



Gastric stimulation to treat the type 2 diabetes: results on week 16

Gastrična stimulacija u terapiji dijabetesa tip 2: rezultat posle 16. nedelje od implantacije pejsmejckera

Miloš Bjelović*[†], Tamara Babić[‡], Bratislav Špica[†], Dragan Gunjić[†],
Milan Veselinović[‡], Snežana Polovina*[‡]

University of Belgrade, *Faculty of Medicine, Belgrade, Serbia; Clinical Center of Serbia, First Surgical Clinic, Clinic for Digestive Surgery, [†]Department for Minimally Invasive Upper Digestive Surgery, [‡]Clinic for Endocrinology, Diabetes and Diseases of Metabolism, Belgrade, Serbia

Abstract

Background/Aim. Gastric contraction modulation (GCM) with the implanted DIAMOND device improves glycemic control and decreases weight. The main aim of this study was to evaluate the early efficacy of GCM using the DIAMOND (previously named TANTALUS) System in the improvement of glycemic control measured by changes in glycosylated hemoglobin (HbA1c). The effects of GCM on weight loss, body mass index (BMI), reduction of the waist circumference and metabolic parameters other than HbA1c were also evaluated. **Methods.** A total of 18 adult patients with type 2 diabetes were surgically treated at the Department for Minimally Invasive Upper Digestive Surgery, Clinic for Digestive Surgery in Belgrade, Serbia, using gastric pacemaker (DIAMOND System) from November 2014 to March 2016. Out of the total number of patients, 11 finished week 16 visit and were enrolled in this prospective cohort study. **Results.** During the observed period, the average weight loss amounted to 8.05 kg ($p < 0.05$). The average difference between the baseline fasting glucose level and the level after 16 weeks period is 2.56 mmol/L. Similar findings were noted in fasting insulin levels, with an average decrease of 6.44 mU/L after 16 weeks. The majority of patients experienced a decrease in HbA1c value: in 4 patients higher than 2%, and in 4 patients up to 2% ($p < 0.05$). Lower level of fasting insulin with simultaneous decrease in fasting glucose indicates improvement in insulin sensitivity on week 16 [homeostatic model assessment of insulin resistance (HOMA IR) average 5.25]. **Conclusion.** Gastric stimulation using the DIAMOND System for 16 weeks causes significant early improvement in glycemic control and insulin resistance. There is an additional positive effect on weight loss, body mass index (BMI) and reduction of the waist circumference as a main parameter of the metabolic syndrome.

Key words:

diabetes mellitus, type 2; obesity; stomach; electric stimulation therapy; treatment outcome; hemoglobin A, glycosylated; blood glucose.

Apstrakt

Uvod/Cilj. Stimulacija želuca [*gastric contraction modulation* (GCM)] implantiranim sistemom DIAMOND poboljšava glikemijsku kontrolu i smanjenje telesne mase. Primarni cilj studije bio je da se proceni inicijalna efikasnost stimulacije želuca upotrebom DIAMOND sistema (ranije poznatog kao TANTALUS) u cilju poboljšanja glikoregulacije merene promenom nivoa glikoziliranih hemoglobina (HbA1c). Sekundarni ciljevi bili su analiza sniženja telesne mase, indeksa telesne mase (BMI), obima struka i drugih metaboličkih parametara. **Metode.** U Odeljenju za minimalno invazivnu hirurgiju gornjeg digestivnog trakta Klinike za digestivnu hirurgiju u Beogradu, u periodu između novembra 2014. godine i marta 2016. godine, kod 18 bolesnika sa dijabetesom tipa 2, laparoskopski je postavljen gastrični pejsmejker (DIAMOND sistem). Od ukupnog broja bolesnika, 11 bolesnika je bilo praćeno najmanje 16 nedelja posle operacije i uključeno u prospektivnu kohortnu studiju. **Rezultati.** U toku perioda praćenja, prosečan gubitak telesne mase iznosio je 8.05 kg ($p < 0.05$). Prosečna razlika između inicijalne vrednosti glikemije i glikemije posle 16 nedelja od implantacije pejsmejckera iznosila je 2.56 mmol/L. Sličan rezultat dobijen je prilikom procene vrednosti insulina natašte; prosečno smanjenje vrednosti posle 16 nedelja iznosilo je 6.44 mU/L. Kod većine bolesnika konstatovano je i smanjenje vrednosti HbA1c: kod 4 bolesnika veće od 2% i kod 4 osobe do 2% (prosečno 1.19%, $p < 0.05$). Niži nivo insulina natašte i istovremeno smanjenje visine glikemije natašte ukazalo je na poboljšanje insulinske senzitivnosti posle 16 nedelja od implantacije pejsmejckera [*homeostatic model assessment of insulin resistance* (HOMA IR) prosek 5.25]. **Zaključak.** Stimulacija želuca DIAMOND sistemom tokom 16 nedelja od implantacije, prouzrokuje statistički značajno poboljšanje glikoregulacije i insulinske rezistencije. Dodatan pozitivan terapijski efekat odnosi se na smanjenje telesne mase, BMI i smanjenje obima struka kao glavnog parametra metaboličkog sindroma.

Ključne reči:

dijabetes melitus, insulin-nezavisan; gojaznost; želudac; elektroterapija; lečenje, ishod; hemoglobin, glukozilovan; glikemija.

Introduction

Type 2 diabetes mellitus already affects over 500 million people, out of which 60% are obese¹. The upsurge in obesity and the concomitant rise in diabetes have imposed a substantial burden on public health. Total costs for diabetes treatment are expected to reach \$192 billion by the year 2020².

Significant and durable weight loss associated with a clinically beneficial improvement of metabolic control in patients with type 2 diabetes mellitus was reported after bariatric surgical procedures in recent publications^{3,4}. However, the surgical risk and significant physiological and anatomical changes associated with bariatric procedures as well as the number of bariatric surgeons are currently the main obstacles for wider use of this technique. It was found that overweight type 2 diabetics can benefit from a fully reversible minimally invasive surgical procedure which could improve their metabolic control and help them to lose weight.

Multiple clinical studies designed to evaluate the TANTALUS System for the treatment of obesity, type 2 diabetes and comorbid conditions, have been and are currently being conducted worldwide. As with most organs, electrical stimulation used in TANTALUS System serves to regulate many aspects of gastric function⁵⁻⁷.

Gastric stimulation [gastric contraction modulation (GCM)] to treat the type 2 diabetes mellitus was, for the first time, performed at the Department for Minimally Invasive Upper Digestive Surgery, Clinic for Digestive Surgery in Belgrade, Serbia, in November 2014.

The main objectives of this study was to evaluate the early efficacy of GCM using the DIAMOND (previously named TANTALUS) System in the improvement of glycemic control measured by changes in glycosylated hemoglobin (HbA1c). The effects of GCM on weight loss, body mass index (BMI), reduction of the weight circumference and metabolic parameters other than HbA1c were also evaluated.

Methods

Study design

A total of 18 adult patients with type 2 diabetes were surgically treated at the Department for Minimally Invasive Upper Digestive Surgery, Clinic for Digestive Surgery in Belgrade, Serbia, using gastric pacemaker (DIAMOND System) from November 2014 to March 2016. Out of the total number of patients, 11 finished week 16 visit and were enrolled in this prospective cohort study.

Patients underwent baseline evaluation during which the stability of their glycemic parameters, medical treatment and medical condition were assessed. All patients gave informed consent prior to study enrolment. The study was reviewed and approved by the Clinical Center of Serbia Institutional Review Board. Patients fulfilling all inclusion/exclusion criteria were implanted. Inclusion criteria were as follows: male and female subjects aged between 18 and 70 years of age; body mass index (BMI) > 30 and < 45 kg/m²; type 2 diabetes duration of at least 6 months; type 2 diabetic

subjects treated with oral antidiabetic agents [sulfonylurea, metformin, thiazolidinedione (TZD) or dipeptidyl peptidase 4 (DPP-4) inhibitors]; stable antidiabetic medications for at least 3 months prior to enrolment, 6 months for TZD; the subject was under routine diabetes care of the investigator or another single physician that can supply a medical record for at least 6 months prior to enrolment; HbA1c $\geq 7.3\%$ and $\leq 9.5\%$ on the first visit; stable HbA1c, defined as no significant change (variation $\leq 0.5\%$) between a historical value recorded in the subject's medical record within 3 months prior to enrolment and the HbA1c gathered on the first visit; fasting blood glucose >120 and < 350 mg/dL on the first visit; stable weight, defined as no significant weight change (variation less than 3%) within 3 months prior to enrolment as documented in the subject's medical record. For the subject treated with TZD, the criteria also included: stable weight within 6 months; if taking these medication, stable antihypertensive and lipid-lowering medication for at least 1 month prior to enrolment; able to provide voluntary informed consent.

Exclusion criteria were: insulin therapy in last 3 months; taking glucagon-like peptide-1 (GLP-1) agonists or taking them over the last 3 months before the enrolment; currently taking fibrates, nicotinamide and omega-3 fatty acids as antilipidemic treatment; subjects with an ejection fraction (EF) less than 35%, or otherwise, indicated for an implantable cardiac defibrillator (ICD); taking medications known to affect gastric motility such as narcotics (chronic use) and anticholinergics/antispasmodics; experiencing severe and progressing diabetic complications (i.e. retinopathy not stabilized, nephropathy with macroalbuminuria); prior wound healing problems due to *staphylococcus* or *candida*; diagnosed with an eating disorder such as bulimia or binge eating; obesity due to an endocrine disorder (e.g. Cushing disease); pregnant or lactating; diagnosed with impaired liver function (liver enzymes 3 times greater than normal); any prior bariatric surgery.

Surgical procedure

Implantation was typically performed under general anesthesia using a laparoscopic procedure. Two sets of bipolar stitch leads were placed in the antrum, one set in the anterior wall and the other set in the posterior wall. A third set was placed in the fundus (Figures 1 a and b). Endoscopy was performed during the implantation to ensure that the stitch electrodes are placed entirely within the muscle of the gastric wall without perforation of the gastric mucosa. The leads were tunneled and connected to the implantable pulse generator (IPG) (Figure 2). An abdominal subcutaneous pocket was created for the IPG and charge coil. The pocket should only be large enough to accommodate the IPG and charge coil before closing, proper electrode contact with the tissue was verified by measuring leads impedances using the programmer (placed in a sterile nylon sleeve) over the IPG. In the perioperative period the patient's blood glucose was monitored using a calibrated glucose meter to avoid any hypo or hyperglycemic events.

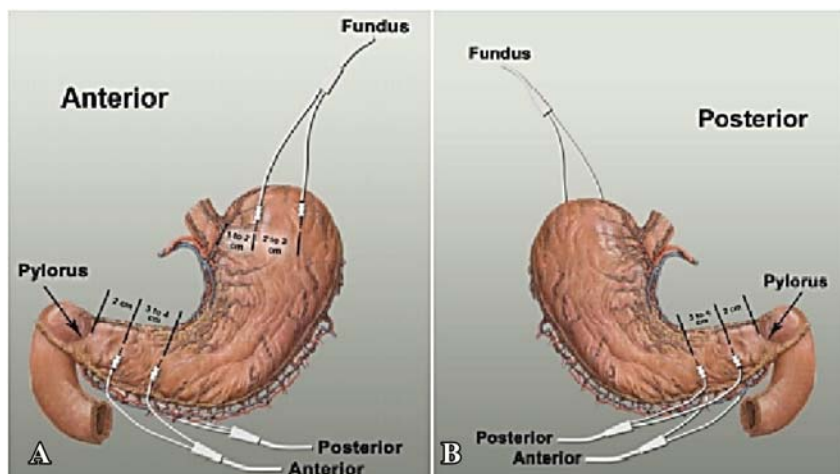


Fig. 1 – Lead placement: a) anterior and b) posterior view.



Fig. 2 – Implantable pulse generator (IPG).

The patients were released from the hospital with their diabetes treatment reinitiated and the device set so that no GCM signals are applied. It was stressed out that compliance (acceptance of the lifestyle advices and dietary regimen) is necessary to achieve therapeutic goals. Two weeks after the surgery, the IPG was turned on to continuously delivered signal.

Anthropometric (body mass, BMI, waist circumference) and laboratory data (fasting insulin, fasting blood glucose, HbA1c) were collected before the surgery, on week 2, week 8 and week 16 after the surgery.

Statistical analysis

Descriptive statistics for all efficacy and safety endpoints will include a number of subjects, mean, standard deviation, minimum and maximum for continuous variables.

Results

The study population included 11 patients who underwent DIAMOND System implantation and finished week 16 visit between November 2014 and March 2016. The study group consisted of 6 male and 5 female patients, with

an average age of 52 years (range from 43 to 68 years). There were 2 males and 2 females in the group of 40–49 years, 1 male and 3 females in the group of 50–59 years and 3 males and no female in the group of 60–69 years.

During the observed period, the average weight loss amounted to 8.05 ± 5.09 kg (range 2 to 18 kg). Four patients lost more than 10 kg, 3 patients lost between 5–10 kg, 4 of them lost up to 5 kg. BMI correlated with the weight loss, and the difference between the baseline value and the value at the end of week 16 ranged from 1.1 to 4.5 kg/m², with an average reduction of 2.42 kg/m² (Table 1).

We also noted a waist circumference reduction in the majority of the patients. Reduction of more than 5 cm waist circumference was noted in 4 patients and up to 5 cm in 6 patients. One patient gained 3 cm in waist, without a change in weight.

Even though the 16 weeks period is considered to be relatively short, substantial metabolic effects could be detected. The average difference between the baseline fasting glucose level and the level after 16 weeks period is 2.56 ± 2.96 mmol/L (range 0.9 to 8.6 mmol/L). The decrease in fasting glucose level higher than 6 mmol/L was observed in 2 patients, between 3–6 mmol/L in other 2 and up to 3 mmol/L in 5 patients. We detected higher levels of fasting

Table 1

Change in anthropometric and laboratory data from the baseline until the end of week 16 visit

Parameters	Baseline ($\bar{x} \pm SD$)	Week 2 ($\bar{x} \pm SD$)	Week 8 ($\bar{x} \pm SD$)	Week 16 ($\bar{x} \pm SD$)	Difference Base- line-Week 16 ($\bar{x} \pm SD$)	Difference range (min/max)
Anthropometric						
weight (kg)	119.17 \pm 21.93	113.78 \pm 20.17	111.34 \pm 18.38	111.13 \pm 18.34	8.05 \pm 5.09	(2/18)
BMI (kg/m ²)	39.35 \pm 4.14	37.57 \pm 4.57	36.95 \pm 4.18	36.93 \pm 3.94	2.42 \pm 1.00	(1.1/4.5)
Waist circumference (cm)	126.27 \pm 10.61	123.86 \pm 11.77	122.36 \pm 11.43	119.91 \pm 9.76	6.36 \pm 6.74	(-3/20)
Laboratory						
fasting glucose (mmol/L)	11.15 \pm 2.74	9.22 \pm 3.57	8.49 \pm 3.41	8.59 \pm 2.83	2.56 \pm 2.96	(-0.90/8.6)
fasting insulin (mIU/L)	23.81 \pm 11.76	19.95 \pm 6.52	18.72 \pm 9.50	17.37 \pm 6.33	6.44 \pm 11.06	(-5.06/35.49)
HbA1C (%)	8.74 \pm 0.54	8.19 \pm 1.13	7.35 \pm 1.04	7.55 \pm 1.22	1.19 \pm 1.16	(-0.7/2.6)
HOMA IR	11.58 \pm 5.76	7.86 \pm 3.03	7.02 \pm 4.08	6.33 \pm 2.15	5.25 \pm 5.94	(-1.11/20.47)

BMI – body mass index; HbA1C – glycosylated hemoglobin; HOMA-IR – insulin resistance index; \bar{x} – mean; SD – standard deviation.

glucose in 2 patients. One of them experienced worse glycoregulation due to inability to conduct a dietary regimen between week 12 and 16. The other had an increase just in fasting glucose in week 16, without change in HbA1c value (Table 1).

Similar findings were noted in fasting insulin levels, with an average decrease of 6.44 ± 11.06 mU/L after 16 weeks (range 5.06/35.49). Most of the patients had more or less pronounced reduction in fasting insulin level. One patient had an increase in fasting insulin level up to 0.2 mU/L compared to the baseline value (Table 1).

The majority of patients experienced a decrease in HbA1c value: in 4 patients higher than 2%, and in 4 patients up to 2% (average $1.19 \pm 1.16\%$, range -0.7% to 2.6%. In one patient HbA1c level raised by 0.7% (Table 1).

Lower level of fasting insulin with simultaneous decrease in fasting glucose indicates improvement in insulin sensitivity in week 16 (HOMA IR 5.25 ± 5.94 , range -1.11/20.47 (Table 1).

Discussion

Obesity and type 2 diabetes (diabesity) are global epidemic problem. Less than 50% patients accept lifestyle advice and achieve therapeutic goals⁸. In order to improve glucose control, patients committed to insulin treatment frequently experienced weight gain and hypoglycemia. Meal-mediated electrical GCM could be an alternative treatment for the patients with type 2 diabetes with poor glucose control on oral anti-diabetic drugs⁷. This therapy can be applied to patients with sufficient amount of endogenous insulin. Some researchers promote gastric pacing in patients with poor dietary compliance due to the fact that this system automatically delivers electrical impulses, when programmed to. This device can be implanted via laparoscopy, with very low perioperative risk. Gastric pacemaker stimulates afferent fibers of the vagal nerve which interacts with hypothalamic satiation centre. This pathway is responsible for insulin secretion and insulin sensitivity. The patients with electric GCM demonstrate an improvement in glucose and weight control⁹. Previous studies in obese patients suggested that blocking vagal efferent impulses with high-frequency and short pulse width, resulted in weight loss. It was suggested that such weight reduction is a consequence of delayed gastric emptying and inhibition of postprandial gastric contractions¹⁰.

In our study, there was significant decrease in body weight (119.17 ± 21.93 kg vs 111.13 ± 18.34 kg; $p < 0.05$) and BMI (39.35 ± 4.14 kg/m² vs 36.93 ± 3.94 kg/m², $p < 0.05$), 16 weeks after DIAMOND System implantation. The average body weight reduction was 8.05 ± 5.09 kg and BMI reduction was 2.42 ± 1.00 kg/m². Satiety center in ventromedial nuclei and hunger center in ventrolateral nuclei in hypothalamus regulate food intake regarding an energy content, volume and duration of a single meal. Energy homeostasis is achieved via afferent nerve signals from oral and gastric mucosa with support of enteropeptides from gut mucosa. Thus, gut-brain axis plays a role in exchange of information between gut mucosa and food intake centers in the brain,

through vagal nerve^{11, 12}. Vagotomy reverses the obesity in animals with hypothalamic damage induced obesity. The same effect could be achieved with selective efferent vagal stimulation with gastric pacemaker without side effects on cardiovascular system. Long-term effects on weight loss are different in various studies, from 1.3% up to 40% of excessive weight loss (EWL) during two years of treatment. Ghrelin is very potent orexigenic hormone which stimulates gastrin release. Ghrelin also stimulates gastric acid secretion and has prokinetic effect on the small bowel. Gastric bypass decreases ghrelin secretion. Similar effect on ghrelin secretion has vagal nerve dissection as well as gastric pacemaker with electrodes positioned in the fundus of the stomach^{13, 14}.

Many studies demonstrated undesirable effect of antidiabetic drugs on body weight. Weight gain varied from 1.5 kg on oral antidiabetic drugs, up to 10 kg on insulin therapy. Weight reduction with DIAMOND System in obese type 2 diabetes mellitus patients is an added benefit to glucose control¹⁰. In our study, waist circumference decreased 6.36 ± 6.74 cm, from initially 126.27 ± 10.61 cm to 119.91 ± 9.76 cm at week 16 which indirectly indicates reduction of visceral fat. It was reported previously that the reduction in the amount of intraabdominal fat is associated with positive effect on metabolic parameters¹⁵.

Fasting glucose decreased in average 2.56 ± 2.96 mmol/L (11.15 ± 2.74 mmol/L vs 8.59 ± 2.83 mmol/L; $p = 0.05$) and positive therapeutic effect regarding fasting glucose level was observed in 80% of patients. The other 20% had higher levels of fasting glucose. The one of them had deterioration of glycoregulation (the both, fasting glucose and HbA1c) due to uncompliance with dietary regimen during the last four weeks. The other had an increase in fasting glucose in week 16, but with change in HbA1c value, which could not be defined as a deterioration in glycoregulation. The exact mechanism of glucose control with this device is not known but it was assumed that the regulation of blood glucose is partially weight loss independent. Gastric contractility reduces fasting and postprandial blood glucose, suppresses glucagon and increases GLP-1 release¹⁶. GLP-1 is an incretine, secreted by L-cells in the ileum and colon in response to food intake. GLP-1, as an anorexigenic peptide, delayed gastric emptying and reduces the postprandial demand of insulin. These effects of GLP-1 are mediated via receptors on vagal nerves^{17, 18}. GLP-1 could be classified as neurohumoral agents with central action as neurotransmitter and with peripheral action as hormone. With this activity, GLP-1 increase satiety in normal-weight subjects as well as in obese subjects, including patients with diabetes^{19, 20}. Therapy with GLP-1 agonist, during 30 weeks decreases HbA1c by 0.8%, but 12 weeks after implantation of gastric pacemaker, HbA1c decreases 1% and remained at lower level for further 6 months⁶. Our results demonstrated that HbA1c decreases $1.19 \pm 1.16\%$ after 16 weeks (8.74 ± 0.54 vs 7.55 ± 1.22 ; $p < 0.05$). In about 40% of patients HbA1c decreases more than 2% and in further 40% patients decreases between 1 and 2%. In 1 patient there was no change in HbA1c level, and in 1 patient, HbA1c increases 0.7% and that was the patient uncompliant with dietary regimen between week 12 and 16.

A greater risk for serious hypoglycemia was found in therapeutical procedures using a combination of two or more oral antidiabetic drugs or treatment by insulin. Very low incidence of hypoglycemia was found in studies with DIAMOND System where strictly blood glucose control was achieved. Lowest level of hypoglycemia registered in patients with this device was 3.8 mmol/L and they had very mild symptoms of hypoglycemia^{6, 7}. In our investigation, 3 out of 10 patients (30%), on gliclazide and metformin experienced hypoglycemia after 8 weeks of enrolment. Blood glucose during the day decreased to 4.1 mmol/L. Those patients had mild symptoms of hypoglycemia and according to the study protocol recommendation, dose of gliclazide was reduced or the drug was completely withdrawn.

All of our patients have hyperinsulinism with insulin resistance at enrolment time (HOMA IR 11.81 ± 5.84). After 16 weeks, fasting insulin decreased to 6.44 ± 11.06 mIU/L (23.81 ± 11.76 vs 17.37 ± 6.33). Lower level of fasting insulin with simultaneous decrease in fasting glucose indicates improvement in insulin sensitivity on week 16 (HOMA IR 5.25 ± 5.94 ; 11.58 ± 5.76 vs 6.33 ± 2.15).

Due to a small sample size and short follow-up period we express the need for further evidence regarding this relatively new treatment option.

Conclusion

The overall conclusion was that in most of 11 patients the metabolic benefits followed the bariatric effect. On the other hand, a lack of compliance predicted poor metabolic bariatric outcome.

Gastric stimulation using the DIAMOND System for 16 weeks causes significant early improvement in glycemic control and insuline resistance. There is an additional positive effect on weight loss, body mass index and reduction of the waist circumference as a main parameter of the metabolic syndrome. In order to achieve therapeutic goals (positive metabolic, as well as bariatric effects) it is crucial to have good adherence and persistence to the lifestyle advice and dietary regimen. However, due to a relatively small number of patients and short follow-up period we express the need for further evidence regarding this treatment option.

R E F E R E N C E S

1. *World Health Organization*. Global status report on noncommunicable diseases. Geneva: World Health Organization; 2014.
2. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics. Atlanta, Health United States, with chartbook on trends of in the health of Americans; 2003.
3. *Sugerman HJ, Wolfe LG, Sica DA, Clore JN*. Diabetes and hypertension in severe obesity and effects of gastric bypass-induced weight loss. *Ann Surg* 2003; 237(6): 751–6; discussion 757–8.
4. *Dixon JB, O'Brien PE*. Health outcomes of severely obese type 2 diabetic subjects 1 year after laparoscopic adjustable gastric banding. *Diabetes Care* 2002; 25(2): 358–63.
5. *Bobdjalian A, Prager G, Rosak C, Weiner R, Jung R, Schramm M, et al*. Improvement in glycemic control in morbidly obese type 2 diabetic subjects by gastric stimulation. *Obes Surg* 2009; 19(9): 1221–7.
6. *Sanmiguel CP, Conklin JL, Cunneen SA, Barnett P, Phillips EH, Kipnes M, et al*. Gastric electrical stimulation with the TANTALUS System in obese type 2 diabetes patients: Effect on weight and glycemic control. *J Diabetes Sci Technol* 2009; 3(4): 964–70.
7. *Lebovitz HE, Ludvik B, Yaniv I, Haddad W, Schwartz T, Avin 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(6): 687–93.
8. *American Diabetes Association*. (6) Glycemic targets. *Diabetes Care* 2015; 38 Suppl: S33–40.
9. *Handgraaf HJ, Nelissen RM, Bianchi R, Meesters B, Greve JW*. A gastric pacemaker in obese type 2 diabetic patients. *Ned Tijdschr Geneesk* 2013; 157(0): A5929. (Dutch)
10. *Bugajski AJ, Gil K, Ziomber A, Zurowski D, Zaraska W, Thor PJ*. Effect of long-term vagal stimulation on food intake and body weight during diet induced obesity in rats. *J Physiol Pharmacol* 2007; 58 Suppl 1: 5–12.
11. *Konturek PC, Konturek JW, Cześnikiewicz-Guzik M, Brzozowski T, Sito E, Konturek SJ*. Neuro-hormonal control of food intake: basic mechanisms and clinical implications. *J Physiol Pharmacol*. 2005; 56 Suppl 6: 5–25.
12. *Konturek SJ, Konturek JW, Pawlik T, Brzozowski T*. Brain-gut axis and its role in the control of food intake. *J Physiol Pharmacol* 2004; 55(1 Pt 2): 137–54.
13. *Faraj M, Havel PJ, Phelis S, Blank D, Sniderman AD, Cianflone K*. Plasma acylation-stimulating protein, adiponectin, leptin and ghrelin before and after weight loss induced by gastric bypass surgery in morbidity obese subjects. *J Clin Endocrinol Metab* 2003; 88(4): 1594–602.
14. *Dobak JD*. Dynamic nerve stimulation for treatment of disorders. United States Patent and Trademark Office 2005. p. 37.
15. *Gil K, Bugajski A, Thor P*. Electrical vagus nerve stimulation decreases food consumption and weight gain in rats fed a high-fat diet. *J Physiol Pharmacol* 2011; 62(6): 637–46.
16. *Bobdjalian A, Prager G, Avin R, Policker S, Schindler K, Kretschmer S, et al*. One-year experience with Tantalus: A new surgical approach to treat morbid obesity. *Obes Surg* 2006; 16(5): 627–34.
17. *Bertoli S, Leone A, Vignati L, Spadafranca A, Bedogni G, Vanzulli A, et al*. Metabolic correlates of subcutaneous and visceral abdominal fat measured by ultrasonography: a comparison with waist circumference. *Nutr J* 2016; 15: 2.
18. *Bobdjalian A, Ludvik B, Guerci B, Bresler L, Renard E, Nocca D, et al*. Improvement in glycemic control by gastric electrical stimulation (TANTALUS) in overweight subjects with type 2 diabetes. *Surg Endosc* 2009; 23(9): 1955–60.
19. *Nauck MA, Niedereichholz U, Ettler R, Holst JJ, Orskov C, Ritzel R, et al*. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. *Am J Physiol* 1997; 273(5 Pt 1): E981–8.
20. *Drucker DJ, Nauck MA*. The incretin system: Glucagon-like-peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006; 368(9548): 1696–705.

Received on March 14, 2016.

Accepted on May 27, 2016.

Online First November, 2016.