Effect of GLP-1 on gastric volume, emptying, maximum volume ingested, and postprandial symptoms in humans

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Delgado-Aros, Silvia, Doe-Young Kim, Duane D. Burton, George M. Thomforde, Debra Stephens, Benjamin H. Brinkmann, Adrian Vella, and Michael Camilleri. Effect of GLP-1 on gastric volume, emptying, maximum volume ingested, and postprandial symptoms in humans. Am J Physiol Gastrointest Liver Physiol 282: G424–G431, 2002.—Glucagon-like peptide-1 (GLP-1) relaxes the stomach during fasting but decreases hunger and food consumption and retards gastric emptying. The interrelationships between volume, emptying, and postprandial symptoms in response to GLP-1 are unclear. We performed, in healthy human volunteers, a placebo-controlled study of the effects of intravenous GLP-1 on gastric volume using 99mTc-single photon emission computed tomography imaging, gastric emptying of a nutrient liquid meal (Ensure), and maximum tolerated volume (MTV) of Ensure, and postprandial symptoms 30 min after MTV. The role of vagal cholinergic function in the effects of GLP-1 was assessed by human pancreatic polypeptide (HPP) response to the Ensure meal. GLP-1 increased fasting and postprandial gastric volumes and retarded gastric emptying; MTV and postprandial symptoms were not different compared with controls. Effects on postprandial gastric function were associated with reduced postprandial HPP levels. GLP-1 does not induce postprandial symptoms despite significant inhibition of gastric emptying and vagal function; this may be partly explained by the increase in postprandial gastric volume.

accompanies; single photon emission computed tomography; vagus; satiation; diabetes

GLUCAGON-LIKE peptide-1(7–36)amide (GLP-1) is produced by the processing of proglucagon in enteroendocrine L cells of the intestinal mucosa. It is released in response to meal ingestion (6, 27), exerting a glucose-dependent effect on β cells of the pancreas and enhancing insulin release. GLP-1 also has an inhibitory effect on the pancreatic α cells, reducing glucagon release (12, 30). These properties provide the rationale for reducing glycemia and for its use in diabetes mellitus (7, 29, 40).

However, GLP-1 also exerts several effects on the upper digestive tract: inhibition of gastric acid and pancreatic exocrine secretions (42–44) and delay in gastric emptying for liquids and solids in health (28) and diabetes (29). The latter may result from enhanced pyloric tone or diminished antroduodenal motility during the interdigestive and fed states in health (26). Preliminary data also indicate relaxation of the proximal stomach in response to intravenous GLP-1 during fasting (41). GLP-1 has also been reported to reduce the amount of food and fluid consumed and to reduce hunger and enhance the feeling of fullness in health (8) and diabetes (35); however, its effects on postprandial symptoms are unclear.

Previous studies showed dose-related, reversible inhibition of human pancreatic polypeptide (HPP) release in response to a meal after subcutaneous or intravenous infusion of GLP-1. GLP-1 also inhibits centrally induced pancreatic and gastric acid secretions (42), and these effects are lost after abdominal vagotomy in humans (45) and pigs (44), suggesting an inhibition of efferent vagal-cholinergic function.

Postprandial gastric accommodation is a vagally mediated reflex (31, 34). Impaired gastric accommodation is an important cause of postprandial symptoms (5, 22–24). We hypothesized that GLP-1 diminishes the postprandial gastric accommodation response by inhibition of vagal function, reducing maximum volume ingested and increasing postprandial symptoms. The aims of this study were to compare the effects of GLP-1 on postprandial gastric volumes, gastric emptying, maximum tolerated volume (MTV) of a nutrient liquid meal, postprandial symptoms, and vagal function in healthy volunteers.

METHODS

Study Population

Healthy volunteers over 18 yr of age were recruited from the local community by public advertisement. Exclusion criteria included pregnant or breast-feeding women, prior abdominal surgery other than appendectomy or tubal ligation; positive symptoms on an abridged bowel disease question-
naire; present or previous chronic gastrointestinal illness; and systemic disease or use of medications that may alter gastrointestinal motility.

**Study Design**

This study was approved by the Mayo Institutional Review Board. Eligible volunteers gave their written informed consent and were randomized to receive either GLP-1 (Bachem, San Diego, CA) as an infusion of 1.2 pmol·kg⁻¹·min⁻¹ over 60 min or saline infusion (placebo) in a double-blind design. The study was performed on two consecutive days. On the first day (protocol 1), subjects underwent assessment of gastrointestinal volumes and measurements of fasting and postprandial glucose and HPP. On the second day (protocol 2), MTV, scintigraphic gastric emptying, and postprandial symptoms were assessed. GLP-1 or saline (placebo) was infused for 60 min on both occasions.

GLP-1. GLP-1 was infused at a rate of 1.2 pmol·kg⁻¹·min⁻¹. Previous studies have demonstrated that steady-state levels are achieved within ~30 min from the onset of the infusion (40). Therefore, the physiological measurements of gastric accommodation, emptying, and satiety, as well as the plasma levels of glucose and HPP, were taken under steady levels for a total of at least 30 min.

We used an infusion rate of GLP-1 of 1.2 pmol·kg⁻¹·min⁻¹ since it has been previously shown to affect gastrointestinal function and satiety in humans (26, 40, 41, 43). Higher rates of GLP-1 infusion may cause gastrointestinal distress (36).

**99mTc-SPECT method to measure gastric volume.** We have used a recently developed method to measure the gastric volume using single photon emission computed tomography (SPECT) (13) (Fig. 1). Intravenous 99mTc-sodium pertechnetate is taken up by the gastric mucosa (16, 20); 10 min after intravenous injection of 99mTc-sodium pertechnetate, dynamic tomographic acquisition of the gastric wall was performed using a dual-head gamma camera (Helix SPECT System, Elscint, Haifa, Israel) in a multiorbit mode system. In this mode, the system performs orbits of 360° at 10 min/orbit. A three-dimensional rendering of the stomach and its volume was obtained using the AVW 3.0 image processing libraries (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN). This was accomplished by identifying the stomach in the transaxial SPECT images and separating it from the background noise using a semiautomated segmentation algorithm.

A customized algorithm was developed to estimate the volume of the proximal stomach; this algorithm estimates the longest axis of the reconstructed stomach and divides it into a proximal two-thirds and distal one-third. The volume corresponding to the length of the proximal two-thirds was then also obtained.

The accuracy and reliability of the SPECT method to measure gastric volume change have been demonstrated (1, 3) by simultaneous measurement of postprandial volume change by SPECT and by means of a barostatically controlled balloon. The latter is currently considered the gold standard for the measurement of gastric accommodation.

**Protocol 1:** measurement of gastric volumes, plasma levels of glucose, and HPP. After an 8-h period of fasting, patients lay down on the SPECT camera and the 10 mCi 99mTc-sodium pertechnetate was injected intravenously. Ten minutes later, a first orbit (360° over 10 min) was performed for baseline (preinfusion) tomographic images (Fig. 2). Infusion of 1.2 pmol·kg⁻¹·min⁻¹ GLP-1 or saline placebo was started. After 30 min of infusion (time to achieve steady...
levels), a second image was obtained over 10 min to assess effects of the GLP-1 on fasting gastric volumes.

A nutrient liquid meal (Ensure, 237 ml, 250 kcal, 6 g fat, 40 g carbohydrate, and 9 g protein) was ingested over 3 min, and two further 10-min images were obtained to measure postprandial gastric volumes.

Blood samples were taken at baseline (preinfusion), after 30 and 40 min of infusion (fasting period), and at 10 and 20 min postprandially for measurement of glucose and HPP. Plasma glucose concentrations were measured using a glucose oxidase method (using a glucose analyzer). Plasma levels of HPP were analyzed using a radioimmunoassay kit (11, 25).

Protocol 2: measurement of MTV, gastric emptying, and postprandial symptoms. To compare the effects of GLP-1 and placebo on MTV (that is, the volume ingested until maximum satiety is reached), we adapted the method used by Tack et al. (33), appending a scintigraphic evaluation of gastric emptying by radiolabeling Ensure ingested during the test (Fig. 3).

After 30 min of GLP-1 or saline placebo infusion to achieve steady state, subjects were asked to ingest Ensure at a constant rate (30 ml/min) by refilling a glass with a perfusion pump and drinking at the filling rate. Participants scored their level of satiety during the drink test by using a graphic rating scale graded 0–5 (0 = no symptoms; 5 = maximum or unbearable satiety). Participants were told to stop meal intake when a score of 5 was reached. The total volume ingested was the MTV.

To assess gastric emptying, the second glass of Ensure was radiolabeled with 50 μCi of 111In-diethylenetriaminepentaacetic acid, and 1-min-duration scans of the abdomen were obtained at 10-min intervals for the first 30 min and then at 15-min intervals until at least 50% of the meal was emptied or for a maximum of 3 h after the meal.

Thirty minutes after completing ingestion of the Ensure, participants were requested to score their postprandial symptoms (nausea, bloating, fullness, pain) using a 10-cm visual analog scale anchored with the words “unnoticeable” and “unbearable” at the left and right ends of the lines, respectively. This symptom assessment is consistent with previous studies in the literature (38).

Data and Statistical Analysis

Gastric volumes. Total and proximal gastric volume at baseline (preinfusion), fasting, and during two postprandial periods (0–10 min and 10–20 min) were measured; the postprandial gastric volume was calculated from the average of the two postprandial volumes. Volume change from baseline (preinfusion) to fasting and postprandial periods were assessed as differences and as ratios over baseline volumes (fasting difference = fasting volume – baseline volume; fasting ratio = fasting volume/baseline volume; postprandial difference = postprandial volume – baseline volume; postprandial ratio = postprandial volume/baseline volume).

MTV and postprandial symptoms. The total volume ingested (MTV) was recorded. The aggregate postprandial symptoms score (30 min after ingestion of Ensure was completed) was calculated as the sum of visual analog scale scores for each postprandial symptom (maximum 400).

Gastric emptying. Gastric emptying during the drink test was measured by scintigraphy by radiolabeling the second glass of Ensure for all participants and as described above. The primary end point for assessment of effects on gastric emptying was the proportion emptied at 30 min, which corresponded with the time when the GLP-1 or placebo infusion was completed. This time was selected in view of the very short half-life of infused GLP-1, estimated as ~5 min (17). At this time point, all of the participants had ingested approximately the same volume since the rate of ingestion of the nutrient liquid meal was standardized and all of the participants, except one, were still drinking at 30 min. Four of the participants who reached full satiety at that point did not completely drink the last glass of Ensure (200 ml) and had slightly less volume and caloric intake: three were in the GLP-1 group (875, 822, and 772 ml), and one was in the placebo group (882 ml). Thus the volumes and caloric intakes were identical for 19 of the participants. The secondary end point was the proportion emptied at 90 min (1 h after the infusion ended); this was intended to determine whether there were longer-lasting effects of the infused hormone.

Plasma glucose and HPP. Fasting and postprandial plasma levels of glucose and HPP were calculated from the average of the two fasting measurements and the two postprandial measurements, respectively. Changes in the levels
Table 1. Demographic and baseline variables

<table>
<thead>
<tr>
<th></th>
<th>GLP-1</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, M/F</td>
<td>5/8</td>
<td>5/6</td>
<td>0.7</td>
</tr>
<tr>
<td>Age, yr</td>
<td>33(26–39.5)</td>
<td>33(28–43)</td>
<td>0.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25(21–28)</td>
<td>28(24–29)</td>
<td>0.4</td>
</tr>
<tr>
<td>Baseline glucose, mg/dl</td>
<td>90(82–99)</td>
<td>92(88–95)</td>
<td>0.6</td>
</tr>
<tr>
<td>Baseline gastric volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal %, ml</td>
<td>115(80–180)</td>
<td>112(82–164)</td>
<td>0.8</td>
</tr>
<tr>
<td>Total, ml</td>
<td>239(169–346)</td>
<td>205(176–262)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Values are medians (interquartile ranges); n = 13 for GLP-1 group and 11 for placebo group. GLP, glucagon-like peptide; BMI, body mass index; HPP, human pancreatic polypeptide. All differences between GLP-1 and placebo groups were nonsignificant (i.e., P > 0.05).

Table 2. Total gastric volumes and ratios

<table>
<thead>
<tr>
<th></th>
<th>GLP-1</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline volume</td>
<td>239(169–346)</td>
<td>205(176–262)</td>
<td>0.6</td>
</tr>
<tr>
<td>Fasting volume</td>
<td>312(253–365)</td>
<td>225(185–239)</td>
<td>0.002</td>
</tr>
<tr>
<td>Fasting difference</td>
<td>80(61–128)</td>
<td>17(21–25)</td>
<td>0.005</td>
</tr>
<tr>
<td>Fasting ratio</td>
<td>1.48(1.26–1.6)</td>
<td>1.08(0.9–1.12)</td>
<td>0.003</td>
</tr>
<tr>
<td>Postprandial volume</td>
<td>848(789–899)</td>
<td>651(602–801)</td>
<td>0.004</td>
</tr>
<tr>
<td>Postprandial difference</td>
<td>608(532–671)</td>
<td>435(401–549)</td>
<td>0.008</td>
</tr>
<tr>
<td>Postprandial ratio</td>
<td>3.53(3.19–4.39)</td>
<td>3.14(2.79–3.61)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Values are medians (interquartile ranges); P values < 0.05 are considered significant.

GLP-1 and HPP were used when available, that is, in all comparisons except those indicated above. There were no statistically significant differences among demographic and baseline variables between the two study groups (Table 1).

Total Gastric Volumes

Figure 4 shows examples of the stomach reconstructions at baseline (preinfusion), fasting, and postprandially in the GLP-1 and placebo groups. Table 2 shows the data for total gastric volumes, differences in volumes, and ratios. The fasting volume was significantly greater in the group that received GLP-1 (312 ml; IQR 253–365) compared with the placebo group (225 ml; IQR 185–239; P = 0.002).

The difference between fasting and baseline volume was 80 ml (IQR 61–128) for the participants who received GLP-1 and 17 ml (IQR 21 to 25) for those who received placebo (P = 0.005). The ratio of fasting over baseline volume was also greater for the GLP-1 group (1.48; IQR 1.26–1.60) than for the placebo group (1.08; IQR 0.90–1.12; P = 0.003).

Postprandial volumes were also greater in the GLP-1 group (848 ml; IQR 789–899) compared with the placebo group (651 ml; IQR 602–801; P = 0.004). The difference between postprandial and baseline volume was 608 ml (IQR 532–671) for the GLP-1 group and
MTV and Postprandial Symptoms

No significant differences were found between groups when comparing total gastric volume ratios postprandially [3.53 (IQR 3.19–4.39) for the GLP-1 group and 3.14 (IQR 2.79–3.61) for the placebo group; P = 0.15].

Proximal Gastric Volumes

Table 3 shows gastric volumes, differences, and ratios for the proximal stomach in the two groups. No significant differences were found when comparing fasting absolute volumes, differences between fasting and baseline volumes, or the fasting/baseline ratios.

In contrast, the postprandial proximal volumes were significantly greater in the GLP-1 group (461 ml; IQR 3.41–7.45) compared with the placebo group (302 ml; IQR 2.23–3.89; P = 0.0003). There was a trend toward a greater postprandial ratio in the GLP-1 group (5.77; IQR 2.84–4.81) compared with the placebo group (3.72; IQR 2.84–4.81; P = 0.08).

MTV and Postprandial Symptoms

As shown in Table 4, the median volume ingested to reach full satiety was 1,119 ml (IQR 874–1,546) for the GLP-1 group and 1,350 ml (IQR 1,082–1,606) for the placebo group (P = 0.16). The individual values are shown in Fig. 5.

The aggregate postprandial symptom score was 185 (IQR 121–250) in the GLP-1 group and 169 (IQR 121–199) in the placebo group (P = 0.54). No differences were found when comparing each of the symptoms separately (nausea, bloating, fullness, and abdominal pain; see Table 4).

Gastric Emptying of Nutrient Liquid

One volunteer, subsequently shown to be in the GLP-1 group, vomited after the satiety test was completed. These data were excluded from the analysis of gastric emptying.

Figure 6 shows the gastric emptying of the radiolabeled liquid nutrient meal. The proportion emptied was significantly lower for the GLP-1 group than for the placebo group at the point that the infusion ended at 30 min [7% (IQR 3.5–19) vs. 23% (IQR 14–23), respectively; P = 0.008]. However, this effect was transient; 1 h after the infusion ended, the proportion emptied was not different for the two groups, being 21% (IQR 14.5–38) for the GLP-1 group vs. 35% (IQR 21.75–38.25) for the placebo group (P = 0.28).

<table>
<thead>
<tr>
<th>Table 3. Proximal gastric volumes and ratios</th>
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<tbody>
<tr>
<td><strong>Parameter</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Baseline volume</td>
</tr>
<tr>
<td>Fasting volume</td>
</tr>
<tr>
<td>Fasting difference</td>
</tr>
<tr>
<td>Fasting ratio</td>
</tr>
<tr>
<td>Postprandial volume</td>
</tr>
<tr>
<td>Postprandial difference</td>
</tr>
<tr>
<td>Postprandial ratio</td>
</tr>
</tbody>
</table>

Values are medians (interquartile ranges); **P** values <0.05 are considered significant.

<table>
<thead>
<tr>
<th>Table 4. Maximum tolerable volume and postprandial symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>MTV, ml</td>
</tr>
<tr>
<td>Aggregate satiety score</td>
</tr>
<tr>
<td>Aggregate symptoms score</td>
</tr>
<tr>
<td>Nausea score</td>
</tr>
<tr>
<td>Bloating score</td>
</tr>
<tr>
<td>Fullness score</td>
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<tr>
<td>Pain score</td>
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</table>

Values are medians (interquartile ranges); MTV, maximum tolerable volume. Aggregate satiety score was determined at the end of GLP-1 or placebo infusion. Aggregate symptom score was determined 30 min postprandially.
**Plasma Levels of Glucose and HPP**

During fasting, the glucose change relative to baseline (preinfusion) was $-12.3$ mg/dl (IQR $-19.1$ to $-8$) for the GLP-1 group and $0.5$ mg/dl (IQR $-2.3$ to $3.3$) for the placebo group ($P = 0.0002$). The postprandial increase in glucose levels was $-9.3$ mg/dl (IQR $-18.5$ to $-6.4$) for the GLP-1 group and $19.3$ mg/dl (IQR $15.9$–$26.6$) for the placebo group ($P < 0.0001$; Fig. 7).

The fasting HPP change relative to baseline was similar in the two groups: $-12.0$ pg/ml (IQR $-22.5$ to $-2.0$) for GLP-1 and $-0.25$ pg/ml (IQR $-14.4$ to $31.4$) for placebo ($P = 0.12$). However, GLP-1 significantly reduced the postprandial increase in HPP levels to $6.5$ pg/ml (IQR $-22.4$ to $6.9$) for GLP-1 compared with $119.8$ pg/ml (IQR $60.1$–$357.0$) for placebo ($P = 0.0001$). The increased gastric volume observed with GLP-1 may result from inhibition of cholinergic innervation during fasting and postprandially. An alternative hypothesis is that GLP-1 enhances gastric volumes by activation of vagal nitrergic pathways, which mediate the normal postprandial accommodation response.

**DISCUSSION**

The results of the present study suggest that GLP-1 increases gastric volume during fasting and in the postprandial period and retards gastric emptying. These effects are not associated with changes in maximum volume of Ensure tolerated or in postprandial symptoms.

Wank et al. (41) showed that slightly lower infusion rates of $0.3$ and $0.9$ pmol·kg$^{-1}$·min$^{-1}$ of GLP-1 diminished fasting gastric tone recorded with an electronic barostat device. We confirmed this finding in our study using SPECT and expanded the knowledge base by showing that the effect is observed in both proximal and whole stomach. Before our study, the effects of GLP-1 on postprandial gastric volumes or accommodation had not been reported. In our study, greater postprandial gastric volumes (proximal and whole stomach) with GLP-1 were demonstrated compared with placebo, using a validated method that images the gastric wall rather than the intragastric content. Hence this method is independent of the volume and the rate of emptying of the meal. Our method does not measure tone and therefore cannot measure relaxation of the stomach. However, since the intragastric pressure is subject to the positive intra-abdominal pressure and to equilibration with atmospheric pressure via the belching reflex, and since these conditions were not altered before and after the meal, the postprandial increase in volume, measured by SPECT, constitutes a measure of the gastric accommodation, which is enhanced by intravenous infusion of GLP-1.

The mechanisms by which GLP-1 increases gastric volume are unclear. It is known that, during fasting, gastric tone is maintained via vagal cholinergic input and that $\alpha_2$-adrenergic and nitrergic pathways induce gastric relaxation (34, 37). During the fed state, gastrointestinal motility is partly controlled by nonadrenergic, noncholinergic vagal pathways (21) and nitric oxide modulates the postprandial accommodation response (31). Our study starts to explore the mechanism for the enhanced postprandial gastric volume in response to GLP-1. Thus we have shown that the effect of GLP-1 on postprandial gastric volume is accompanied by a marked inhibition of the normal postprandial increase of HPP. The latter is a hormone of the endocrine pancreas that is under cholinergic control (32). The effect of GLP-1 on the postprandial HPP response has been previously shown to be independent of gastric emptying (26, 29). This suggests that the delay in gastric emptying by GLP-1 is not the cause of the inhibition of pancreatic polypeptide release. Moreover, we focused on the change in HPP levels in the first 20 min after the meal to appraise the cephalic, rather than the enteral, phases of hormone release. Therefore, our data are consistent with GLP-1 inhibition of efferent vagal-cholinergic function.

The increased gastric volume observed with GLP-1 may result from inhibition of cholinergic innervation during fasting and postprandially. An alternative hypothesis is that GLP-1 enhances gastric volumes by activation of vagal nitrergic pathways, which mediate the normal postprandial accommodation response.

In this study, we confirmed the delay of gastric emptying for liquid meals during intravenous infusion of GLP-1 in healthy subjects. Schirra et al. (28) had previously reported that an isolated subcutaneous injection of either 125 or 250 pmol/kg of GLP-1 delays the emptying of a 300 kcal mixed liquid meal. The retarding effect of GLP-1 on gastric emptying is transient, and the postinfusion emptying of the liquid meal (as assessed by the proportion emptied at 90 min, that is, 1 h after the infusion ended) was not different in the two groups. This observation is consistent with the short biological activity of the hormone (~5 min). The mechanism by which GLP-1 delays gastric emptying of liquids is unclear. The reported inhibition of antroduodenal motility during the postprandial state (26, 28) and the increase in isolated pyloric pressure waves may contribute to delayed emptying of solids. However,
GLP-1 AND HUMAN STOMACH

Gastric emptying of liquids is thought to depend on fundic pressure (46) and to be less influenced by antral motility (10, 18). An alternative mechanism for delayed gastric emptying of liquids is that the GLP-1-induced motility (10, 18). An alternative mechanism for delayed gastric emptying of liquids.

REFERENCES


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