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The TANTALUS™ System for Obesity: Effect on Gastric Emptying of Solids and Ghrelin Plasma Levels

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Background: Gastric electrical stimulation (GES), using the implantable TANTALUS™ System, is being explored as a treatment for obesity. The system delivers nonstimulatory electrical signals synchronized with gastric slow waves, resulting in stronger contractions. We hypothesized that this GES may enhance gastric emptying and as a result affect plasma ghrelin and insulin homeostasis. The aim was to test the effect of GES on gastric emptying of solids and on ghrelin and insulin blood levels in obese subjects.

Methods: The system consists of 3 pairs of gastric electrodes connected to an implantable pulse generator. Gastric emptying test (GE) of solids was performed twice, on separate days, a few weeks after implantation, before and after initiation of stimulation. Blood samples for ghrelin and insulin were taken at baseline and at 15, 30, 60 and 120 min after the test meal.

Results: There were 11 females, 1 male, mean age 39.1±8.9 years, mean BMI 41.6±3.4. Data is available from 11 subjects; GE was normal in 9 subjects and accelerated in 2 subjects. GES significantly accelerated GE compared to control: percent retention at 2 hours 18.7±12.2 vs 31.9±16.4, respectively (*$P<0.01$*). Overall, there was no significant change in ghrelin or insulin profile after food intake. Ghrelin levels fell significantly at 60 min compared to baseline during stimulation (*$P=0.014$*) and control (*$P=0.046$*).

Conclusion: GES results in a significant acceleration of gastric emptying of solids in obese subjects. GES did not have a significant effect on postprandial ghrelin levels when compared to control.

Key words: Electrical stimulation, gastric motility, obesity, gastric emptying, ghrelin

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Introduction

The prevalence of obesity is increasing in many countries, and in the US, the National Health and Nutrition Examination Survey (NHANES) found that more than half of all adults in the US (64%) were overweight or obese, and the prevalence of obesity doubled between 1962 and 2002, from 13.4% to 30.5%.[1-3] The economic burden of obesity is increasing accordingly and is estimated at more than $100 billion per year in the US alone,[4] reflecting the large number of co-morbidities associated with obesity.

Currently, treatment for obesity consists of medical and surgical interventions. Medical treatment consists of diets, exercise, behavioral modification and pharmacotherapy, alone or in combination. While these modalities can be effective in the short term, compliance is poor and hence long-term results are unsatisfactory.[5-7] Surgical therapy achieves greater weight loss, that is also better sustained, compared with medical therapy, but has a higher morbidity and mortality.[8-10]

Gastric electrical stimulation (GES) has been developed as an alternative treatment for obesity. The TANTALUS™ (MetaCure USA) is an implantable system that delivers gastric contractility modulation (GCM) signals. These electrical signals are synchronized to the intrinsic electrical activity of the stomach (slow waves, SW). They enhance the force of antral contractions, and increase afferent signaling in the vagus nerve, without interfering with intrinsic gastric electrical rhythm.[11] This type of GES is thought to increase satiation and was tested for weight loss in obese subjects.[12] We postulated that enhanced gastric contractility can modulate gastric emptying. We also postulated that GES can modulate ghrelin levels. Ghrelin is a hormone that plays an important role in appetite control and also has adipogenic and somatotrophic properties that increase food intake and body weight.[13-15] Ghrelin level fluctuates substantially during the day, especially in proximity to meals; it peaks before meals and reaches its lowest levels subsequently.[13] Ghrelin is secreted primarily by the stomach,[16] but the stimulus for secretion appears to be postgastric.[17] GES may modulate ghrelin levels by stimulating its release, or by affecting gastric emptying. We also wanted to explore the effect of enhanced delivery of carbohydrates to the intestine on insulin response.

The aim of this study was to test the effect of short-term gastric electrical stimulation, delivering GCM signals, on gastric emptying (GE) rate and ghrelin and insulin levels in obese subjects implanted with the TANTALUS™ system. This study was part of an FDA-approved multicenter study on the safety and feasibility of the Tantalus™ System for weight loss.

Methods

Patients

The study involved 12 obese subjects who participated in our center as part of the multicenter study. Weight criteria were body mass index (BMI), ≥40 kg/m^2, or a BMI >35 kg/m^2 with an associated morbidity. The study protocol was approved by the Institutional Review Board of Cedars-Sinai Medical Center, and written informed consent was obtained from each individual before study enrollment.

Experimental Design

After the implantation of the TANTALUS™ System, standardized GE test and hormone levels were obtained at 3 and 6 weeks after the surgery. Testing began in the morning after an overnight fast. During the 2-hour GE test, blood samples for measuring plasma ghrelin, glucose and insulin levels were taken. Testing at week 3 was done without stimulation (control). At week 6, the GE test and blood tests were repeated under the same conditions, but this time with stimulation for 1 hour upon meal intake. Subjects did not follow a specific diet.

Surgical Procedure

All procedures were done by laparoscopy. Three bipolar leads (TIZER™, MetaCure USA) were implanted in the muscular layer of the stomach. All were placed perpendicular to the long axis of the stomach, with a distance of 2 cm between electrodes in each pair, positioned in the following manner: one pair in the fundus (3-4 cm from the GE junction), and one pair each in the anterior and posterior wall of the antrum, positioned 2-3 cm from the pylorus (Figure 1). Intraoperative gastroscopy was performed in all subjects to ensure that the electrodes did not penetrate into the gastric lumen. Leads were connected to an implantable pulse generator (TANTALUS™ System, MetaCure USA), located in a subcutaneous pocket in the left anterior abdominal wall. The system was interrogated and programmed using transcutaneous radiofrequency telemetry and a portable laptop computer (series tablet PC keyboard, Hewlett-Packard, Korea).

Gastric Emptying Test

The test was performed after an overnight fast. The test meal consisted of 1 egg omelet, labeled with 1.0 mC of technetium 99m sulfur colloid (99mTc), 2 white bread toasts and 120 ml of fruit juice (385 kcal, 27% fat, 13% protein, and 60% carbohydrate).

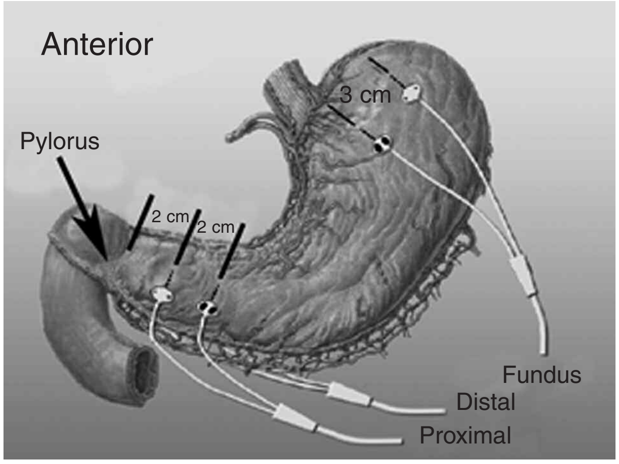

Figure 1. Scheme of the set up of implanted leads in the stomach.

Patients were asked to finish the test meal within 5 min and then to lay down in supine position on a table for the entire examination period. Anterior and posterior images were obtained every one minute using a standard ADAC TransCam gamma camera.

Readings were obtained at 15, 30, 45, 60, 75, 90, 105 and 120 minutes following the beginning of the meal, and the percentage of radiotracer retained in the stomach at 2 hours was obtained. Delayed gastric emptying was considered if retention was >60% at 2 hours, and fast GE was defined as a gastric retention <16% at 2 hours. These data were obtained from a multicenter study on gastric emptying in healthy subjects.[18] Patients, but not Nuclear Medicine personnel, were aware of the sequence of the studies.

Ghrelin, Insulin and Glucose

Blood samples for glucose and hormones were obtained before the meal, and at 15, 60, and 120 min after the meal, when scintigraphic recordings were obtained. Blood was collected in EDTA tubes. Samples were stored at 4°C during collection; then they were centrifuged at 4°C for 10 minutes, after which plasma samples were stored at -80°C in 1.5 ml aliquots until analysis.

Plasma ghrelin and insulin levels were measured in duplicate using ELISA and RIA, respectively, by Linco Diagnostics Services Inc. (St Charles, MO, USA). Plasma levels of glucose were measured by the same laboratory.

Gastric Electrical Stimulation

GCM signal was delivered for 1 hour, starting at the onset of the GE test meal. Electrical pulses were delivered to the antral electrodes using a biphasic symmetric waveform, phase duration: 6 ms, frequency: 83 Hz, wave duration: up to 1200 ms, synchronized to local intrinsic gastric slow waves. The amplitude and timing of the waveform were adjusted to each individual subject (amplitude range: 6-10 mA).

Data and Statistical Analysis

Hormone levels, demographics, and gastric emptying results are expressed as mean±standard deviation. Area under the curve (AUC) was calculated for ghrelin and insulin. Comparison of gastric retention and AUC of hormones between the two periods was assessed by a two-tailed, paired Student's *t*-test, $P<0.05$ for significance. ANOVA of repeated measures was used for analysis of hormone levels at different time-points.

Results

Eleven females and 1 male were studied with a mean age of 39.1±8.9 years (range 22 to 51), BMI 41.6 ± 3.4 kg/m^2. Three subjects had type 2 diabetes mellitus, and were on oral hypoglycemic medications.

Effect of GCM on Gastric Emptying

Eleven subjects completed the GE test; one subject could not lie on the examination table for the duration of the test and was excluded. All fasting glucose levels at the beginning of the GE test were under 200 mg/dl in both the control and stimulation sessions (plasma glucose 111.1±18.3 vs 109.7±29.0 mg/dl, control vs stimulation, respectively $P= 0.23$), and overall glucose profile was not affected by stimulation (Figure 2). None of the subjects had delayed gastric retention. Nine subjects had normal GE with percent retention at 2 hours of 20-55.6. Two subjects (non-diabetics) displayed fast GE at 2 hours (7.2 and 13.2% gastric retention, respectively).

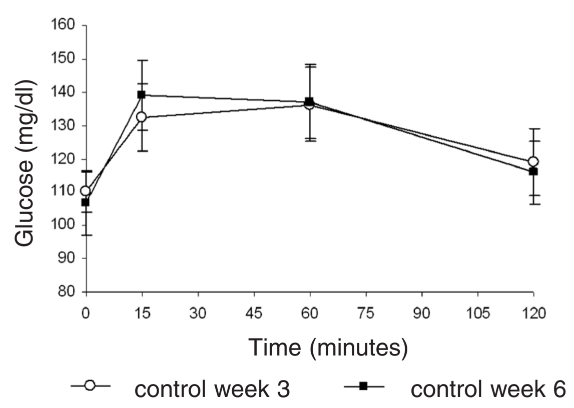

Figure 2. Effect of GES (GCM) on blood glucose levels. This graph shows blood glucose levels at different times after the meal during both control (open circles) and stimulation (closed squares). Glucose levels did not change significantly between sessions.

GCM delivery significantly accelerated GE of solids, reducing gastric retention at 2 hours from 31.9±16.4 to 18.7±12.2%, control vs stimulation, respectively, P=0.008 (Figure 3). GCM delivery was well tolerated by all subjects. Specifically, there were no symptoms of abdominal pain, nausea, vomiting, sweating or diarrhea.

Effect of GCM on hormones

Ghrelin levels were obtained from 11 subjects. Baseline ghrelin levels were not significantly different between control and stimulation sessions (657.6±240.6 vs 649.2±234.4 pg/ml, respectively, P=0.82). Overall, there was no significant difference in AUC of the ghrelin levels between the two sessions, 1211±325 vs 1160±355 pg/mL/h, control vs stimulation respectively, P=0.42 (Figure 4). During control, ghrelin levels decreased slightly after the meal, reaching nadir at 60 min (change of -72.4±160.6 pg/mL from baseline, P=0.046). During GCM stimulation, ghrelin levels also reached a nadir at 60 min that was significantly lower than baseline value (change of -91.2±103.3 pg/mL from baseline, P=0.014).

Insulin levels were obtained in 10 patients. Baseline insulin levels were not significantly different between control and stimulation sessions (26.6±10.1 vs 27.7±15 μU/mL, respectively, P=0.80). Five patients displayed elevated baseline insulin (>27 μU/mL). During both control and stimulation, insulin levels significantly increased soon after a meal (15 min) and remained significantly elevated at 60 and 120 min

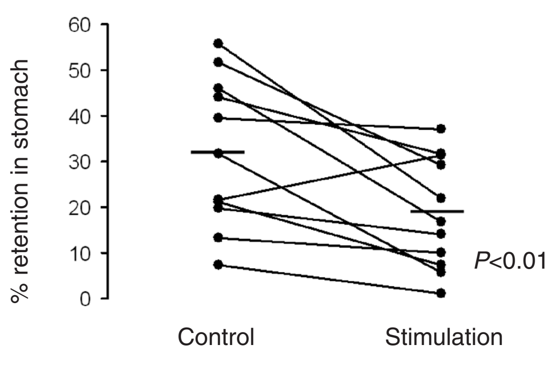

Figure 3. Effect of GES (GCM) on gastric retention at 2 hours. This graph depicts the effect of GES on gastric retention at 2 hours in each individual. GES significantly diminished gastric retention in all but 2 subjects (31.9±16.4 vs 18.7±12.2%, control vs stimulation, P <0.01).

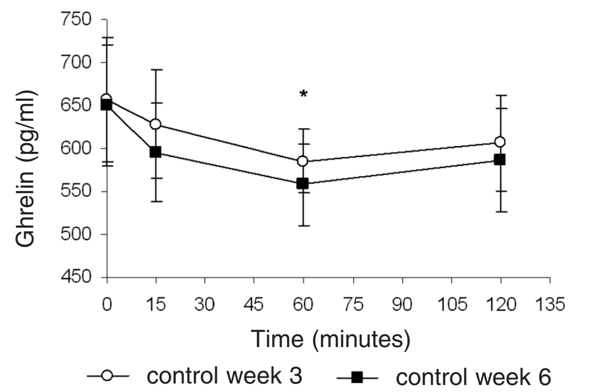

Figure 4. Effect of GES (GCM) on ghrelin levels. This graph shows ghrelin levels at different times after the meal during both control (open circles) and stimulation (closed squares). Ghrelin levels significantly diminished at 60 min when compared to baseline (*P<0.05) during control and stimulation sessions.

post meal (Figure 5). When AUC was compared, there was no significant difference between control and stimulation sessions (126±62 vs 136±56 μU/mL/h, respectively, P=0.55).

Discussion

This study showed that GES using the TANTALUS™ system significantly accelerated gastric emptying of solids in obese patients. This type of GES did not produce significant changes in ghrelin levels in those patients.

The relationship between obesity and gastric emptying is controversial. An animal model suggested that rapid gastric emptying may be a factor in obesity genesis.[19] Studies in humans however, have shown that gastric emptying in obese subjects was delayed,[20-23] accelerated,[20,24-26] or comparable to that observed in lean subjects.[27-30] The inconsistent results may reflect the use of various methods and analyses of the gastric emptying test. Our results, using a standardized method of gastric emptying,[18] though up to 2 hours only after the meal, support the findings of other groups that did not find a significant change in gastric emptying in obese subjects.

Of major interest is the finding that GCM significantly enhanced gastric emptying. We hypothesized that by enhancing antral contractility, GCM may accel-

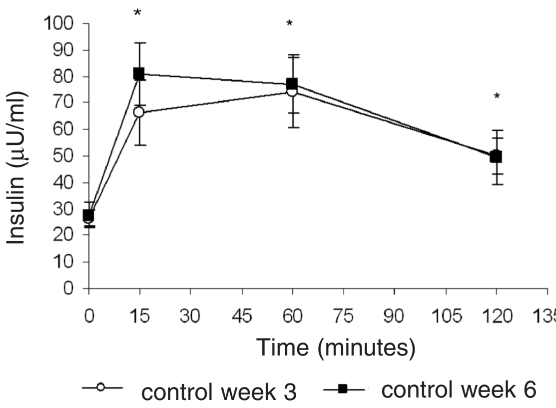

Figure 5. Effect of GES (GCM) on insulin levels. This graph displays insulin levels at different times after the meal during both control (open circles and stimulation (closed squares). Insulin levels were significantly higher at 15, 60 and 120 min compared to baseline, during both sessions (*P<0.05). However, there was not significant difference in insulin levels between sessions.

erate gastric emptying, acting like a prokinetic agent. Delayed gastric emptying is associated with postprandial fullness and vomiting in patients with functional dyspepsia.[31] Thus, research on other types of GES has explored the possibility that disruption of gastric emptying, among other mechanisms, may induce weight loss. We have shown that short-term low-frequency/long-pulse GES to the distal stomach of dogs disrupted gastric electrical activity, and caused a significant reduction in food ingestion that resulted in weight loss, but without significant delay in gastric emptying.[32] In humans, pharmacologically-induced delay in gastric emptying with agents such as octreotide[33] or atropine[34] had little effect on food consumption. Also, there was no correlation between slow gastric emptying and reduction in *ad libitum* intake during GLP-1 infusion in overweight subjects.[35] Contrary to these findings, a study in dogs showed that acute electrical stimulation of the pylorus delayed gastric emptying and reduced food intake.[36] Similar results were also observed during acute duodenal electrical stimulation in healthy volunteers.[37] It is unclear though whether it is the delayed gastric emptying or other factors associated with GES, such as activation of afferent neural pathways to the brain[38] that predominantly influence food intake and weight loss. Importantly, rapid gastric emptying can also modulate food intake. In patients with functional dyspepsia, rapid gastric emptying was associated with decreased meal size and postmeal symptoms,[39] while in obese subjects, pharmacologically-induced acceleration of gastric emptying resulted in intra- and postprandial nausea.[34] Rapid gastric emptying may reduce food intake and induce symptoms such as fullness, nausea and bloating, by activating postgastric mechanisms, such as intestinal distension and/or release of neuropeptides and hormones that mediate satiation.

We also postulated that GCM might affect ghrelin response to meal, through either a direct effect on the stomach or by acceleration of gastric emptying. Ghrelin is a gut peptide that modulates food intake and weight control. Ghrelin levels peak before meals, and decline significantly thereafter.[13] High ghrelin levels are associated with meal initiation and correlate with higher hunger scores, even in the absence of food-related cues.[40] Ghrelin levels after a meal predict the energy intake of the next meal: lower levels are associated with reduced intake.[41] Finally, drug-induced delay in gastric emptying results in reduced ghrelin suppression.[42] Thus, we hypothesized that acceleration of gastric emptying by GES will result in earlier activation of postgastric inhibitory mechanisms leading to earlier meal-related suppression of ghrelin level, and perhaps earlier termination of the meal. Overall, there were not significant changes in postprandial ghrelin profile with or without stimulation, in agreement with a previous study that showed no change in ghrelin levels in obese subjects in whom gastric emptying was accelerated with erythromycin.[34] Plasma ghrelin levels after a meal ,however, tended to be lower at all time-points during stimulation, compared to the control session.

In conclusion, GCM delivered to the distal stomach significantly accelerates gastric emptying of solids. Further investigation should be conducted to test the long-term effect of GCM on gastric emptying and on postgastric mechanisms involved in meal termination.

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