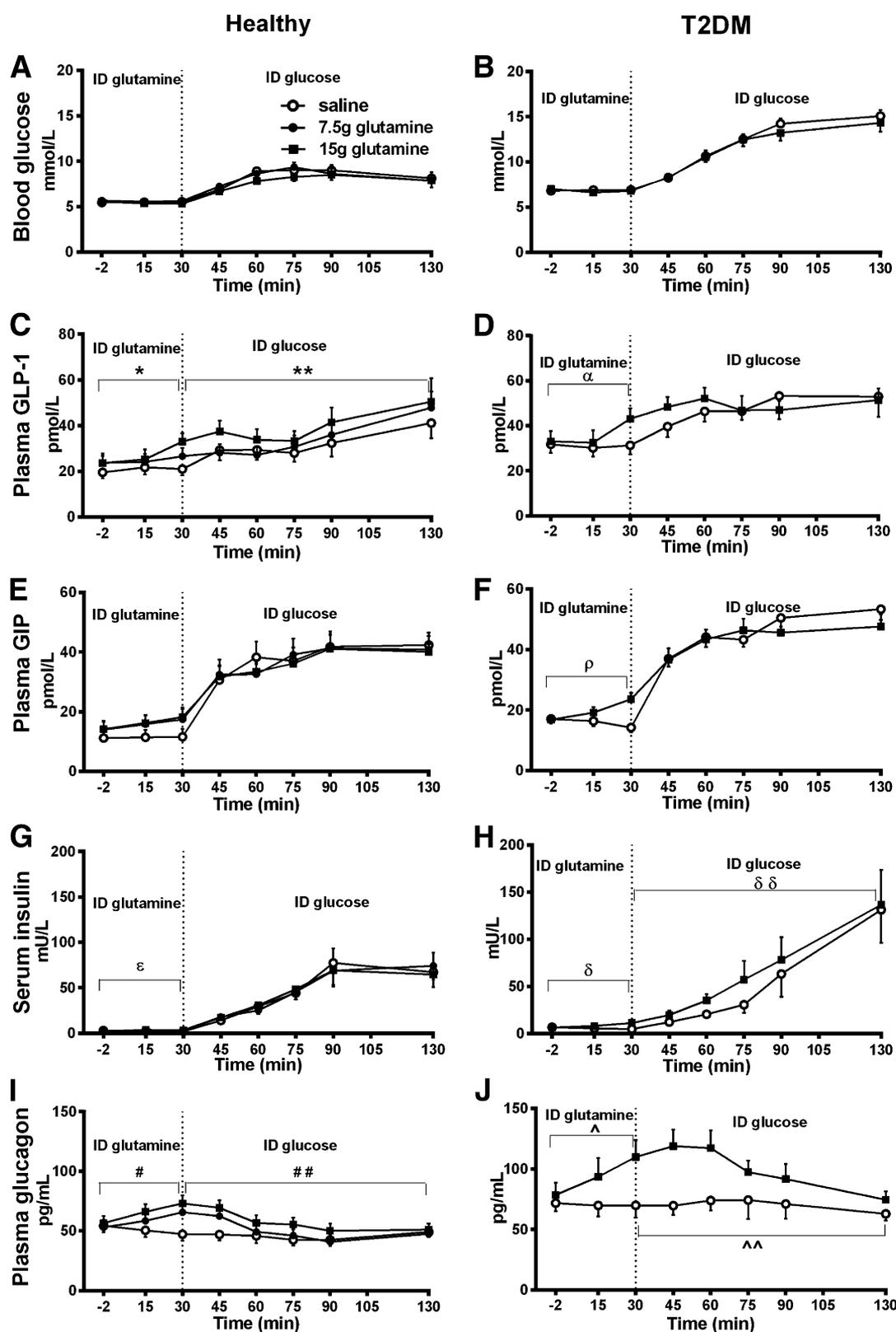
Figure 1—*Effects of ID saline (control) and 7.5 or 15 g glutamine infusions on blood glucose (A and B), plasma GLP-1 (C and D), plasma GIP (E and F), serum insulin (G and H), and plasma glucagon (I and J) concentrations in 10 healthy subjects and 9 patients with T2DM, before (t = 0–30 min) and during (t = 30–130 min) ID glucose infusion. *P = 0.05 for greater iAUC for 15 vs. 7.5 g glutamine or saline (127.1 ± 33.1 vs. 45.1 ± 12.7 vs. 51.4 ± 23.1 pmol/L/min), **P < 0.05 for greater iAUC for 15 vs. 7.5 g glutamine (1,715 ± 440 vs. 1,099 ± 354 pmol/L/min), α P < 0.05 for greater iAUC for 15 g glutamine vs. saline (84.6 ± 19.3 vs. 37.0 ± 27.1 pmol/L/min), ρ P < 0.05 for greater iAUC for 15 g glutamine vs. saline (110.3 ± 36.6 vs. 10.8 ± 7.0 pmol/L/min), ε P = 0.05 for greater iAUC for 15 vs. 7.5 g glutamine or saline (32.3 ± 9.4 vs. 20.1 ± 8.4 vs. 8.3 ± 3.9 mU/L/min), δ P < 0.01 for greater iAUC for 15 g glutamine vs. saline (62.8 ± 19.9 vs. 5.7 ± 3.4 mU/L/min), δδ P < 0.05 for greater iAUC for 15 g*

were compared using one-factor ANOVA for healthy subjects and paired *t* tests for patients with T2DM. Post hoc comparisons, adjusted for multiple comparisons by Bonferroni's correction, were performed if ANOVAs revealed significant effects. Calculations were done with SPSS 19 software (IBM Corporation, Armonk, NY). Data are means $\pm$ SE. Statistical significance was accepted at $P < 0.05$.

RESULTS—The study was well tolerated; one patient with T2DM was excluded due to marked nausea with glutamine.

Blood glucose was unchanged during ID glutamine/saline infusion. The increase in blood glucose during ID glucose infusion did not differ between treatments in health or T2DM (Fig. 1*A* and *B*).

Plasma GLP-1 increased during ID glutamine infusion in health ($P = 0.05$) and T2DM ($P < 0.05$). During ID glucose infusion, GLP-1 concentrations in health increased more after 15 g glutamine than 7.5 g glutamine or saline ($P < 0.05$), whereas in T2DM, the increment was nonsignificantly greater after 15 g glutamine ($P = 0.056$; Fig. 1*C* and *D*).

Plasma GIP increased during ID glutamine infusion in T2DM ($P < 0.05$), but not significantly in health ($P = 0.098$). During ID glucose infusion, GIP concentrations increased similarly with all treatments in both groups (Fig. 1*E* and *F*).

Serum insulin increased slightly during ID glutamine infusion in health ($P = 0.05$) and T2DM ($P < 0.01$). During ID glucose infusion, insulin concentrations increased without any difference between treatments in health, whereas in T2DM, the increment in insulin was greater after glutamine than after saline ($P < 0.05$; Fig. 1*G* and *H*).

Plasma glucagon increased during ID glutamine infusion in health, with a greater increment for 15 g than for 7.5 g glutamine ($P < 0.005$), and also increased in T2DM ($P < 0.005$). During ID glucose infusion, glucagon concentrations in health were greater after 15 and 7.5 g glutamine than after saline ($P < 0.01$) and were greater after glutamine in T2DM ($P < 0.001$; Fig. 1*I* and *J*).

Antropyloroduodenal pressures
There were more IPPWs during 15 g glutamine infusion than 7.5 g glutamine

or saline in health (19.5 ± 6.7 vs. 7.9 ± 3.6 vs. 3.6 ± 1.6, $P < 0.05$), and more IPPWs during glutamine than saline in T2DM (16.1 ± 5.1 vs. 5.5 ± 1.8, $P < 0.05$). During ID glucose infusion, the number of IPPWs did not differ between treatments in either group (healthy: 28.4 ± 8.7 vs. 24.5 ± 8.7 vs. 24.5 ± 8.2; T2DM: 57.9 ± 9.4 vs. 60.5 ± 14.7).

The number of antral waves did not differ between treatments during ID glutamine/saline infusion in health (26.5 ± 10.7 vs. 30.5 ± 7.7 vs. 44.3 ± 15.1), but antral waves were fewer in T2DM after glutamine compared with saline (10.6 ± 5.6 vs. 32.9 ± 10.3, $P < 0.05$). During ID glucose infusion, the number of antral waves did not differ between treatments in either group (healthy: 18.9 ± 15.2 vs. 20.2 ± 12.9 vs. 22.9 ± 8.7; T2DM: 10.5 ± 2.3 vs. 14.3 ± 9.2).

The number of duodenal waves did not differ between treatments during ID glutamine/saline (healthy: 289.7 ± 50.4 vs. 376.6 ± 43.8 vs. 295.4 ± 62.0; T2DM: 215.3 ± 63.2 vs. 213.9 ± 39.6) or ID glucose infusion (healthy: 160.5 ± 72.6 vs. 156.4 ± 64.1 vs. 128.3 ± 33.8; T2DM: 75.1 ± 24.7 vs. 84.9 ± 32.9) in either group.

CONCLUSIONS—We demonstrated that 15 g ID glutamine stimulated GLP-1 secretion in health and T2DM, associated with modest insulin stimulation. However the glycemic response to a subsequent ID glucose load was not diminished, probably because of increased glucagon. Glutamine stimulated pyloric motility, which would delay gastric emptying. The effects of glutamine on hormone secretion and motility appeared to be dose-dependent, because the effects of 7.5 g glutamine were no different from saline.

We infused glutamine over 30 min based on the timing of the maximal GLP-1 response to oral glutamine (6). A higher dose might have had greater effects, but in pilot studies, 30 g infused over 30 min tended to induce nausea. Despite relatively few subjects, the effects were consistent, and it is unlikely that studying more subjects would alter the outcomes substantially. An additional day giving

glucose orally would be of interest, as would an evaluation of other amino acids and inclusion of patients with less well controlled diabetes. Nevertheless, slowing of gastric emptying appears the predominant mechanism by which glutamine can lower glycemia.

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glutamine vs. saline ($5,994 \pm 1,783$ vs. $4,689 \pm 1,553$ mU/L/min), #$P < 0.005$ for greater iAUC for 15 vs. 7.5 g glutamine (289.7 ± 77.9 vs. 183.9 ± 41.1 pg/mL/min), ##$P < 0.01$ for greater iAUC for 15 and 7.5 g glutamine vs. saline (529.5 ± 100.8 and 363.5 ± 53.4 vs. 132.0 ± 65.3 pg/mL/min), $\wedge P < 0.005$ for greater iAUC for 15 g glutamine vs. saline (362.1 ± 77.1 vs. 16.6 ± 11.1 pg/mL/min), and $\wedge\wedge P < 0.001$ for greater iAUC for 15 g glutamine vs. saline ($2,131.8 \pm 280.1$ vs. 263.2 ± 117.2 pg/mL/min).

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