Ghrelin Enhances Gastric Emptying In Diabetic Gastroparesis: A Double-Blind, Placebo-Controlled, Cross-Over Study

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Keywords: Ghrelin; diabetic gastroparesis; pancreatic polypeptide

Abbreviations: GH Growth Hormone,
PP Pancreatic polypeptide,
CAN Cardiovagal autonomic neuropathy,
GER Gastric emptying rate

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Abstract

**Background:** Diabetic gastroparesis is a disabling condition with no consistently effective treatment. In animals, ghrelin increases gastric emptying and reverses post-operative ileus. We present the results of a double-blind placebo-controlled cross-over study of ghrelin in gastric emptying in patients with diabetic gastroparesis.

**Methods:** Ten insulin requiring diabetic patients (5 men, 6 Type I) referred with symptoms indicative of gastroparesis received a two hour infusion of either ghrelin (5pmol/kg/min) or saline on two occasions. Blood glucose was controlled by euglycaemic clamp. Gastric emptying rate (GER) was calculated by real-time ultrasound following a test meal. Blood was sampled for ghrelin, growth hormone (GH) and pancreatic polypeptide (PP) levels. Cardiovagal neuropathy was assessed using the Mayo CASS scale [range 0(normal)-3].

**Results:** Baseline ghrelin levels were 445±36 pmol/l (mean±SEM). Ghrelin infusion achieved a peak plasma level of 2786±188 pmol/l at 90 minutes, corresponding with a peak GH of 70.9±19.8 pmol/l. Ghrelin increased gastric emptying in seven of ten patients (30±6% to 43±5%, p=0.04). Impaired cardiovagal tone correlated inversely with peak post-prandial PP values (p<0.05), but did not correlate with GER.

**Conclusions:** Ghrelin increases gastric emptying in patients with diabetic gastroparesis. This is independent of vagal tone. We propose that analogues of ghrelin may represent a new class of prokinetic agents.
Introduction

Delayed gastric emptying occurs in up to 50% of patients with chronic diabetes and is associated with significant impairments in both quality of life and diabetic control. Whilst this delay is not always clinically apparent, the range of gastrointestinal symptoms may include early satiety, nausea, vomiting, regurgitation, fullness and bloating (1). Impaired gastric emptying in diabetic patients can be associated with a number of possible metabolic consequences: poor glycaemic control, increased risk of postprandial hypoglycaemia, and variable drug absorption. At its worst, gastroparesis can lead to intractable vomiting and an inability to feed, and carries a poor prognosis (2).

Diabetic gastroparesis remains an extremely difficult condition to treat effectively. Present management involves the empirical use of prokinetic drugs such as domperidone, metoclopramide and cisapride (2;3). Erythromycin, which has motilin analogue properties, is also of some value in a subset of patients (4). The effects of these drugs however are unpredictable. Short term administration may accelerate gastric emptying but not necessarily improve symptoms. Furthermore, with chronic administration, the short term benefits are frequently lost (5). One possible explanation for this lack of sustained response to treatment is that gastroparesis may be aetiologically associated with progressive autonomic neuropathy. Assessing autonomic tone to the gut in diabetic patients has primarily been through assessment of cardiovagal autonomic parameters (6). An alternative, more gut specific assessment of autonomic tone is by the measurement of plasma pancreatic polypeptide (PP) in response to sham feeding (7).

The discovery in 1999 of the gastric-derived peptide ghrelin presents us with another potential gastric prokinetic agent (8). Human ghrelin exhibits a 36% identity with motilin, whilst their respective receptors exhibit 50% homology (9). Ghrelin levels rise prior to eating and fall post-prandially, and this hormone may have a role in meal initiation (10) and energy homeostasis (11). In addition to increasing food intake, ghrelin administration in animals has been shown to increase gastric emptying (9;12) and induce fasting motor activity of the gastrointestinal tract (13). It has also been demonstrated that ghrelin induces the migrating motor complex (MMC) in fed rats and increases the frequency of the MMC in the fasted state, suggesting potential as an enterokinetic (13). In the rat, ghrelin stimulates motility in the small intestine through intrinsic cholinergic neurones (14), but does not appear to affect colonic motility (15).

Parenteral administration of ghrelin in man increases appetite and food intake (11;16), stimulates GH secretion and has positive inotropic cardiovascular effects (17). There have been no reported serious side effects in any of these studies, which supports the safety of its administration in man. In view of the controversy over the clinical effect of known gastrokineic drugs (18) we report a “proof-of-concept” study investigating the effect of ghrelin in patients with diabetic gastroparesis. We present the results of a double-blind, placebo-controlled cross-over study (conducted on secondary and tertiary...
referral patients), efficacy being assessed both in terms of gastric emptying and autonomic function.

**Methods**

**Patient selection**

The aim of the study was to investigate whether ghrelin improved gastric emptying in patients with diabetic gastroparesis. The primary outcome was change in gastric emptying rate. The study was approved by the Northwick Park and St Mark’s committee and was performed in accordance with the Declaration of Helsinki. Ten diabetic patients (5 men, mean age 46 (range 36-63)) were recruited from the outpatients department of a secondary and tertiary referral specialist gastroenterology hospital where they had been referred with persistent upper GI symptoms including vomiting. Six were Type I diabetics and all were insulin-treated. Since the accuracy of gastric emptying studies has been questioned by some authors (19;20), recruitment to this trial was based primarily on symptoms. Recently, the symptom of bloating has been identified as a reliable predictor of gastroparesis (21). Subjects were therefore recruited on the presence of bloating plus two other upper GI symptoms on a validated questionnaire (22).

All patients had undergone normal upper GI endoscopies within six months of enrolment to the study, to rule out gastric outlet obstruction or other pathology. Based on a negative CLO-test, all patients were *Helicobacter pylori* negative at the time of the study (three after previous eradication therapy which had been confirmed with subsequent urea breath test before enrolment). All patients had a negative hydrogen breath test for bacterial overgrowth. Patients were ask to stop using proton pump inhibitors, any prokinetic medication and any autonomically active drugs for at least one week prior to study. Clinical data was collected for all subjects including body mass index (BMI), duration of diabetes and presence of diabetic complications. Symptoms of peripheral neuropathy were assessed using a validated questionnaire (23). Baseline creatinine, HbA1c, urea and electrolytes, full blood count and thyroid function were all assessed.

**Test Meal**

The test meal of rice pudding (330kcal, 10%protein, 58% carbohydrate, 32% fat) was given at t=60 minutes and the subjects asked to consume it within 5 minutes.
Ultrasound Assessment of Gastric Emptying Rate (GER)

The methods for this procedure have been previously described and have been validated in healthy controls and diabetic patients, correlating well with scintigraphic measurement (24;25). Realtime ultrasound scanning was carried out using a 5.2mHz curved array probe using SonoSite 180plus (SonoSite, Herts, UK). Gastric emptying was monitored indirectly by determining the longitudinal (D₁) and anteroposterior (D₂) diameters of a single section of gastric antrum, using the abdominal aorta and the left lobe of the liver as internal landmarks (24). For both the longitudinal (D₁) and anteroposterior (D₂) diameters three measurements were done using the mean values of the longitudinal (D₁mean) and anteroposterior (D₂mean) diameters to calculate the antral area. The antral cross-sectional area (A_{antrum}) was calculated in all subjects using the formula:

\[ A_{antrum} = \frac{\pi \times D_{1mean} \times D_{2mean}}{4} \]

Measurements were made at 15 and 90 minutes postprandially. The GER was estimated and expressed as the percentage reduction in cross-sectional area from 15 to 90 minutes, calculated as follows:

\[ \text{GER} = \frac{(A_{area}^{90\text{min}} / A_{area}^{15\text{min}})-1} \times 100 \]

All of the ultrasound measurements were made by a single radiologist (ST) who was also blinded to the infusion order.

Glycaemic clamp

Blood glucose was maintained between 5-8mmol/l in all subjects throughout each study. Patients omitted their dose of insulin on the morning of the study. Human Actrapid (Novo Nordisk) (apart from one patient used Hypurin Porcine neutral (CP)) was diluted in saline and infused at a constant basal rate, equal to the patient’s total daily insulin dose divided by 24. To maintain euglycaemia, saline was infused at 80mls/hr together with a variable infusion of 20% glucose to maintain blood glucose at a concentration between 5-8mmol/l according to blood glucose measurements using a glucometer (Medisense Optimum™, Abbott Laboratories Ltd, Maidenhead, UK) every 15minutes.

Preparation of ghrelin

Synthetic human ghrelin was purchased from Bachem (UK) Ltd. (Merseyside, UK). The *Limulus* amebocyte lysate assay test for pyrogen was negative (Associates of Cape Cod, Liverpool, UK), and the peptide was sterile on culture. Vials of ghrelin and saline were indistinguishable visually; they were labelled by subject and infusion numbers and
stored in a sealed container (16). Patients and investigators were blinded to the infusion order until study completion.

**Infusions**

The study was a randomised, double-blinded, cross-over design. The order of infusions was randomised using the statistics package, Sigmastat version 2.0 (SPSS, Inc., Chicago, IL). Five patients had ghrelin first, and five had saline first. On infusion days, patients attended hospital after an eight hour fast, and had three intravenous cannulae sited in their forearms at 0800hrs. Ghrelin was infused at a rate of 5pmol/kg/min, which has been shown previously to stimulate appetite and growth hormone (GH) secretion (11;16). Each infusion continued for 120 minutes. Subjects were continuously attached to a cardiac monitor with blood pressure and heart rate recorded every 30 minutes (Dinamap, GE Medical Systems, Freiburg, Germany).

**Autonomic Assessment**

The degree of autonomic neuropathy was assessed using an adapted Mayo clinic Composite Autonomic Severity Score (CASS) (26). The CASS assesses post-ganglionic sudomotor, adrenergic and cardiovagal function: in the study we assessed the latter two. Sympathetic adrenergic function was assessed by beat-to-beat blood pressure and heart rate responses to head-up tilt and the Valsalva manoeuvre (score 0-4). Cardiovagal function was evaluated by the heart rate responses to deep breathing and the Valsalva manoeuvre (Score 0-3). An increased score is correlated with a loss of function.

**Blood sampling**

Blood samples were drawn at -75, 0, 30, 60, 90, 120, 150 and 180 minutes during the study. 10ml samples were collected into plastic lithium heparin tubes containing 0.6mg aprotonin. Samples were immediately centrifuged, and plasma separated and stored at -80 °C until assay.

**Plasma GH concentration**

Plasma GH was analysed using Advantage automated chemiluminescent immunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA).
**Plasma PP concentrations**

Plasma PP concentrations were measured with a specific and sensitive radioimmunoassay, as previously described (27). The assay cross-reacted fully (100%) with human PP and did not cross-react with any other member of the pancreatic polypeptide family or gastrointestinal hormone. Antisera against human pancreatic polypeptide was produced in rabbits and used at a final dilution of 1: 560,000. The $^{125}$I PP was prepared by the iodogen method and purified by high pressure liquid chromatography. The specific activity of the $^{125}$I PP label was 54 Bq/fmol. The assay was performed in total volume of 0.7 ml of 0.06 M phosphate buffer PH 7.2 containing 0.3% bovine serum albumin. The assay was incubated for three days at 4ºC before separation of the free and antibody bound label by charcoal absorption. The detection limit of the assay was 3.5 pmol/l and the intra-assay coefficient of variation was 5.7%. All samples were measured in one assay to avoid inter-assay variation.

**Plasma ghrelin**

Ghrelin-like immunoreactivity was measured with a specific and sensitive radioimmunoassay as previously described (28). Briefly the assay cross-reacts fully (100%) with both octanoyl and des octanoyl ghrelin and did not cross-react with any other known gastrointestinal or pancreatic hormone. The antisera (SC-10368) was obtained from Santa Cruz biotechnology and used at a final dilution of 1:50,000. The $^{125}$I ghrelin was prepared with Bolton & Hunter reagent (Amersham International UK) and purified by high pressure liquid chromatography using a linear gradient from 10 to 40% acetonitrile, 0.05% TFA over 90 minutes. The specific activity of ghrelin label was 48 Bq/fmol. The assay was performed in a total volume of 0.7 ml of 0.06 M phosphate buffer PH 7.2 containing 0.3% bovine serum albumin and was incubated for 3 days at 4ºC before separation of free and bound antibody label by charcoal absorption. The assay detected changes of 20 pmol/l of plasma ghrelin with a 95% confidence limit. The intra-assay coefficient of variation was 5.5%. All samples were measured in one assay to avoid inter-assay variation.

**Symptom Scores**

On both infusion days, visual analogue scores of the symptoms of bloating, hunger and nausea were assessed at baseline and thereafter at 30 minute intervals until 180 minutes.

**Statistical analysis**


Statistical analysis was carried out using SPSS software version 12.0 (SPSS Inc., Chicago, IL). Differences in peptide levels were measured by analysis of variance. GER data were found to be normally distributed. The GER results from the first study day were subtracted from the results of the second study day to remove effect of order from the analysis. The treatment effect was then evaluated by comparing the differences between treatment orders using a two-sample test. Correlations were carried out using Pearson's correlation. Symptom scores were assessed using analysis of variance. GER and peptide data are presented as mean ± SEM unless otherwise stated.

**Results**

**Patients**

10 patients were studied on two separate occasions. The demographics of the patient group are outlined in Table 1.

**Gastric Emptying**

Gastric emptying rate did not correlate with duration of diabetes \((r=-0.128, p=0.807)\) or HbA\(_{1c}\) \((r=0.48, p=0.161)\). Ghrelin significantly increased gastric emptying in seven out of ten patients, from 30±6% to 43±5%, \(p=0.04\). (Figure 1). Figure 1 shows that the three patients with the highest levels of gastric emptying with saline infusion had the least response to ghrelin.

**Cardiovagal neuropathy (CAN) score**

The CAN scores are included in Table 1. There was an inverse correlation between peak PP level and cardiac autonomic neuropathy score during both saline \((r=-0.702, p=0.024)\) and ghrelin \((r=-0.851, p=0.002)\) infusions (Figure 2). There was no correlation between cardiovagal score and peak GH following ghrelin infusion \((r=-0.179, p=0.620)\). There was no correlation between gastric emptying rate with ghrelin and CAN score \((r=-0.089, p=0.807)\).

**Plasma ghrelin and PP**

**Effect of ghrelin and saline infusion**

The mean fasting plasma ghrelin concentration was 445 ± 36 pmol/l (mean±SEM), with levels ranging from 120-1020 pmol/l. Fasting ghrelin levels inversely correlated with BMI \((r=-0.71, p=0.023)\). Ghrelin infusion achieved steady state at 90 minutes (Table 2). GH
rose as expected and peaked at 90 minutes confirming that the ghrelin infused was biologically active (Table 3). GH levels did not increase significantly above baseline during the saline infusion (Table 3).

**Effect of test meal**

Ghrelin levels during euglycaemia did not change significantly following the test meal. Plasma PP peaked within 30 minutes of the meal and did not differ between the two infusions (p=0.07) (Figure 3). Peak plasma PP did not correlate with GER during either saline (r= -0.172, p=0.634) or ghrelin (r= 0.062, p= 0.864) administration.

**Symptoms**

There were no significant differences between ghrelin and saline in any of the symptoms of bloating, hunger and nausea during the infusions (p>0.05) (Figure 4A, 4B, 4C).

**Discussion**

We have demonstrated for the first time that ghrelin improves gastric emptying in diabetic gastroparesis. To date, the only previous study to assess the effects of ghrelin on gastric emptying in man, employed the relatively insensitive method of the paracetamol absorption test (11). The potential of ghrelin as a prokinetic agent has been shown previously in vitro and in vivo studies. In vitro tissue bath studies have demonstrated that ghrelin increases neurally induced contractions secondary to electrical field stimulation in rodent fundus and antrum (9;29) In both anaesthetised and conscious rats and mice, an increase in gastric emptying has been demonstrated after ghrelin administration (9;12). Ghrelin has also been shown to be able to reverse post operative ileus in the rat and dog (30;31). In the former study, it did so even though motilin and its analogue erythromycin had no effect, suggesting a potent prokinetic action. This ability to reverse ileus has been supported recently in a rodent model of septic ileus, where low doses of ghrelin were effective at reversing the ileus induced in rats by injection of lipopolysaccharide endotoxin (32).

The mechanism by which ghrelin exerts enterokinetic effects is unclear. Ghrelin is an endogenous ligand for the growth hormone secretagogue receptor (GHS-R). In the rat the GHS-R is expressed in the vagal afferent neurons of the nodose ganglion and migrates caudally (33). Immunohistochemistry studies have also demonstrated the presence of GHS-R in the myenteric plexus of stomach and colon in both rat and man (15) and the guinea pig ileum (34). Centrally, the GHS-R is also found in the hypothalamus and pituitary (35). Hence it is likely that ghrelin can act at both central and peripheral levels. The structural homology of ghrelin with motilin, and indeed the similarities between the human motilin receptor (GPR-38) and the motility are via the
motilin receptor. This was not supported by a recent study showing that ghrelin interacted only weakly with the rabbit motilin receptor (36).

Recent studies have demonstrated that the vagus may be important in mediating the effects of ghrelin on gastrointestinal motility (13;37). Fujino et al have shown that the stimulatory effects of peripheral ghrelin on antral and duodenal motility in rats are greater in vagotomised rats than intact rats (13). This suggests that vagotomy may up-regulate ghrelin receptors in the myenteric plexus.

Ghrelin may be exacting its effect by altering autonomic tone to the gut. The increase in PP levels after either a sham or test meal is known be a marker of vagal integrity (7). However, this PP response may be blunted in diabetic patients with CAN (38). Nevertheless, delayed gastric emptying does not necessarily correlate with vagal neuropathy, since a study has shown that although diabetics with CAN had a decreased PP response following a test meal, this was independent of gastric emptying (39). Our results are consistent with these findings. In the present study, PP secretory response, in terms of peak plasma PP level, correlated with the presence of CAN, but not with GER. We did not demonstrate any significant changes in pre-prandial or post-prandial PP levels during ghrelin administration. It has previously been shown that a ghrelin intravenous (IV) bolus in fasted healthy subjects increases plasma PP levels (40), but currently there are no comparative studies of the effects on continuous ghrelin infusion on PP levels in either healthy or diabetic subjects.

In agreement with previous studies, ghrelin increased GH secretion (11). Takeno et al have recently described a normal GH response to continuous IV ghrelin administration in vagotomised humans (41). In support of this, in the current study, all subjects showed a significant GH secretory response to IV ghrelin with no correlation between CAN and GH levels.

We did not observe the expected fall in plasma ghrelin levels in our diabetic patients following the test meal. The meal was 330kcal and of mixed macronutrient composition, which would be expected to elicit a fall in levels in healthy controls. To control for the effects of hypo- and hyperglycaemia on gastric emptying we employed a euglycaemic clamp throughout the studies. However, this did not control for circulating insulin levels which may have inhibitory effects on ghrelin release (42). In the current study, we measured total ghrelin, whereas differing effects of desacyl and acetylated ghrelin on gastric emptying in mice have recently been described (43). Finally, ghrelin dynamics in diabetic patients may also be affected by excretion and metabolism of the peptide. Some of our patients had renal impairment, which may lead to variable or delayed clearance of ghrelin, since it has been shown that patients with renal failure have increased ghrelin levels (44). It is unlikely that our observation is due to the presence of vagal neuropathy, since it has been demonstrated that vagotomy does not affect the nutrient induced suppression of ghrelin levels (45).

Despite the evident increase in gastric emptying, ghrelin did not favourably improve symptoms in patients with diabetic gastroparesis. This phenomenon of enhanced gastric emptying not being accompanied by symptomatic improvement has been previously
observed (46) and remains unexplained. Symptoms of hunger, bloating and nausea relate to a complex interplay of cortical and peripheral factors, and it seems that a simple effect at a gastric level is insufficient to alter symptom perception.

In conclusion, we present novel data that ghrelin increases gastric emptying in patients with diabetic gastroparesis. Although further studies are needed to investigate the mechanism by which this occurs, we propose that ghrelin and/or its analogues may represent a new class of prokinetic agents for the treatment of diabetic gastroparesis. Following the confirmation of acute efficacy in improving gastric emptying from this study, longer term studies of these compounds are indicated.

**Competing interests:** None declared

**Acknowledgements:** We would like to thank Paul Bassett for his statistical advice.
Reference List


Table 1  Demographic details and diabetic history

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<th>Creatinine (mmol/l)</th>
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<th>Cardiovagal function score (0-3)</th>
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Table 2
Plasma ghrelin levels with saline and ghrelin infusions at 0, 60, 90, 120 and 180

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<th>Ghrelin (pmol/l)</th>
<th>0 min (infusion starts)</th>
<th>60 min (pre-meal)</th>
<th>90 min (post-meal)</th>
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Ghrelin (pmol/l)
Table 3 Plasma GH levels with saline and ghrelin infusions at 0, 90, 120, 180 min

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Legends to Figures

Figure 1  The effect of ghrelin on gastric emptying in diabetic gastroparesis. The horizontal bars represent the mean gastric emptying rate during each infusion. Ghrelin increases gastric emptying from 30±6% to 43±5%. Patients with the highest levels of gastric emptying with saline demonstrated the least effect with ghrelin infusion.

Figure 2:  The correlation between cardiovagal neuropathy score and peak pancreatic polypeptide (PP) level during ghrelin infusion. There was an inverse correlation between peak PP level and cardiac autonomic neuropathy score during both saline (r= -0.702, p=0.024) and ghrelin (r= -0.851, p=0.002) infusions.

Figure 3  The effect of ghrelin and saline infusions on pancreatic polypeptide (PP) release. PP levels increased significantly within 30 minutes of the test meal in all patients during both infusions (**p<0.05). There were no significant differences in peak PP levels between the saline and ghrelin study days (p>0.05). The arrow represents the test meal, and the straight bar the period of infusion.

Figure 4  There were no significant differences over time in symptoms of bloating (A), hunger (B) or nausea (C) between the two infusion days (p>0.05, ANOVA).
FIGURE 2

PP level (pmol/l) vs. Cardiovagal Score
FIGURE 3

The figure shows a graph plotting the change in PP level (pmol/l) over time (min) after an infusion and a meal. Two groups are compared: Saline (dashed line) and Ghrelin (solid line). The graph indicates a significant increase in PP levels after the meal, with a peak around 100 minutes. The Saline group shows a smaller increase compared to the Ghrelin group. The data points are marked with error bars, indicating variability. The peak is marked with a "**" symbol, indicating statistical significance. The x-axis represents time in minutes, ranging from 0 to 200, and the y-axis represents PP level (pmol/l), ranging from 0 to 70.
Figure 4A

- Saline
- Ghrelin

Meal

Infusion

Time (min)

VAS (mm)
Figure 4B

Meal

Infusion

Time (min)

VAS (mm)

Saline

Ghrelin
Figure 4C

VAS (mm) vs. Time (min)

- Saline
- Ghrelin

Meal
Infusion

Mean ± SD
Ghrelin enhances gastric emptying in diabetic gastroparesis: a double-blind, placebo-controlled, cross-over study

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