

The DIAMOND system in the treatment of type 2 diabetes mellitus in an obese patient

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Abstract

Obesity and type 2 diabetes mellitus have reached epidemic proportions worldwide. As the majority of antidiabetic medications are of limited efficacy and patient adherence to long-term therapy is one of the main limiting factors of effective blood glucose and body weight control, new therapies are still looked for. The DIAMOND system seems to be one of the most promising among them. This system recognizes natural electrical activity of the stomach and automatically applies electrical stimulation treatment during/after eating with subsequent modulation of signals transmitted to the regulatory centers in the brain in order to provoke an early response of the gut typical of a full meal. We present the case of a 47-year-old obese woman with type 2 diabetes. During treatment with this system, serum glucose and hemoglobin A_{1c} levels significantly decreased. Body weight loss and waist circumference reduction were observed. Additionally, beneficial effect on lipid profile was found.

Key words: gastric electrical stimulation, obesity, diabetes mellitus.

Introduction

Obesity has reached epidemic proportions, with an estimated 1.7 billion people worldwide classified as either overweight or obese [1]. As obesity is clearly associated with an increased risk for diabetes, this disease affects nearly 346 million people worldwide [2]. Unfortunately, the majority of antidiabetic medications are of limited efficacy. Moreover, patient compliance is one of the main limiting factors of effective blood glucose control [3]. For these reasons new therapies are still looked for.

Control of food intake is a crucial component of energy balance [4, 5]. During eating some of the neurons in the stomach are activated by stretch receptors and generate electrical impulses with subse-

quent detectable changes in muscle function. These small electromechanical changes mainly during the initiation of food intake are responsible for gastric contractility. This increase in the force of gastric contractions relating to stomach distension increases vagal afferent activity. Impulses are sent to the nucleus tractus solitarius and area postrema, generating the sensation of satiety [6]. In the first studies in animals, implantation of gastric leads enabled detection of these signals generated at the beginning of food intake [7, 8]. The DIAMOND system (Metacure, Ltd, Orangeburg, USA) – a novel method of therapy of type 2 diabetes associated with obesity based on new technology, Gastric Contractility Modulation (GCM) – recognizes natural electrical activity

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of the stomach and automatically applies nonexcitatory electrical stimulation treatment during eating, with subsequent modulation of signals transmitted by the vagus nerve to the regulatory centers in the brain, in order to provoke an early response of the gut typical of a full meal. In recent clinical trials the system proved its efficacy and safety [9–14].

Case report

A 47-year-old obese women (LGG) with type 2 diabetes came to our outpatient clinic willing to be treated under the prospective, randomized “The DIAMOND™ for the Treatment of Type 2 Diabetes: A Single Blind Cross Over Study”. Her history was elicited. Obesity developed in childhood, from 1974. Type 2 diabetes was diagnosed in 2004. Additionally, she was hypertensive from 2007 and her history included varicose veins in the legs diagnosed in 2002, surgery of metrorrhagia also in 2002, and cholecystectomy via laparoscopy because of a biliary stone in 2004. The patient has attempted to achieve a diabetic diet and has taken medicines: glimepiride 4 mg q.d., metformin 850 mg t.i.d., ramipril 5 mg q.d. and betaxolol 10 mg q.d. Physical examination revealed both central and peripheral type of obesity. Body weight was 91.7 kg, waist circumference 112.6 cm, and body mass index (BMI) 32.0 kg/m². No significant abnormalities in the respiratory and cardiovascular system (except varicosed superficial leg veins) were found. Hemoglobin A_{1c} (HbA_{1c}) was

9.3% and fasting serum glucose level was 188 mg/dl. The patient was enrolled in the study. Three bipolar leads were laparoscopically implanted in the subserosa of the gastric wall (Figure 1). The leads were connected with the device located in the subcutaneous pocket in the left subcostal region of the abdomen (Photo 1).

According to the study protocol 15 control visits in the next 48-week follow-up (period 1 and period 2) were performed (Figure 2).

Each visit included eliciting of history since the former visit and physical examination with anthropometric measurements together with assessment of vital systems. Blood samples were taken for estimation of HbA_{1c} and glucose levels as well as for other enzymatic, biochemical and hormonal indices indicated in the protocol. At each visit parameters from the device – battery voltage, eat rate episode and impedance, eat detect, antrum anterior and posterior impedance, and fundus impedance – were read with a special computer program.

During the first 6 months of the treatment (first period) the device was switched on. In this period an impressive gradual decrease in fasting glucose and HbA_{1c} levels (of 3.3%) and in homeostatic model of assessment (HOMA) was observed accompanied by a reduction of body weight (–9.1 kg) and waist circumference (–16.0 cm). Additionally, decreases in leptin, high-sensitivity C-reactive protein (hsCRP) and triglyceride levels as well as an increase in

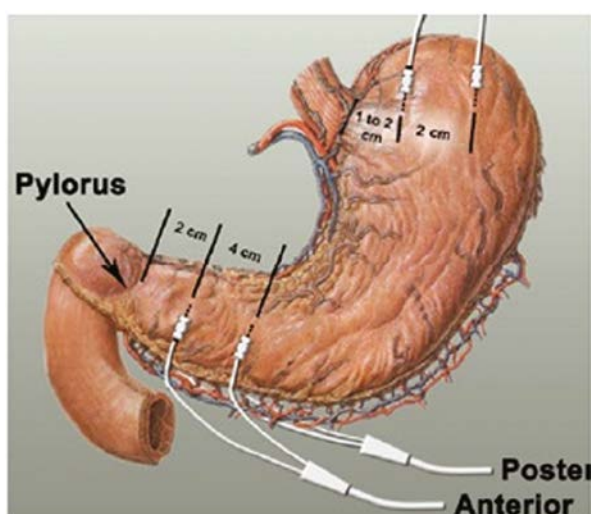


Figure 1. Placement of the leads implanted in the wall of the stomach (permission from MetaCure Ltd)



Photo 1. Rechargeable implantable pulse generator (IPG) (permission from MetaCure Ltd)

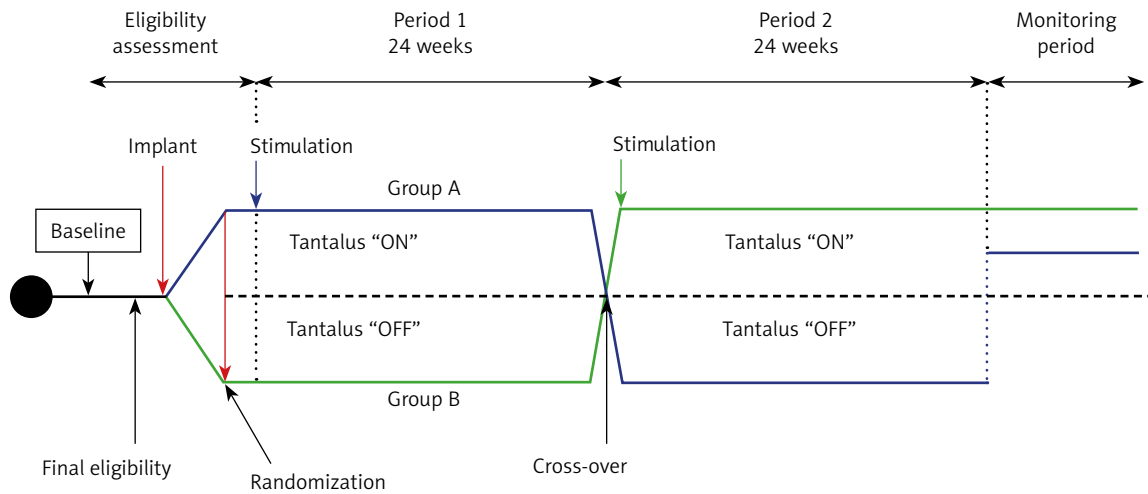


Figure 2. Scheme of the study protocol

HDL-cholesterol levels were found (Table I). After the first months of treatment the dose of glimepiride could be reduced from 4 mg to 3 mg, after 19 weeks to 2 mg, after 25 weeks to 1 mg, and after 24 weeks it could be completely discontinued. Regarding adverse events (AE), the patient experienced one epi-

sode of hypoglycemia with a drop of blood glucose to 58 mg/dl. No other serious AE occurred.

In the next 6 months (second period), the device was switched off, according to the study protocol. This time fasting glucose and HbA_{1c} levels, and in turn the HOMA index, rose gradually. Meanwhile,

Table I. Results of first 24 weeks of treatment (period 1) when the device was switched on

Parameter	Visit 1 week -3	Visit 2 week -2	Visit 6 week 2	Visit 7 week 5	Visit 8 week 13	Visit 9 week 19	Visit 10 week 25
HbA _{1c} (%)	9.3		7.6	5.7	5.8	6.3	6.0
Glucose [mg/dl]	188	206	155	143	165	171	141
Insulin [µIU/ml]	11.0	12.0				9.0	
HOMA	5.13	6.12				3.81	
TC [mg/dl]		171			184		189
TG [mg/dl]		140			129		91
HDL-C [mg/dl]		54.2			56.4		55.1
LDL-C [mg/dl]		89.0			102		116
Adiponectin [µg/ml]		7.5					6.7
Leptin [µg/ml]			24.7				17
hsCRP [mg/l]		1.83					0.81
Body weight [kg]	91.7		89.7	88.4	87.9	87.4	82.6
WC [cm]	112.6		108.1	105.2	110.1	106.6	99.6
SBP [mm Hg]	120		150	140	130	108	125
DBP [mm Hg]	80		95	90	90	73	73

HOMA – homeostatic model of assessment, TC – total cholesterol, TG – triglycerides, HDL-C – high-density cholesterol, LDL-C – low-density cholesterol, hsCRP – high-sensitivity C-reactive protein, WC – waist circumference, SBP – systolic blood pressure, DBP – diastolic blood pressure

Table II. Results of treatment in weeks 25–48 (period 2), when the device was switched off

Parameter	Visit 11 week 26	Visit 12 week 31	Visit 13 week 37	Visit 14 week 43	Visit 15 week 49
HbA _{1c} (%)	6.2	6.0	5.9	5.6	7.5
Glucose [mg/dl]	122	133	144	146	150
Insulin [μ IU/ml]		5.0			5.0
HOMA		1.65			1.91
TC [mg/dl]		166.0			213.5
TG [mg/dl]		83.0			102.1
HDL-C [mg/dl]		55.7			66.3
LDL-C [mg/dl]		94.0			126.7
Adiponectin [μ g/ml]					8.8
Leptin [μ g/ml]					17
hsCRP [mg/l]					1.29
Body weight [kg]	81.3	80.7	80.0	80.9	82.4
WC [cm]	99.3	99.3	98.5	99.4	95.0
SBP [mm Hg]	108	130	112	135	130
DBP [mm Hg]	73	80	85	83	75

HOMA – homeostatic model of assessment, TC – total cholesterol, TG – triglycerides, HDL-C – high-density cholesterol, LDL-C – low-density cholesterol, hsCRP – high-sensitivity C-reactive protein, WC – waist circumference, SBP – systolic blood pressure, DBP – diastolic blood pressure

body weight and waist circumference did not change significantly. The HsCRP, triglycerides, LDL cholesterol, but also HDL cholesterol increased (Table II). No significant AE, including hypoglycemic episodes, were seen.

After completing period 1 and 2 of the study, the subject decided to continue treatment for the next weeks, and the follow-up is ongoing.

Discussion

The improvement in glucose metabolism parameters observed in our patient during the study was rather gradual and not very rapid. It should be considered as beneficial, as in a randomized study of 10 251 patients (mean age: 62.2 years) intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events [15]. These findings identified a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes.

It is worth paying attention to normal patient baseline triglyceride levels. Analysis of 40 subjects

who had undergone detailed longitudinal studies for 12 months revealed that in patients with normal fasting plasma triglycerides the HbA_{1c} decrease was clearly more significant, and they lost more weight than did patients with hypertriglyceridemia. This may suggest the existence of a triglyceride lipotoxic mechanism that interferes with gastric/neural mediated pathways that can regulate glycemic control in patients with type 2 diabetes. It seems in preliminary observations of gastric electric stimulation that method efficacy is strongly dependent on this parameter, and in fact there is an inverse relationship between serum fasting triglyceride levels at baseline and decrease in HbA_{1c} during treatment [14]. In the discussion of this finding, a direct or indirect impact of elevated serum levels of triglycerides (i.e. above 150 ng/ml) to inhibit the glycemic effect of gastric stimulation is considered. In animal studies an intestine-brain-liver axis was found by which lipids in the upper intestine stimulate neural transmission to the hindbrain, and therefore, after transformation is conducted through vagus nerve branches, hepatic glucose production is suppressed [16]. Further pro-

spective studies should elucidate the mechanism of the relationship between initial triglyceride levels and hypoglycemic efficacy of gastric electrical stimulation.

Conclusions

This novel method of treatment intended for type 2 diabetes patients with overweight/obesity may become an important alternative to the use of incretins or insulin. It may also substitute for bariatric surgery in obese patients who are unwilling to undergo a vast and anatomically irreversible operation or do not meet all required criteria to justify these procedures.

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