Treatment of Patients with Obese Type 2 Diabetes with Tantalus-DIAMOND® Gastric Electrical Stimulation: Normal Triglycerides Predict Durable Effects for at Least 3 Years

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Key words
- diabetes mellitus type 2
- HbA1c
- hepatic glucose production
- body weight
- neuropeptides
- obesity

Abstract
The objectives of the present work are to evaluate long-term benefit of nonexcitatory gastric electrical stimulation (GES) by the DIAMOND® device on glycemic control and body weight in patients with type 2 diabetes inadequately controlled with oral agents and to determine the magnitude of the modulating effects of fasting plasma triglyceride (FTG) levels on these effects of GES. Sixty one patients with type 2 diabetes [HbA1c > 7.0 % (53 mmol/mol) to < 10.5 % (91 mmol/mol)] were implanted with the DIAMOND® GES device and treated with meal-mediated antral electrical stimulation for up to 36 months. The effects of baseline HbA1c and FTG on glycemic control, body weight, and systolic blood pressure were measured. GES reduced mean HbA1c by 0.9% and body weight by 5.7%. The effects were greater in patients with normal fasting plasma triglycerides (NTG) as compared to those with hypertriglyceridemia. The mean decrease in HbA1c in patients with NTG averaged 1.1% and was durable over 3 years of follow-up. ANCOVA indicated that improvement in HbA1c was a function of both baseline FTG group (p = 0.02) and HbA1c (p = 0.001) and their interaction (p = 0.01). Marked weight loss (≥10%) was observed in a significant proportion of NTG patients by 12 months of treatment and persisted through the 3 years. GES improves glycemic control and reduces body weight by a triglyceride-dependent mechanism in patients with type 2 diabetes inadequately controlled on oral agents. It is postulated that this is through a gut-brain interaction that modulates effects on the liver and pancreatic islets.

Introduction
Physiologic regulation of cellular function is mediated by the central nervous system through the generation of electrical impulses. Claude Bernard reported in 1854 that lesions in the floor of the fourth ventricle of rabbits induced diabetes mellitus [1]. The role of the central nervous system in the regulation of nutrient homeostasis and its relationship to diabetes mellitus has been the subject of numerous recent studies in rodent models [2–4]. Those studies have led to the recognition of nutrient sensing mechanisms in the gut [5], the gut-brain-liver regulatory axis [6], and brain centered glucoregulatory systems [7,8]. The degree to which these systems exist and regulate physiologic functions in humans has been difficult to establish. The DIAMOND® device recognizes food intake by stretch activation of a pair of electrodes attached to the gastric fundus [9]. Activation sends signals to a pulse generator implanted in a pocket in the abdominal subcutaneous fat. The activated pulse generator sends non-stimulatory electrical pulses to pairs of electrodes attached to the anterior and posterior antral regions of the stomach causing increased contractile force of the antral muscles and transmission of neural impulses to the hind-brain [10]. This cascade of events causes the metabolic improvements seen in patients with type 2 diabetes. The fasting plasma triglyceride level determines the magnitude of these effects [11]. During the last several years, we have been examining the effects of gastric electrical stimulation (GES) on metabolic regulation in patients with type 2 diabetes in an attempt to determine the extent to which gut-central nervous system regulatory pathways are relevant in humans. Gastric electrical stimulation with the DIAMOND® device improves glycemia, decreases body weight and lowers systolic blood pressure in obese patients with type 2 diabetes inadequately controlled by oral anti diabetic medications [11–14]. Studies with one year duration of
treatment have shown that the glycemic effect of the DIAMOND® is related to the fasting plasma triglyceride levels [11]. Patients with baseline HbA1c of 8.4±0.13% (68±1.6 mmol/mol) and normal fasting plasma triglyceride levels (≤1.7 mmol/l) decreased HbA1c by a mean of 1.3±0.26% (-14±3.0 mmol/mol), which was a significantly greater reduction than observed in subjects with high baseline triglycerides (>1.7 mmol/l) in whom the mean HbA1c decreased by a mean of 0.4±0.16% (-5±1.7 mmol/mol) [13]. These observations suggest that electrical stimulation of the gastric antrum and adjacent areas in humans activates a neural axis that regulates metabolic homeostasis and is modulated by the nutrient status. This effect was maintained for at least one year.

An important clinical question is whether the fasting plasma triglycerides predict the long-term magnitude and durability of the DIAMOND® metabolic effects. The present analysis was undertaken to determine the cross-sectional and longitudinal responses of patients treated with the DIAMOND® device for periods up to 36 months.

Materials and Methods

Device

The DIAMOND® device consists of 3 pairs of bipolar electrodes: one pair attached to the gastric fundus and the other 2 pairs attached to the anterior and the posterior antrum [11]. The electrodes are implanted laparoscopically and connected to a pulse generator, which is located in a surgically constructed pocket created in the abdominal subcutaneous adipose tissue. The pulse generator battery is rechargeable using an external power source. The delivered electrical signal characteristics are set by a programmer within the first week after the implantation. The postprandial pulse is non-excitatory and is applied intermittently over a 90 min period following the detection of a threshold antral stretch stimulus.

Patient population

The patient population consisted of 75 type 2 diabetic patients who were inadequately controlled [HbA1c > 7% (53 mmol/mol) to < 10.5% (91 mmol/mol)] on one or more oral antidiuretic medications (metformin, sulfonylureas, pioglitazone). The patients were recruited in 11 medical centers in 6 countries (Austria, France, Germany, Italy, Israel, and USA). Data from 61 patients are included in the analysis. Patients were excluded who violated the protocol: patients with baseline HbA1c unavailable or outside the inclusion range (n = 4), patients on insulin (n = 5), patients whose therapy was modified by their primary care physician during the early phases of the study (n = 3), and patients who voluntarily dropped out of the study in the first several weeks for personal reasons (n = 4). Some early studies pre-specified treatment for 12 or 24 months and at completion the device was removed. However, in several studies, the patients have been followed up for periods extending up to 3 years. Based on our previous triglyceride data, the patient population has been divided into those who had baseline fasting plasma triglycerides ≤1.7 mmol/l and those with fasting plasma triglycerides >1.7 mmol/l.

Study design

The study protocol was approved by each institution’s ethical review board. All patients signed informed consent. Ethical principles were adhered to as prescribed in the World Medical Association Declaration of Helsinki. Each of the individual trials was registered separately with ClinicalTrials.gov (NCT00276471, NCT00547482, NCT00779363, NCT01303302). After screening, those patients with a stable HbA1c > 7.0% (53 mmol/mol) and <10.5% (91 mmol/mol) and stable weight for the preceding 3 months had baseline laboratory studies and were implanted laparoscopically with the DIAMOND® device. They were instructed to maintain their usual diabetic diet. Within one week of the implantation, the amplitude and characteristics of the stimulatory impulse were programmed into the pulse generator. HbA1c and weight were measured at the following time intervals: prior to implantation, 6, 12, 18, 24, 30, and 36 months after implantation or as long as the patients were on active treatment. Blood pressure was monitored at most patient visits.

Statistical analyses

For the cross-sectional analysis, the mean ± SE of the HbA1c values available for each time point were calculated for those patients whose baseline fasting triglycerides were ≤1.7 mmol/l or >1.7 mmol/l. The significance of the difference between the mean baseline HbA1c and the mean at each time point was determined by the 2-tailed t-test. In order to correct for differences due to variable numbers of measurements available at each time point, an additional analysis compared the mean paired difference between the individual HbA1c at each time point from its baseline HbA1c. The significance of this difference at each time point as well as between patients with high and normal fasting plasma triglycerides at the same time points were determined by the 2-tailed t-test.

A subset of 7 patients had HbA1c measurements from baseline through 36 months. The statistical significance of the mean values of the decrease in HbA1c at each time point was determined by 2-tailed t-test. ANCOVA analysis was used to determine the covariance between high and normal triglyceride levels, baseline HbA1c levels and the decrease in HbA1c after 12 months of treatment with the DIAMOND® device. The statistical significance of the difference in the percentage of patients with normal triglyceride levels vs. high triglyceride levels achieving a weight loss ≥10% was determined by Fisher’s exact test. Pearson’s correlation determined the relationship between weight loss ≥10 kg and baseline patient characteristics.

Results

Cross-sectional data from the 61 patients with type 2 diabetes who received non-excitatory gastric electrical stimulation with the DIAMOND® device showed a mean HbA1c decrease of 0.8–0.9% which persisted for the duration of the 24 month follow-up [baseline: HbA1c 8.32±0.14% (67±1.6 mmol/mol), n = 61; 12 months: HbA1c 7.48±0.15% (57.9±1.6 mmol/mol), n = 47; 24 months: HbA1c 7.44±0.26% (57.7±2.3 mmol/mol), n = 23, p < 0.001 at both time points]. Mean weight loss for 12 and 24 months of treatment were -3.8±0.76%, n = 56, p < 0.001 and -5.7±1.28%, n = 29, p < 0.001, respectively. When the patients were divided into those with fasting plasma triglyceride levels ≤1.7 mmol/l (normal TG levels) and >1.7 mmol/l (high TG levels) there was no difference in mean baseline HbA1c or body weight. Thirty seven patients with normal fasting plasma triglyceride levels (mean FTG 1.31±0.04 mmol/l) had mean HbA1c 8.32±0.14% (67±1.6 mmol/mol) and mean body
weight 101 ± 4.7 kg. The 24 patients with high triglycerides (FTG 27.2 ± 0.27 mmol/l) had mean baseline HbA1c 8.33 ± 0.16 (68 ± 2.0 mmol/mol) and body weight 112.7 ± 4.8 kg. Table 1 analyzes the difference in the HbA1c response to DIAMOND GES treatment between type 2 diabetic patients with normal triglyceride levels and high triglyceride levels. Cross-sectional data for the patients are divided into those with normal and those with elevated fasting plasma triglyceride levels. The HbA1c data are expressed as the mean value for each group as well as the mean difference of the HbA1c between each patient’s value at the specific time point and the patient’s baseline HbA1c. The reduction in HbA1c from baseline in the patients with normal triglyceride levels decreased by more than 1% at most time points and was durable for the entire 3 years. In contrast, the patients with high triglyceride levels had a minimal decrease in HbA1c which was progressively less throughout the 24 months. Fig. 1 compares the 3-year cross-sectional data in the patients with normal triglyceride levels to the longitudinal data in 7 patients with normal triglyceride levels followed for the entire 3 years. The cross-sectional and longitudinal data show comparable improvements in HbA1c over the 3-year period.

The difference in magnitude of the DIAMOND® effect on glycemic control in patients with type 2 diabetes as a function of the fasting plasma triglyceride levels is further reflected by the different dependence of HbA1c decrease as a function of baseline HbA1c as shown in Fig. 2. The slope of the relationship between the decreases in HbA1c at 12 months in the normal triglyceride group was −1.27% (95% confidence interval −1.80 to −0.74, p < 0.0001) as contrasted to that in the high triglyceride patients which was −0.28% (95% confidence interval −0.85 to 0.29, p = 0.33). ANCOVA including all 47 observations showed a significant interaction of the triglyceride group with the relationship between baseline HbA1c and the decrease in HbA1c associated with the treatment (p = 0.01). Baseline HbA1c, the triglyceride group and their interaction accounted for 40% of the variability in the HbA1c response.

As presented above, treatment of obese type 2 diabetic patients with the DIAMOND® device consistently shows a modest, statistically significant decrease in body weight. Whether the DIAMOND®-induced weight loss is modulated by the fasting plasma triglyceride was examined. At 12, 24, and 36 months of treatment, there was a tendency for greater weight loss in the normal triglyceride group (12 months −4.7 ± 1.1%, n = 33; 24 months −9.4 ± 2.2%, n = 13; 36 months −9.4 ± 1.9%, n = 8) as contrasted to the high triglyceride group (12 months −2.6 ± 0.8%, n = 23; 24 months −2.8 ± 1.1%, n = 16). Because of the high varia-

Table 1 DIAMOND® gastric electrical stimulation: Effects on HbA1c over 3 years in poorly controlled patients with type 2 diabetes with normal or elevated fasting plasma triglyceride levels.

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Fasting triglycerides ≤ 1.7 mmol/l</th>
<th>Fasting triglycerides &gt; 1.7 mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HbA1c (% mmol/mol)</td>
<td>Δ HbA1c from baseline (%)</td>
</tr>
<tr>
<td>0</td>
<td>8.32 ± 0.14, 67.4 ± 1.5</td>
<td>-1.19 ± 0.19 ***</td>
</tr>
<tr>
<td>3</td>
<td>7.14 ± 0.16,**</td>
<td>-2.01 ± 0.32 ***</td>
</tr>
<tr>
<td>6</td>
<td>7.06 ± 0.13,**</td>
<td>-1.23 ± 0.17 ***</td>
</tr>
<tr>
<td>12</td>
<td>7.22 ± 0.19,**</td>
<td>-0.93 ± 0.24 ***</td>
</tr>
<tr>
<td>18</td>
<td>7.16 ± 0.29, 53.7 ± 1.4</td>
<td>-1.27 ± 0.32 ***</td>
</tr>
<tr>
<td>24</td>
<td>7.16 ± 0.30, 55.1 ± 3.2</td>
<td>-1.36 ± 0.49 *</td>
</tr>
<tr>
<td>30</td>
<td>6.45 ± 0.13, 46.8 ± 1.5</td>
<td>-1.95 ± 0.28 ***</td>
</tr>
<tr>
<td>36</td>
<td>7.04 ± 0.49, 53.4 ± 5.3</td>
<td>-1.61 ± 0.46 *</td>
</tr>
</tbody>
</table>

Significance from baseline: *** p < 0.001, ** p < 0.01, * p < 0.05
Significance between normal and high triglyceride groups: † p < 0.0002, †† p < 0.03, † p = 0.05
The major new findings from this study are that a sustained reduction in HbA1c and weight is achievable with non-stimulatory post-prandial electrical stimulation of the stomach in obese diabetic patients with normal triglyceride levels, but not in those with elevated triglycerides. The Diamond® device provides significant advantages for the treatment of patients with type 2 diabetes inadequately controlled on oral antidiabetic treatments. It is an implantable, re-chargeable gastric surface device, which detects meal ingestion and activates a nonstimulatory electrical signal postprandially for 90 min. The chronic effects are an improvement in glycemic control, a decrease in body weight, and a decrease in systolic blood pressure. The device does not cause hypoglycemia unless accompanied with sulfonylurea treatment and is not associated with significant gastrointestinal symptoms. A most remarkable recent finding is that the Diamond® effects are modulated by the fasting plasma triglyceride levels. Patients with normal triglycerides (≤1.7 mmol/l) have significantly greater decreases in HbA1c than patients with hypertriglyceridemia (>1.7 mmol/l) [11].

The present analysis of 61 patients with a follow-up as long as 3 years extends those observations and shows that treatment with the DIAMOND® improves the HbA1c levels in normal triglyceridemic type 2 diabetic patients inadequately controlled with oral antihyperglycemic agents by more than 1.0%. This is shown in the cross-sectional analysis of all the patients. A longitudinal analysis of 7 patients with serial measurements for 3 years showed data almost identical to the cross-sectional data. Equally as intriguing is the observation that the cross-sectional data show that patients with elevated plasma triglycerides show little if any improvement in HbA1c after the initial 12 to 18 months. Previous preliminary data had suggested that the DIAMOND® weight loss effect was modulated by the triglyceride levels. The present data show the same trends in that the mean weight loss at 24 and 36 months in the normal triglyceride group was approximately 9% of the body weight, while in the high triglyceride group it was about 3%. Because of the great variability of the weight loss, the difference between the normal and high triglyceride groups was not significant (24 months, p = 0.18). However, an analysis of patients with more extensive weight loss (≥10%) showed a highly significant benefit of the DIAMOND® in patients with normal plasma triglyceride levels treated for 12 months or longer.

Limited data in this analysis confirm previous data indicating that DIAMOND treatment of patients with type 2 diabetes is associated with a reduction in systolic blood pressure which appears to be unrelated to the plasma triglyceride levels [14]. The present study analyzes patients who had DIAMOND GES treatment for varying periods of time. Initial studies were planned for fixed duration of 12 or in some instances 24 months at which times device stimulation was discontinued and the device subsequently explanted. As more experience was obtained with the Tantalus device, patients were treated for longer periods and the device has remained in place. As can be noted from Table 1, DIAMOND GES treatment and follow-up occurred in 98% of the patients after 6 months, 77% after 12 months and 38% after 24 months. Currently DIAMOND GES therapy is continuing in 17 patients of this population.

With the exception of the usual mild post-operative discomfort from the laparoscopic procedure, one significant adverse event
attributable to the DIAMOND device was observed. One patient had repeated infections around the implanted pulse generator requiring device removal.

The hypothalamus senses hormones and nutrients to regulate energy balance and weight. Recently several peptides have been detected to play a key role in this brain mediated regulation of food intake and fat selection [15–18]. Furthermore, different forms of diet and lipids exert a differential regulation of insulin sensitivity and metabolism [19, 20]. Based upon recent data in animals on the role of nutrient ingestion’s regulatory role on metabolism through its effects on the brain and our data, we have developed a hypothesis which could explain our findings.

The gastrointestinal tract has an extensive intrinsic nerve network which integrates nutrient ingestion with gastrointestinal hormone secretions, intestinal motility and central nervous system regulatory centers [21, 22]. It has been shown in animal models that the intestine has nutrient sensing mechanisms, which in concert with the brain are able to regulate nutrient intake, hepatic nutrient production and pancreatic islet hormone secretion [2–8]. These nutrient sensing mechanisms are defective in high fat fed and diabetic rodent models. There are some differences in the nutrient sensing mechanisms in different parts of the small intestine. The duodenal mucosa generates long chain fatty acid acyl CoA (LCFA-CoA) from ingested lipids. The LCFA-CoA stimulates an increase in mucosal cholecystokinin, which binds to cholecystokinin 1 receptors on afferent vagus nerve terminals in the duodenal mucosa [3, 23, 24]. These nerve fibers synapse in the nucleus tractus solitarius located in the brain stem. The signal is then transmitted to and integrated in the hypothalamus which has its own sensing mechanism for lipids [25]. Appropriate neural signals are sent back through the hepatic branch of the vagus nerve and the celiac axis to regulate hepatic glucose production and pancreatic islet hormone secre-
tions. This gut-brain-liver-islet nutrient regulatory pathway is proposed to play a major physiologic role in regulating energy intake and nutrient metabolism.

DIAMOND® stimulation of the gastric antral region occurs immediately on the detection of food entering the stomach and causes a 2- to 4-fold increase in the contractile force of the antrum and is associated with an increase in afferent vagus nerve activation and signaling [10]. We hypothesize that this improves the metabolic regulation of the type 2 diabetic patient in 2 ways. Firstly, the activation of the antral contractions and signaling occur at least 10 min earlier than would have been expected by meal ingestion alone (Fig. 3) [10] and the rate of gastric emptying is increased [26]. This is especially important in diabetic patients where hyperglycemia delays gastric emptying by reducing motility, delaying the antral response to meal ingestion [27–31]. DIAMOND® restores a more normal mechanoelectrical neural signal sequence. The second benefit of the DIAMOND signal is a direct activation of the nutrient mediated pathway to the brain stem bypassing the native nutrient stimulus which is markedly impaired in both obesity and diabetes mellitus. Hypertriglyceridemia blunts the gut brain regulatory pathway in the type 2 diabetic patients as it probably does in high fat feed rodents [5, 6]. The triglyceride effect likely occurs at the level of the median eminence of the hypothalamus, which utilizes ATP-dependent potassium channels for nutrient metabolic regulation [25].

If our hypothesis is correct, then high triglyceride levels should blunt other gastrointestinal neurally mediated regulation of body weight and glycemia. A recently published study in db/db diabetic mice has shown that bezafibrate, a triglyceride lowering agent, increases the effect of chronic exendin-4 (a GLP-1 agonist with neural regulatory activity) treatment in decreasing hyperglycemia and improving oral glucose tolerance [32]. Some regulatory peptides such as amylin and GLP-1 have been shown to activate the nucleus tractus solitarii by either circulating levels or neural transmission [33]. These hormones increase satiety and decrease glucagon secretion both of which are effects thought to be neurally mediated. The possible mechanisms by which hypertriglyceridemia interferes with the DIAMOND® device’s metabolic effects are several. High triglyceride levels may directly block gut-brain neurally-mediated regulatory centers in which case lowering plasma triglyceride levels in hypertriglyceridemic patients with type 2 diabetes should increase their metabolic responses to the DIAMOND device. Alternatively, high triglyceride levels are associated with other metabolic abnormalities such as insulin resistance, hepatic steatosis, smaller brain volumes and decreased survival of islet transplants [34–38]. If the hypertriglyceridemia decrease in DIAMOND effect is related to a triglyceride-related abnormality rather than the triglyceride level itself, lowering the plasma triglyceride levels in hypertriglyceridemic patients may not improve the DIAMOND effects. The more likely alternative is that the triglyceride level itself is blocking the neurally-mediated pathway as illustrated in Fig. 3. We are currently carrying out a randomized clinical trial comparing the DIAMOND® treatment in patients with inadequately controlled type 2 diabetic with normal plasma triglycerides, elevated plasma triglycerides treated with placebo and elevated plasma triglycerides being treated with a triglyceride lowering agent to test this hypothesis. Other ongoing studies are measuring changes in meal-mediated islet hormone secretions in normal triglyceridemic and hypertriglyceridemic patients with inadequately controlled type 2 diabetes undergoing treatment with the DIAMOND® device.

We postulate that the DIAMOND® device is a neurofascilitating device that mimics in humans, the effects that lipid ingestion causes in rodent models and increases the rapidity with which this effect occurs since it bypasses the delay in gastric emptying associated with hyperglycemia. The clinical consequences of DIAMOND® treatment in patients with type 2 diabetes are to improve glycemia, reduce weight and lower systolic blood pressure. The current study shows that the glycemic improvement and weight loss are triglyceride dependent and durable. Of particular relevance are the practical issues that the DIAMOND® effects are activated by automatic meal detection and compliance issues are therefore minimized. Additionally, the DIAMOND® effects, while similar to those reported for GLP-1 agonists, are without the significant gastrointestinal side effects.

Author Contributions
Harold E. Lebovitz was involved in the design of the study, the analysis of the data and the writing of the manuscript. Bernhard Ludvik was the Principle Investigator at Medical University of Vienna and managed many study patients. Irit Yanov designed and supervised the studies. Tse'ela Schwartz was a statistical consultant for the study. Mateusz Zelewski assisted in supervision of the studies. David D. Gutterman was involved in the manuscript preparation and editing. Some of the data were presented as an abstract at The International Diabetes Federation Meeting in Melbourne, Australia Dec. 3, 2013. Guarantor–The validity of the data and the contents of the manuscript are guaranteed by Harold E. Lebovitz.

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Conflict of Interest
HEL is Chairperson of Metacure Scientific Advisory Board. IY, MZ were employees of Metacure Ltd. TS and DDG are advisors of Metacure Ltd.

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