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

Authors H. E. Lebovitz[1], B. Ludvik[2, 3], I. Yaniv[4], T. Schwartz[5], M. Zelewski[4], D. D. Gutterman[6]; Metacure Investigators

Affiliations Affiliation addresses are listed at the end of the article

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.

received 11.03.2015
accepted 27.03.2015

Bibliography
DOI http://dx.doi.org/10.1055/s-0035-1548944
Published online: April 16, 2015
Horm Metab Res 2015; 47: 456–462

ISSN 0018-5043

Correspondence
H. E. Lebovitz, MD
Professor of Medicine
Department of Medicine
450 Clarkson Avenue
State University of New York
Health Science Center at Brooklyn
New York 11203
USA
Tel.: + 1/718/720 1618
Fax: + 1/718/720 1628
hlebovitz1@hotmail.com

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 hindbrain [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 antidiabetic 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 implanted 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 ClinicalTrials02).go (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 of ≥ 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 ± 0.10 % (67.4 ± 1.1 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

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.

Time (months)	Fasting triglycerides ≤ 1.7 mmol/l)			Fasting triglycerides > 1.7 mmol/l		
	HbA1c (%, mmol/mol)	Δ HbA1c from baseline (%)	n	HbA1c (%, mmol/mol)	Δ HbA1c from baseline (%)	n
0	8.32 ± 0.14, 67.4 ± 1.5		37	8.33 ± 0.16, 67.4 ± 1.7		24
3	7.14 ± 0.16,† 54.6 ± 1.8	−1.19 ± 0.19***	36	7.66 ± 0.21, 60.1 ± 2.3	−0.59 ± 0.17**	23
6	7.06 ± 0.13,‡ 53.7 ± 1.4	−1.23 ± 0.17***	37	7.90 ± 0.23, 62.8 ± 2.6	−0.42 ± 0.13**	24
12	7.22 ± 0.19,†† 55.3 ± 2.1	−0.93 ± 0.24***	29	7.91 ± 0.24, 62.8 ± 2.6	−0.33 ± 0.20	18
18	7.16 ± 0.29, 54.6 ± 3.1	−1.27 ± 0.32***	15	7.45 ± 0.21, 57.8 ± 2.3	−0.56 ± 0.22*	13
24	7.16 ± 0.30, 55.1 ± 3.2	−1.36 ± 0.49*	12	7.68 ± 0.45, 60.4 ± 5.0	−0.34 ± 0.42	11
30	6.45 ± 0.13, 46.8 ± 1.5	−1.95 ± 0.28***	6			
36	7.04 ± 0.49, 53.4 ± 5.3	−1.61 ± 0.46*	7			

Significance from baseline: *** $p<0.001$, ** $p<0.01$, * $p<0.05$

Significance between normal and high triglyceride groups: ‡ $p<0.0002$, †† $p=0.03$, † $p=0.05$

weight 101 ± 4.7 kg. The 24 patients with high triglycerides (FTG 2.72 ± 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-

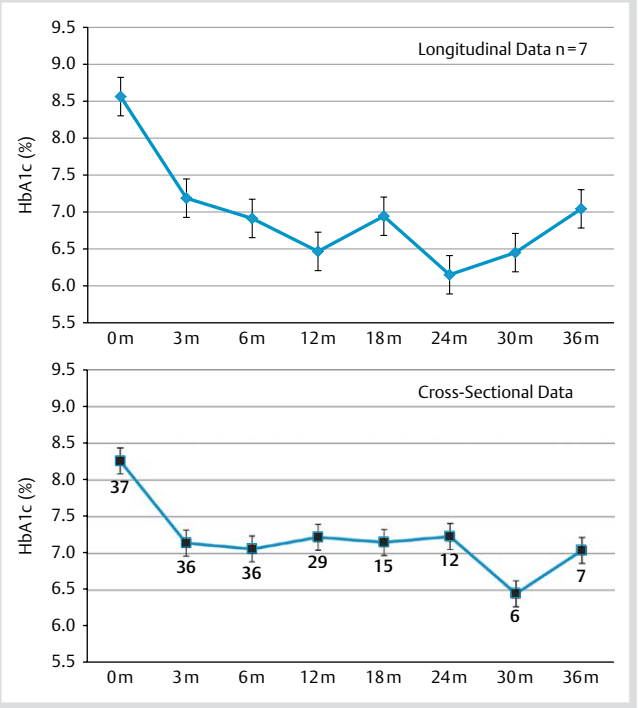

Fig. 1 Change in HbA1c of normotriglyceridemic patients with type 2 diabetes managed with the DIAMOND® device. Cross-section data are from the 31 normotriglyceridemic patients in **Table 1**. The longitudinal data are for a subset of 7 normotriglyceridemic patients who had complete data for the entire 3 years of follow-up. The cross-sectional and longitudinal data are quite similar. (Color figure available online only).

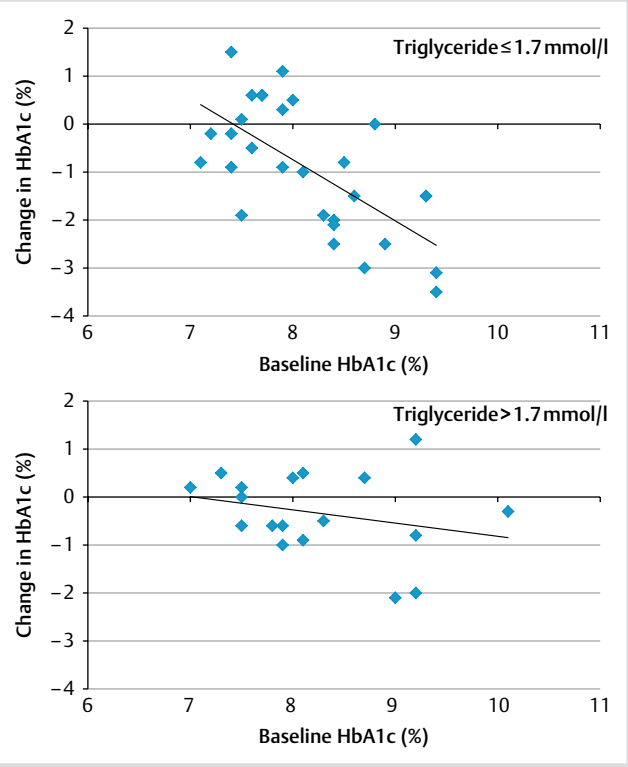

Fig. 2 Analysis of the relationships between baseline HbA1c level, triglyceride group and the decrease in HbA1c by 12 months of DIAMOND® gastric electrical stimulation treatment. ANCOVA analysis showed a statistically significant interaction between the variables: triglyceride group ($p = 0.02$), baseline HbA1c ($p = 0.001$) and decrease in HbA1c at 12 months. Their interaction was statistically significant ($p = 0.01$). The slope in the normal triglyceride group was estimated to be −1.27 ($p = 0.0001$) and that in the high triglyceride group to be −0.28 ($p = 0.33$). Baseline HbA1c, the triglyceride group and their interaction accounted for 40% of the variability in the HbA1c decrease. (Color figure available online only).

bility in weight loss, the difference did not achieve statistical significance (p-value at 24 months = 0.18). It was noted that some patients treated with the DIAMOND® lost considerable weight (≥ 10% of their body weight). Data in our population on the effect of baseline fasting plasma triglyceride levels in predicting those who lost ≥ 10% of body weight indicated that 7 of 13 (54%) of patients with normal triglycerides lost 10% or greater by 2 years of treatment as contrasted to 0 of 16 (0%) patients in the high triglyceride group (Fisher's exact test, $p < 0.001$). Pearson correlation of baseline characteristics with weight loss ≥ 10 kg were statistically significant for waist circumference ($p = 0.033$) and fasting plasma triglycerides ($p = 0.035$) but not for baseline A1C, fasting plasma glucose or systolic or diastolic blood pressure.

In a subset of 18 patients who had appropriate blood pressure measurements at baseline and 24 months 143 ± 2.6/86 ± 2.2 and 132 ± 2.3/84 ± 1.7 mm Hg respectively), it appeared that DIAMOND® therapy is associated with a significant decrease in systolic blood pressure ($p = 0.002$) which is independent of the baseline fasting plasma triglyceride levels (normal TG decrease from 143 ± 5.0 to 129 ± 2.9 mm Hg; high TG from 144 ± 2.5 to 134 ± 3.3 mm Hg). No change in diastolic blood pressure was observed with DIAMOND® treatment in this population.

Discussion

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

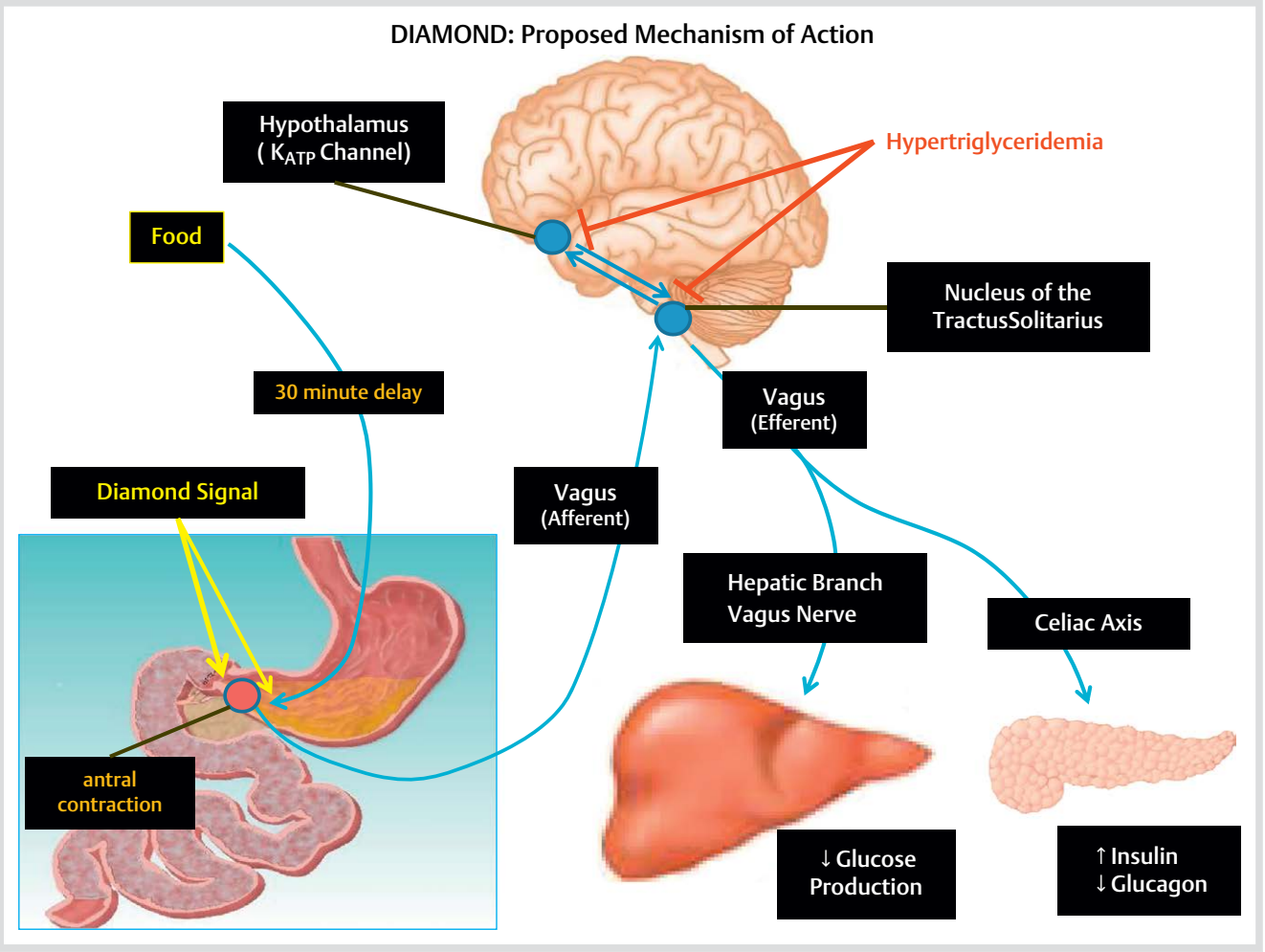

Fig. 3 Proposed hypothesis for the mechanisms of the DIAMOND® effect. The DIAMOND has 2 modes by which it can improve metabolic regulation in patients with type 2 diabetes. Detection of food intake activates DIAMOND causing an immediate increase in antral contractile force and stimulation of the nutrient dependent vagal afferent neuronal plexus. The direct activation of the antrum overcomes delays in antral activation related to food mixing and movement in the stomach and their further inhibition by hyperglycemia. The impulses from the neuronal plexus travel via the vague nerve to the hindbrain where they synapse in the tractus nucleus solitarius. This results in stimulation of the satiety center. The neural signal is further transmitted forward to the hypothalamus which senses circulating lipids by a K_{ATP} channel mechanism. This signal is integrated with other hypothalamic signals and generates a message that travels back through the hindbrain and the hepatic branch of the vagus nerve to the liver where it regulates hepatic nutrient production. Simultaneously, signals are sent via the celiac axis to the pancreatic islets where insulin and glucagon secretion are modified. High circulating triglycerides most likely block the intestinal nutrient sensing signal at the hypothalamic level so that nutrient signals from the intestines are less effective and the metabolic responses blunted.

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 (**Fig. 3**) 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 30 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 solitariues by either circulating levels or neural transmission [33]. These hormones increase satiety and decrease glucagon secretion both of which are effects thought to be neutrally mediated.

The possible mechanisms by which hypertriglyceridemia interferes with the DIAMOND's metabolic effects are several. High triglyceride levels may directly block gut-brain neutrally-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 neutrally-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.

Acknowledgements

The authors express their appreciation for additional statistical analyses by Dimitri Stefanov Ph.D., State University of New York Health Science Center at Brooklyn. The funding for the study came from Metacure, Ltd.

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.

Affiliations
[1] State University of New York Health Science Center at Brooklyn, Staten Islands, New York, USA
[2] Medical University of Vienna, Internal Medicine: Vienna, Austria
[3] Krankenanstalt Ruldolfstiftung, Wien, Austria
[4] Metacure Ltd., Orangeburg, NY, USA
[5] Biostatistics and Medical Device Research Division at GCP Clinical Studies, Tel Aviv, Israel
[6] Medical College of Wisconsin, Milwaukee, WI, USA

References

1 *Bernard C*. Lecons de Ohysiologie Experimentale Appliques a le Medecine. Paris: J.-B. Balliere, 1854
2 *Wang PYT, Caspi L, Lam CKL, Chari M, Li X, Light PE, Gutierrez-Juarez R, Ang M, Schwartz GJ, Lam TKT*. Upper intestinal lipids trigger a gut-brain-liver axis to regulate glucose production. Nature 2008; 452: 1012–1016

3 *Breen DM*, *Yue JTY*, *Rasmussen BA*, *Kokorovic A*, *Cheung GWC*, *Lam TKT*. Duodenal PKC-δ and cholecystokinin signaling axis regulates glucose production. Diabetes 2011; 60: 3148–3153
4 *Rasmussen BA*, *Breen DM*, *Luo P*, *Cheung GWC*, *Yang CS*, *Sun B*, *Kokorvic A*, *Rong W*, *Lam TKT*. Duodenal activation of cAMP-dependent protein kinase induces vagal afferent firing and lowers glucose production in rats. Gastroenterology 2012; 142: 834–843
5 *Breen DM*, *Rasmussen BA*, *Cote CD*, *Jackson M*, *Lam TKT*. Nutrient-sensing mechanisms in the gut as therapeutic targets for diabetes. Diabetes 2013; 62: 3005–3012
6 *Lam TKT*. Neuronal regulation of homeostasis by nutrient sensing. Nat Med 2010; 16: 392–395
7 *Schwartz MW*, *Woods SC*, *Porte D Jr*, *Seeley RJ*, *Baskin DG*. Central nervous system control of food intake. Nature 2000; 404: 661–671
8 *Schwartz MW*, *Seeley RJ*, *Tschop MH*, *Woods SC*, *Morton GJ*, *Myers MG*, *D'Alessio D*. Cooperation between brain and islet in glucose homeostasis and diabetes. Nature 2013; 503: 59–66
9 *Policker S*, *Lu H*, *Haddad W*, *Aviv R*, *Kliger A*, *Glasberg O*, *Goode P*. Electrical stimulation of the gut for the treatment of type 2 diabetes: the role of automatic eating detection. J Diabetes Sci Technol 2008; 2: 906–912
10 *Peles S*, *Petersen J*, *Aviv R*, *Policker S*, *Abu-Hatoum O*, *Ben-Haim SA*, *Gutterman DD*, *Sengupta JN*. Enhancement of antral contraction and vagal afferent signaling with synchronized electrical stimulation. Am J Physiol Gastrointest Liver Physiol 2003; 285: G577–G585
11 *Lebovitz HE*, *Ludvik B*, *Yaniv I*, *Haddad W*, *Schwartz T*, *Aviv R*, *Metacure Investigator Group*. Fasting plasma triglycerides predict the glycaemic response to treatment of type 2 diabetes by gastric electrical stimulation. A novel lipotoxicity paradigm. Diabet Med 2013; 30: 687–693
12 *Sanmiguel CP*, *Conklin JL*, *Cunneen SA*, *Barnett P*, *Phillips EH*, *Kipnes M*, *Pilcher J*, *Soffer EE*. Gastric electrical stimulation with the Tantalus® system in obese type 2 diabetes patients: effect on weight and glycemic control. J Diab Sci Technol 2009; 3: 964–970
13 *Bohdjalian A*, *Prager G*, *Rosak C*, *Weiner R*, *Jung R*, *Schramm M*, *Aviv R*, *Schindler K*, *Haddad W*, *Rosenthal N*, *Ludvik B*. Improvement in glycemic control in morbidly obese type 2 diabetic subjects by gastric stimulation. Obes Surg 2009; 19: 1221–1227
14 *Wong SK*, *Kong AP*, *Osaki R*, *Ng VW*, *Chan LL*, *Lam CC*, *Lebovitz HE*, *Ng EK*, *Chan JC*. A prospective case-control study to compare the efficacy of laparoscopic placement of gastric contraction modulator (TANTALUS II® vs. supplementary insulin treatment in obese T2DM patients. Diabetes Technol Therap (in press 2015)
15 *Primeaux SD*, *Barnes MJ*, *Braymer HD*. Hypothalamic QRFP: regulation of foof intake and fat selection. Horm Metab Res 2013; 45: 967–974
16 *Sekar R*, *Chow BK*. Role of secretin peptide family and their receptors in the hypothalamic control of energy homeostasis. Horm Metab Res 2013; 45: 945–954
17 *Tonon MC*, *Lanfray D*, *Castel H*, *Vaudry H*, *Morin F*. Hypothalamic glucose-sensing: role of Glia-to-neuron signaling. Horm Metab Res 2013; 45: 955–959
18 *Knauf C*, *Drougard A*, *Fournel A*, *Duparc T*, *Valet P*. Hypothalamic actions of apelin on energy metabolism: new insights on glucose homeostasis and metabolic disorders. Horm Metab Res 2013; 45: 928–934
19 *Kavalkova P*, *Touskova V*, *Roubicek T*, *Trachta P*, *Urbanova M*, *Drapalova J*, *Haluzikova D*, *Mraz M*, *Novak D*, *Matoulek M*, *Lacinova Z*, *Haluzik M*. Serum preadipocyte factor-1 concentration in females with obesity and type 2 diabetes mellitus: the influence of very low calorie diet, acute hyperinsulinemia, and fenofibrate treatment. Horm Metab Res 2013; 45: 820–826
20 *Stirban A*, *Nandrean S*, *Gotting C*, *Stratmann B*, *Tschoepe D*. Effects of n-3 polyunsaturated fatty acids (PUFAs) on circulating adiponectin and leptin in subjects with type 2 diabetes mellitus. Horm Metab Res 2014; 46: 490–492
21 *Berthoud HR*, *Patterson LM*. Anatomical relationship between vagal afferent fibers and CCK-immunoreactive entero-endocrine cells in the rat small intestinal mucosa. Acta Anat 1996; 158: 123–131
22 *Timmermans J-P*, *Hens J*, *Adriaensen D*. Outer submucous plexus: an intrinsic nerve network involved in both secretory and motility processes in the intestine of large mammals and humans. Anat Rec 2001; 262: 71–78
23 *Cheung GWC*, *Kokorovic A*, *Lam CKL*, *Chari M*, *Lam TKT*. Intestinal cholecystokinin controls glucose production through a neuronal network. Cell Metab 2009; 10: 99–109
24 *Cote CD*, *Zadeh-Tahmasebi M*, *Rasmussen BA*, *Duca FA*, *Lam TKT*. Hormonal signaling in the gut. J Biol Chem 2014; 289: 11642–11649
25 *Lam TKT*, *Pocai A*, *Gutierrez-Juarez R*, *Obici S*, *Bryan J*, *Aguilar-Bryan L*, *Schwartz GJ*, *Rossetti L*. Hypothalamic sensing of circulating fatty acids is required for glucose homeostasis. Nat Med 2005; 11: 320–327
26 *Sanmiguel CP*, *Haddad W*, *Aviv R*, *Cunneen SA*, *Phillips EH*, *Kapella W*, *Soffer EE*. The TANTALUS™ system for obesity: effect on gastric emptying of solids and ghrelin plasma levels. Obes Surg 2007; 17: 1–6
27 *Jones KL*, *Horowitz M*, *Wishart JM*, *Maddox AF*, *Harding PE*, *Chatterton BE*. Relationships between gastric emptying, intragastric meal distribution and blood glucose concentrations in diabetes mellitus. J Nucl Med 1995; 36: 2220–2228
28 *Schvarcz E*, *Palmer M*, *Aman J*, *Horowitz M*, *Stridsberg M*, *Berne C*. Physiological hyperglycemia slows gastric emptying in normal subjects and patients with insulin-dependent diabetes mellitus. Gastroenterology 1997; 113: 60–66
29 *Woerle H-J*, *Albrecht M*, *Linke R*, *Zschau S*, *Neumann C*, *Nicolaus M*, *Gerich J*, *Goke B*, *Schirra J*. Importance of changes in gastric emptying for postprandial plasma glucose fluxes in healthy humans. Am J Physiol Endocrinol Metab 2008; 294: E103–E109
30 *Woerle HJ*, *Albreche M*, *Linke R*, *Zschau S*, *Neumann C*, *Nicolaus M*, *Gerich JE*, *Goke B*, *Schirra J*. Impaired hyperglycemia-induced delay in gastric emptying in patients with type 1 diabetes deficient for islet amyloid polypeptide. Diabetes Care 2008; 31: 2325–2331
31 *Phillips LK*, *Rayner CK*, *Jones KL*, *Horowitz M*. Measurement of gastric emptying in diabetes. J Diab Complicat 2014; 28: 894–903
32 *Kang ZF*, *Deng Y*, *Zhou Y*, *Fan RR*, *Chan JCN*, *Laybutt DR*, *Luzuriaga J*, *Xu G*. Pharmacological reduction of NEFA restores the efficacy of incretin-based therapies through GLP-1 receptor signaling in the beta cell in mouse models of diabetes. Diabetologia 2013; 56: 423–433
33 *Roth JD*, *Erickson MR*, *Chen S*, *Parkes DG*. GLP-1R and amylin agonism in metabolic disease: complementary mechanisms and future opportunities. Brit J Pharmacol 2011; 166: 121–136
34 *Van de Woestijne AP*, *Monajemi H*, *Kalkhoven E*, *Visseren LJ*. Adipose tissue dysfunction and hypertriglyceridemia: mechanisms and management. Obes Rev 2011; 12: 829–840
35 *Graner M*, *Pentikainen MO*, *Siren R*, *Nyman K*, *Lundbom J*, *Hakkarainen A*, *Lauerma K*, *Lundbom N*, *Nieminen MS*, *Taskinen MR*. Electrocardiographic changes associated with insulin resistance. Nutr Metab Cardiovasc Dis 2014; 24: 315–320
36 *Tiehuis AM*, *van der Graaf Y*, *Mali WP*, *Vincken K*, *Muller M*, *Geerlings MI*, *SMART Study Group*. Metabolic syndrome, prediabetes, and brain abnormalities on MRI in patients with manifest arterial disease: the SMART-MR study. Diabetes Care 2014; 37: 2515–2521
37 *Schilling S*, *Tzourio C*, *Dufouil C*, *Zhu Y*, *Berr C*, *Alperovitch A*, *Crivello F*, *Mazoyer B*, *Deberre S*. Plasma lipids and cerebral small vessel disease. Neurology 2014; 83: 1844–1852
38 *Lupi R*, *Dotta F*, *Marselli L*, *Del Guerra S*, *Masini M*, *Santangelo C*, *Patane G*, *Boggi U*, *Piro S*, *Anello M*, *Bergamini E*, *Mosca F*, *Di Mario U*, *Del Prato S*, *Marchetti P*. Prolonged exposure to free fatty acids has cytostatic and proapoptotic effect on human pancreatic islets. Diabetes 2002; 51: 1437–1442