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Gastric Electrical Stimulation with the TANTALUS® System in Obese Type 2 Diabetes Patients: Effect on Weight and Glycemic Control

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Abstract

Background:

The TANTALUS® System is an investigational device that consists of an implantable pulse generator connected to gastric electrodes. The system is designed to automatically detect when eating starts and only then deliver sessions of gastric electrical stimulation (GES) with electrical pulses that are synchronized to the intrinsic antral slow waves. We report the effect of this type of GES on weight loss and glucose control in overweight/obese subjects with type 2 diabetes mellitus (T2DM). This study was conducted under a Food and Drug Administration/Institutional Review Board-approved investigational device exemption.

Method:

Fourteen obese T2DM subjects on oral antidiabetes medication were enrolled and implanted laparoscopically with the TANTALUS System (body mass index 39 ± 1 kg/m^2, hemoglobin A1c [HbA1c] 8.5 ± 0.2%). Gastric electrical stimulation was initiated four weeks after implantation. Weight, HbA1c, fasting blood glucose, blood pressure, and lipid levels were assessed during the study period.

Results:

Eleven subjects reached the 6-month treatment period endpoint. Gastric electrical stimulation was well tolerated by all subjects. In those patients completing 6 months of therapy, HbA1c was reduced significantly from 8.5 ± 0.7% to 7.6 ± 1%, $p < .01$. Weight was also significantly reduced from 107.7 ± 21.1 to 102.4 ± 20.5 kg, $p < .01$. The improvement in glucose control did not correlate with weight loss ($R^2 = 0.05$, $p = .44$). A significant improvement was noted in blood pressure, triglycerides, and cholesterol (low-density lipoprotein only).

Conclusions:

Short-term therapy with the TANTALUS System improves glucose control, induces weight loss, and improves blood pressure and lipids in obese T2DM subjects on oral antidiabetes therapy.

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Abbreviations: (ACCORD) Action to Control Cardiovascular Risk in Diabetes, (CVD) cardiovascular disease, (GCM) gastric contractility modulation, (GES) gastric electrical stimulation, (HbA1c) hemoglobin A1c, (HDL) high density lipoprotein, (LDL) low density lipoprotein, (NHANES) National Health and Nutrition Examination Survey, (SW) slow waves, (T2DM) type 2 Diabetes mellitus, (UKPDS) United Kingdom Prospective Diabetes Study

Keywords: diabetes, electrical stimulation, gastric contractility modulation, glucose control, hemoglobin A1c, obesity

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Introduction

The rates of obesity and type 2 diabetes mellitus (T2DM) are rising sharply in the United States and around the world. The National Health and Nutrition Examination Survey (NHANES) reported that almost two-thirds of adults in the United States are overweight or obese.[1–3] Accordingly, the prevalence of T2DM has significantly increased, and the direct economic burden of T2DM in the United States alone is projected to rise from $91 billion in 2002 to $138 billion in 2020.[4,5]

Diabetes is strongly associated with an increased risk of microvascular and macrovascular disease. The incidence and progression of retinopathy are directly related to glycemia control.[6] There is a similar association between glycemic control and the development of diabetic nephropathy: high hemoglobin A1c (HbA1c) accelerates the progression of albuminuria.[7] The United Kingdom Prospective Diabetes Study (UKPDS), which followed over 4000 patients, found that strict glycemic control reduced the risk of microvascular disease in patients with T2DM.[8] The American Diabetes Association recommends that diabetes patients keep glucose tightly controlled to achieve an HbA1c level of less than 7%. Unfortunately, the NHANES survey showed that only 37% of diabetes patients are meeting this goal.[9] Intensive insulin or medical therapy is not without problems and may be associated with more frequent hypoglycemic or cardiovascular events and an unexpected increase in mortality.[10–13]

Failure to achieve adequate glycemic control is related in part to poor dietary habits, inadequate medical care, and limited therapeutic options. Gastric electrical stimulation (GES) may provide an alternative treatment option. The TANTALUS® (MetaCure) is a meal-activated implantable system that delivers gastric contractility modulation (GCM) signals. These electrical signals are synchronized with 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 the intrinsic gastric electrical rhythm.[13] This type of GES is thought to increase satiation and was evaluated as a weight loss therapy for obese subjects.[14] Preliminary data suggest that this system may improve glucose control in T2DM patients regardless of its effect on body weight.[15] The TANTALUS System is implanted laparoscopically; it does not restrict or ablate part of the gastrointestinal tract, does not cause malabsorption, has an outstanding safety profile, and is reversible.[14,15] The TANTALUS System has a built-in capability to automatically detect food intake that initiates the GCM signals. This synchronization of GCM signals to periods of food intake was correlated with improvements in glycemic control in obese subjects with T2DM.[16]

This study was part of a Food and Drug Administration-approved multicenter study on the safety and feasibility of the TANTALUS System for weight loss. The objectives of this feasibility study were to evaluate the safety and functionality of the TANTALUS System with TANTALUS II implantable pulse generator and to assess the effect of GCM signal application on trends of HbA1c, blood glucose, and body weight changes in obese or overweight subjects with T2DM.

Methods

All subjects were on regular treatment with oral antidiabetes medications. Subjects treated with exenatide and/or insulin were excluded. Selected subjects did not achieve good glucose control despite regular oral antidiabetes treatment and were selected using the HbA1c parameter in the range of 7.5% to 9.5%. Patients with HbA1c above 9.5% were excluded because of the immediate need for intensive treatment and higher risk of surgery. Subjects with HbA1c less than 7.5% were excluded since their glycemic control was too close to the desired goal of 7% to justify a surgical procedure. The study was conducted in two U.S. centers.

Experimental Design

This study is part of a 2-year, open-label trial intended to test the safety and feasibility of the TANTALUS System. After enrollment, there was a period of 4 weeks during which patients were evaluated prior the implantation of the system to determine stability of weight. Subjects then underwent laparoscopic implantation of the TANTALUS System. Electrical stimulation started 4 weeks after implantation (time 0). Subjects were counseled about maintaining a healthy diet but were not required, or counseled, to follow any specific diet for the duration for the study.

Subjects were followed closely with regular laboratory tests and physician visits. Body weight, HbA1c, fasting glucose blood pressure, and lipid profile measurements

were obtained at enrollment, 4 weeks after surgery prior to turning on the GCM (Time 0), and 3 and 6 months after GCM treatment was started. Body weight was obtained using a calibrated digital scale while subjects were fasting. Blood samples for HbA1c, fasting glucose, and lipid profiles were also obtained after an overnight fast. Blood pressure levels were measured and registered at every visit in a standardized manner. Gastric contractility modulation stimulation parameters were also closely evaluated.

Surgical Procedure

All implantation procedures were performed via laparoscopy. Three bipolar leads (TIZER®, MetaCure) were implanted in the muscular layer of the stomach. All were placed perpendicular to the long axis of the stomach, with a distance of 2–4 cm between the electrodes constituting each pair. They were positioned in the following manner: one pair of electrodes in the fundus (1–2 cm from gastroesophageal junction) and one pair each in the anterior and posterior wall of the antrum, positioned 2–3 cm from the pylorus. 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, MetaCure) located in a subcutaneous pocket in the left anterior abdominal wall. The system was interrogated and programmed using transcutaneous radiofrequency telemetry and a portable computer (Series 1100 Tablet PC, Hewlett-Packard). All subjects were discharged from the hospital the same day of implantation or the following day.

Gastric Contractility Modulation / Electrical Stimulation

Gastric contractility modulation was delivered for 75 min, starting at the detected onset of a meal. Electrical pulses were delivered to the antral electrodes synchronized to local intrinsic gastric SW. Electrical pulses used a biphasic symmetric waveform having a phase duration of 6 ms, a repetition rate of 83 Hz, and a pulse duration of 1200 ms. The amplitude and timing of the waveform were adjusted to each individual subject (amplitude range, 5–15 mA) and were set at the highest amplitude that did not induce uncomfortable sensation.

Onset of a meal was automatically determined by an algorithm embedded in the implantable pulse generator. The thresholds for automatic eating detection were customized separately for each subject in order to optimize sensitivity and specificity.

Data and Statistical Analysis

We compared values of HbA1c, body weight, fasting glucose, blood pressure, and lipid profiles [including triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol) among all time points: enrollment, time 0 (or beginning of the therapy], and 3 and 6 months after the initiation of the GES. Hemoglobin A1c levels, fasting glucose levels, body weight, blood pressure, lipids, triglycerides, and demographics results are expressed as mean ± standard deviation. Comparison of the variables at enrollment, time 0 (starting of the GCM therapy), 3 and 6 months were done by repeated measures of analysis of variance with Tukey adjustment, $p < .05$ for significance.

The study protocol was approved by the Institutional Review Board of Cedars-Sinai Medical Center in Los Angeles, California, and by the Diabetes and Glandular Diseases Research Associates in San Antonio, Texas. Written informed consent was obtained from each individual before study enrollment.

Results

Two sites enrolled patients in this multicenter study. We included data of all patients enrolled from these two sites. Fourteen obese T2DM patients (10 females) participated in the study. They had a mean age of 42 years (range, 32–54), mean weight of 107.3 ± 20.1 kg, and mean body mass index of 39 ± 1 kg/m^2 (range, 31–45). At enrollment, mean HbA1c was 8.4% (range, 7.5–9.4%). All subjects were on treatment with one or more oral antidiabetes medications. Three subjects were being treated with a single medication, eight subjects with a combination of two medications, and three subjects with a combination of three different medications.

Out of 14 subjects initially enrolled, 11 reached 6 months of GCM therapy. Three subjects exited prior to terminating the study: one subject was lost to follow-up before starting therapy, one subject withdrew because of disease complications unrelated to the TANTALUS System, and one subject withdrew because of poor compliance with study protocol requirements.

Effect of Gastric Contractility Modulation on Glucose Control

Levels of HbA1c at different time points for the 11 available subjects are displayed in **Figure 1**. Gastric contractility modulation treatment significantly improved glucose control at 3 and 6 months of therapy. Levels of HbA1c

decreased from 8.5 ± 0.7% at enrollment to 7.5 ± 0.9% at 3 months and remained at 7.6 ± 1% at 6 months, $p < .05$ for both endpoints compared to enrollment levels.

The improvement in glucose control was not correlated with weight loss ($R^2 = 0.05$, $p = .44$). There were no significant changes in fasting insulin: 16.9 ± 8.4, 18.4 ± 10, and 16.1 ± 8.8, at recruitment, 3 months, and 6 months, respectively ($p > .05$).

Fasting glucose levels tended to diminish over time with treatment, but the differences were not statistically significant. Fasting glucose levels were 166.13 ± 41.18 mg/dl at enrollment, 153.63 ± 57.4 mg/dl at time 0, 141.27 ± 22.28 mg/dl at 3 months, and 143.9 ± 34.87 mg/dl at 6 months.

Effect of Gastric Contractility Modulation on Body Weight, Blood Pressure, and Lipid Profile

There was a sustained weight loss at 3 and 6 months: from 107.7 ± 21.1 kg at enrollment to 104.7 ± 20.8 kg at 3 months and 102.4 ± 20.5 kg at 6 months, $p < .05$ for both endpoints when compared to enrollment (**Figure 2**). The weight loss was also significant when comparing time 0 to 6 months (106.3 ± 20.7 kg versus 102.4 ± 20.5 kg, respectively, $p < .01$).

There was a significant reduction in systolic blood pressure: 124 ± 12 mmHg versus 112 ± 10 mmHg, enrollment versus 6 months, respectively, $p < .05$. Also, there was a significant decrease from enrollment to 6-month levels in total cholesterol (196 ± 27 mg/dl versus 164 ± 31 mg/dl, $p < .05$) and LDL cholesterol (125 ± 26 mg/dl versus 103 ± 28 mg/dl, $p < .05$). No significant changes in HDL cholesterol were observed. In addition, there was a significant reduction in triglycerides and diastolic blood pressure levels between 3 and 6 months of therapy, see **Table 1**.

TANTALUS System Safety

No severe or unexpected side effects related to the system were reported. Common, anticipated, and self-limited postoperative events were observed. The most frequent side effects reported were postoperative pain in 12 subjects, postoperative nausea in 10 subjects, and gastroesophageal reflux-like symptoms in 3 subjects. All these side effects were quickly resolved with no sequelae.

One patient, initially on two antidiabetes medications (sitagliptin and glyburide) experienced two episodes of glucose levels less than 70 mg/dl; however, none of the episodes had glucose values less than 60 mg/dl, and no symptoms were reported, so no treatment was required and no adjustments in antidiabetes treatment were made.

Acute renal failure developed in one subject one week after implantation of the system. This adverse event was classified as possibly related to the implantation procedure, not to the device or GCM therapy, and resolved with no sequelae. Heavy use of narcotic analgesics and nonsteroidal anti-inflammatory drugs by

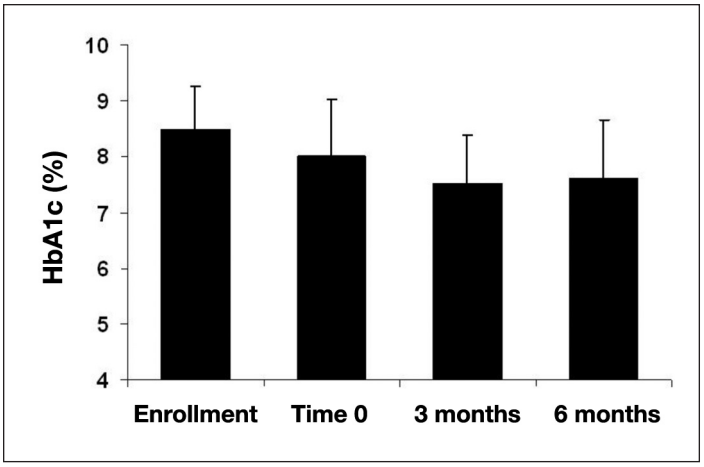

Figure 1. Effect of GCM on HbA1c levels. This bar chart shows HbA1c levels at different times: enrollment, time 0 (initiation of GCM therapy), and 3 and 6 months of therapy. There was a significant and sustained drop in HbA1c at 3 and 6 months when compared to enrollment. Data are shown as mean ± standard deviation. At 3 and 6 months, $p < .05$ when compared to enrollment.

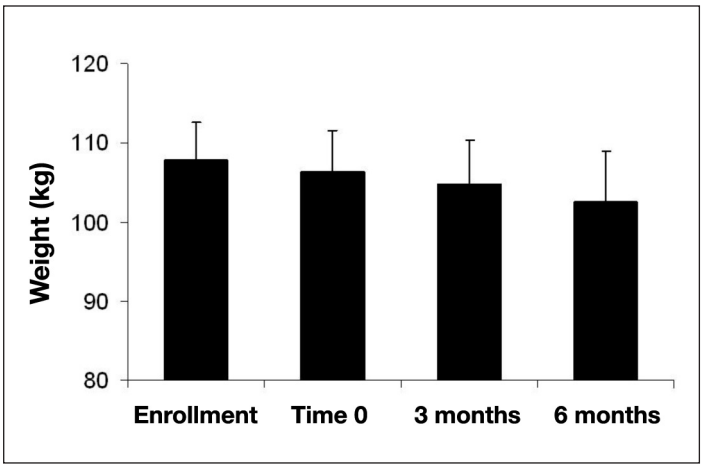

Figure 2. Effect of GCM on body weight. This bar chart depicts body weight in kilograms at different times during the study. There is a significant reduction in body weight at 3 and 6 months of GCM therapy when compared to enrollment. There is also a significant weight loss at 6 months of GCM therapy when compared to the initiation of the treatment or time 0. Data are shown as mean ± standard deviation. At 3 and 6 months, $p < .05$ when compared to enrollment. At 6 months, $p < .01$ when compared to time 0.

Table 1.
Effect of the TANTALUS system on blood pressure and lipids[a]

Variable	*n*	Enrollment	Time 0	3 months	6 months
Systolic blood pressure (mmHg)	11	124 ± 12	120 ± 15	119 ± 12	112 ± 10[b]
Diastolic blood pressure (mmHg)	11	74 ± 9	73 ± 11	77 ± 12	68 ± 9[c]
Total cholesterol (mg/dl)	9	196 ± 27	175 ± 17	184 ± 27	164 ± 31[b]
HDL (mg/dl)	9	41.5 ± 10.1	42.3 ± 8.3	41.5 ± 10.1	41.7 ± 7.6
LDL (mg/dl)	9	125 ± 26	110 ± 20	119 ± 28	103 ± 28[b]
Triglycerides (mg/dl)	9	155 ± 28	154 ± 35	158 ± 38	125 ± 37[c]

[a] The effect of the TANTALUS system on blood pressure and lipid profiles. Values are presented as mean ± standard deviation. Blood tests for lipids were not performed in 2 subjects at 6 months.
[b] $P < 0.05$ compared to enrolment values.
[c] $P < 0.05$ compared to values at 3 months, repeated measure of ANOVA with Tukey adjustment.

the subject over the same time period as the episode of acute renal failure might have contributed to this adverse event.

Discussion

This study demonstrates that GES applied during meal times and synchronized with naturally occurring SW is safe, is well tolerated, and significantly improved glucose control in obese type T2DM patients without changing fasting insulin levels. These subjects had poor glucose control at the time of entry into the trial, despite most of them being on a combination of two or three oral antidiabetes medications. They were not instructed to follow a specific diet or change their lifestyle. The mechanisms underlying this beneficial effect of GES are not altogether clear but, for the most part, are not correlated with weight loss.

The relationship between glucose control and diabetes-related complications is well established. Diabetes is a strong risk factor for cardiovascular disease (CVD); subjects with diabetes have an increased relative risk for CVD two to four times greater than subjects without diabetes.[17] More importantly, diabetes-related increased risk for CVD is independent of other known CVD risk factors. The UKPDS showed that, in T2DM patients, a 1% reduction in HbA1c levels is associated with 35% reduction in microvascular disease, an 18% reduction in myocardial infarction, and a 17% reduction in all causes of mortality.[8,18] Unfortunately, adequate glucose control is difficult to achieve. The UKPDS showed that only 50% of patients were able to achieve adequate glucose control with monotherapy for 3 years, and only 25% did it with monotherapy for 9 years.[19] The younger, more obese, or more hyperglycemic patients were the ones with the highest risk for failure while on monotherapy. Consequently, most T2DM patients require more than one medication to obtain good glucose control. However, patients who have not achieved optimal glucose control with the use of metformin, sulfonylureas, or a combination of both have limited therapeutic options. Comparison of NHANES results from 1988 and 2000 showed that, although the frequency of combined oral antidiabetes and insulin usage increased from 3.1% to 11%, rates of glycemic control actually deteriorated from 44.5% in NHANES III (1988–94) to 35.8% in NHANES 1999–2000.[20] New therapies have been proposed. For example, the addition of glucagon-like peptide 1 analogues (like exenatide) to the regimens of those patients caused a dose-dependent decrease in HbA1c. Subjects taking higher doses of the drug experienced a 0.8% drop in HbA1c at 30 weeks of treatment.[21–23] Similar to those results, in our study, obese subjects were able to decrease their HbA1c levels by 1% after only 3 months of treatment with the TANTALUS System, and even more importantly, that decrease was sustained at 6 months.

At the moment, we do not know the mechanism for the improvement in glucose control with the TANTALUS System. We know that the improvement in HbA1C levels is partially independent from weight loss, as shown in this study, and therefore, it is possible that its beneficial effect on glucose control is also independent in part of reduced caloric intake. We have not measured oral intake before and during GCM therapy. However, another 1-year, open label study found that the GCM therapy significantly reduced hunger scores in obese (diabetes and nondiabetes) subjects.[14] We also measured levels of ghrelin, a hormone that controls appetite, in a similar previous open label study in obese subjects. We found

a tendency toward lower ghrelin levels during GCM therapy; however, those findings were not statistically significant, in part, perhaps, because of a small number of subjects.[24] Clinical trials designed to investigate the involvement of gastrointestinal hormones and the effect of TANTALUS on insulin sensitivity and beta-cell function were initiated in Europe.

The use of the TANTALUS System also caused a sustained mean weight loss of 5.3 kg in study subjects. The reduction in weight seen in this study was similar to one observed in previous studies in obese diabetes and nondiabetes subjects with the TANTALUS System.[14,15] This is an added benefit in addition to glucose control that is not observed with most other therapeutic options for similar subjects. Many studies showed weight gain, an undesirable effect in T2DM. The UKPDS showed that weight gain was significantly higher in the intensive diabetes control group, about 3 kg, than in the conventional treatment group using oral antihyperglycemics.[8] In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, a strict glucose control regimen with a goal of HbA1c <7% resulted in more weight gain compared to the group with a less demanding regimen with a goal of HbA1c >7%.[25] On the other hand, exenatide caused a weight loss of approximately 2 to 3 kg when combined with metformin. No change in weight was observed when combined with sulfonylureas. However, 45% of patients experienced nausea, requiring discontinuation of medication in 3% of patients.[23] No significant change in body weight was observed when sitagliptin, a dipeptidyl peptidase 4 inhibitor, was added to metformin or pioglitazone.[26] Patients in our study showed a small but statistically significant weight loss with the TANTALUS System that was sustained at 6 months.

Close glucose control with combinations of different medications is associated with a greater number of hypoglycemic events. The risk of hypoglycemia is greater as HbA1c levels approximate normal values.[27] Also, there is an increased risk of hypoglycemia in T2DM patients who use insulin.[28] Most episodes of hypoglycemia are not severe but were reported by 41% of patients per year.[8,10] The frequency of severe hypoglycemia was 3% per year and more frequent in patients with stricter glucose control, as in the ACCORD study.[8,10,12]

With the TANTALUS System, there was a low frequency of hypoglycemia; only one subject had glucose levels less than 70 mg/dl on two occasions. This subject was also treated with a sulfonylurea known to increase this risk. However, the subject did not experience any symptoms, and no further adjustments of his antidiabetes medications were required. Treatment with the TANTALUS System also proved to have significant benefits in other metabolic syndrome parameters, such as blood pressure control, and in lipid profile, observed after 6 months of treatment. These effects could be related to weight loss experienced by the subjects, but further studies are needed to identify the cause of the significant drops in blood pressure, cholesterol, and triglyceride levels.

Good compliance with a therapeutic regimen is a crucial factor in achieving better glucose control.[25] Poor compliance is attributed, among other things, to frequent dosing of pills and/or injections. These factors are obviated by the use of the TANTALUS System since therapy is delivered automatically once the device is programmed. The TANTALUS System is safe and easy to implant. All adverse events, i.e., pain and nausea, were as anticipated following a laparoscopic procedure. All adverse events were resolved with no consequences, no termination of study, and no change in therapy.

In conclusion, this study showed that the TANTALUS System is a safe and feasible addition to the anti-hyperglycemic armamentarium. It significantly improves glucose control and decreases body weight, blood pressure, and lipids, and this improvement was sustained for 6 months. The risk–benefit ratio supports introducing this technology as a potential option to treat obese T2DM subjects. However, additional investigations are needed to better understand the mechanisms underlying this unique therapy. In the United States, the TANTALUS System is under investigation, and it is not for sale. However the TANTALUS System is already approved for use in Europe, and the price there for the system is about €12,000.

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Disclosures:

Claudia Sanmiguel is a consultant, and Jeffrey L. Conklin, Scott A. Cunneen, Philip Barnett, Edward H. Phillips, Mark Kipnes, John Pilcher, and Edy E. Soffer are paid researchers.

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