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ORIGINAL CONTRIBUTIONS

A New Endoscopically Implantable Device (SatiSphere) for Treatment of Obesity—Efficacy, Safety, and Metabolic Effects on Glucose, Insulin, and GLP-1 Levels

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Abstract
Background The endoluminal mechanical device SatiSphere is a new endoscopically implantable device designed to delay transit time of nutrients through the duodenum. It consists of a 1-mm nitinol wire with pigtail ends and several mesh spheres mounted along its course, released in the duodenum and gastric antrum to conform to the duodenal C loop configuration and thereby self-anchor.
Methods The objective is to test the safety, efficacy, and effect on body weight in a 2:1 randomized study, as well as incretin secretion in a subgroup.
Results Of 31 included cases (11 men, mean age 42.9 years, mean BMI 41.3 kg/m^2), 21 patients treated with endoscopic device insertion with scheduled device removal after 3 months were compared with 10 controls. In 10 of 21 patients, device migration occurred, in two cases necessitating emergency surgery, which led to termination of the trial. Weight loss after 3 months was 6.7, 4.6, and 2.2 kg in the groups completing therapy, all treatment cases using intention to treat (ITT) analysis and controls. Excess weight loss was significantly increased by endoluminal mechanical device insertion (18.4, 12.2, and 4.4 % in completers, ITT analysis group and controls; p=0.02 for completers vs. controls). Measuring glucose, insulin, and glucagon-like peptide 1 (GLP-1) following a mixed-meal test with the device in place and after removal (n=7), the device delayed glucose absorption and insulin secretion and altered kinetics in GLP-1 levels.
Conclusions The device might be short-term effective in reducing body weight, which might be mediated through alterations in incretin metabolism. However, frequent device migration necessitates device modifications.

Keywords Obesity · GLP-1 · EndoSphere · Weight Loss

Abbreviations

BMI	Body Mass index
CIOMS	Council for International Organizations of Medical Sciences
DPP-4	Dipeptidyl-Peptidase-4
EDTA	Ethylendiamintetraacetat
EWL	Excess Weight Loss
GI	Gastrointestinal
GLP-1	Glucagon-Like Peptide-1
ITT	Intention to Treat
MTT	Meal Tolerance Test
TERIS	Trans-Oral Endoscopic Restrictive Implant System

Introduction

Obesity is a widespread and cost-intensive disease in Western civilizations and therapeutic approaches are challenging [1, 2]. Bariatric surgery has proven to be effective in the treatment of

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morbid obesity as well as associated type 2 diabetes [3–6]. However, operative therapies are not suitable for all obese patients or are not well accepted by all operative candidates. Therefore, several attempts have been made to develop less invasive endoscopic procedures for the treatment of obesity [7, 8]. Of these, the gastric balloon and more recently, the malabsorptive EndoBarrier duodenal sleeve have demonstrated promising results with acceptable safety profiles. Randomized trials could, however, not confirm the general usefulness of balloons vs. controls [9]. In contrast, smaller randomized trials have demonstrated a short-term superiority of duodenal sleeve therapy over sham treatment or open-label conventional low-calorie diets [10, 11], also, with positive effects on diabetes [12] and/or as a bridge to surgery [13]. However, complication rates were variable and long-term results are not known.

The principle of duodenal exclusion may not be the only one effective for weight reduction. A new endoscopic method, the endoluminal mechanical device, aims at increasing satiety by delaying transit time of food through the duodenum. Transit time from the pylorus to the ligament of Treitz of numerous aliquots of ingesta had been measured and recoded in two patients eating a sandwich while drinking barium sulfate with and without the device in place prior to our trial. This unpublished data had shown an increase of transit time from 10 to 40 % with the device in situ.

This may also alter secretion of incretin hormones as glucagon-like peptide 1 (GLP-1). GLP-1 is secreted under the influence of glucose by neuroendocrine L-cells of the intestines and contributes to glucose homeostasis and promotes satiety [14–17]. Recent data have demonstrated the effect of GLP-1-analogs on weight loss in patients with and without type 2 diabetes mellitus [18].

The main aim of the present randomized study was to provide information about feasibility, short-term efficacy, and safety to the new endoluminal mechanical device. Secondly, we wanted to clarify whether a possible weight loss effect of the endoluminal mechanical device might be due to alterations in GLP-1 secretion.

Patients and Methods

Patient Inclusion The clinical trial was approved by the Freiburg Ethics Commission International; the study followed the International Conference on Harmonization: Guideline for Good Clinical Practice and the "International ethical guidelines for biomedical research involving human subjects" as laid down by the CIOMS, in compliance with standards EN ISO 14155-1 and -2 for medical devices. Patients were recruited from the interdisciplinary obesity center of the university hospital in Hamburg-Eppendorf. Inclusion criteria were good general health status, age between 18 and 60 years, and a BMI between 30 and 50 kg/m^2. Patients with a history of Crohn's disease, bowel surgery, severe diseases, or current drug/alcohol addictions were excluded from the study. Patients were then randomized 2:1 to device insertion or controls.

Treatment Group The endoluminal mechanical device is implanted endoscopically and is composed of a nitinol backbone and spheres made of polyethylenterephtalat with two pigtails at each end (Fig. 1a and b). The endoluminal mechanical device (SatiSphere) is a patent of Endosphere Inc. Columbus, OH, USA. The device is implanted into the stomach and duodenum through an endoscope under general anesthesia. The stent form was made to stay in place by mimicking the anatomy of corresponding parts of the human intestine especially the duodenal C-shape down to the ligament of Treitz. It can easily be detected on fluoroscopy/x-ray if necessary; fluoroscopy, however, was not part of the implantation process which was monitored endoscopically. Following implantation, the device was to be routinely removed after 3 months by means of endoscopy. A further follow-up was scheduled 3 months after extraction of the device without further therapeutic intervention. Generally, patients received an additionally personalized nutritional counseling with a calculated diet of 500- kcal/day below daily requirements. Patients' concomitant medications for other pathologies were continued.

Control Group All control patients received a personalized nutritional counseling only with a calculated diet of 500- kcal/day below daily requirements. Patients' concomitant medications for other pathologies were also continued.

Outcome Parameters The *main outcome parameter* of the randomized study was to demonstrate the *efficacy* of the insert with regards to excess weight loss compared to a diet control group after 3 months. Efficacy was defined as average excess weight loss (EWL) more than 10 % greater as compared to the control group. *Primary safety objective* was to analyze the frequency of serious device or procedure-related adverse events over the study period of 3 months. Furthermore, patients were asked for any positive or negative symptoms possibly related to the device at monthly intervals (*secondary outcome*).

Hormone Analyses In a subgroup of seven patients receiving the device, further analysis with meal tolerance tests was conducted in order to clarify the role of GLP-1 in pathophysiologic mechanism of the endoluminal mechanical device. Two mixed-meal tests were performed in these patients: one while the device was placed within the intestines and the second one after retraction of the device. Standard meal tolerance test (MTT) consisted of a total calorie amount of

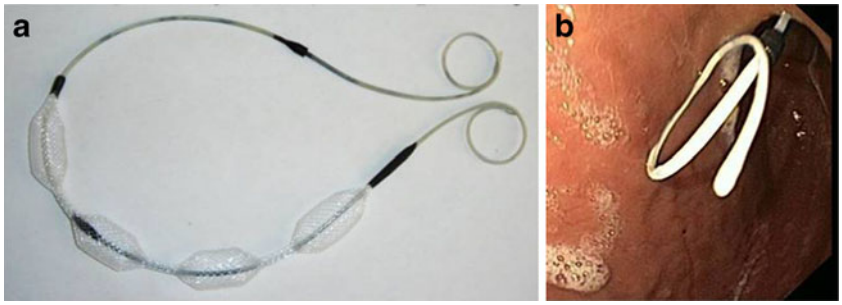

Fig. 1 **a** SatiSphere device (description see text). **b** Proximal pigtail of the device in the stomach.

534 Kcal (2,229.8 kJ), a protein content of 33 g, carbohydrate content of 57.3 g, and a fat content of 18.2 g. Patients were fasting for at least 8 h before starting the MTT. Food had to be consumed within 10 min. GLP-1, glucose, and insulin was measured before food intake and 20, 60, and 120 min after meal completion. In addition, glucose and insulin were measured 90 min after meal completion. Blood samples for GLP-1 measurement were processed as follows: a centrifuge was precooled to 4 °C. Test ethylendiamintetraacetat (=EDTA) tubes contained a dipeptidyl-peptidase(=DPP)-4-inhibitor and were incubated in an ice bath for 30 min before blood withdrawal. After blood withdrawal, EDTA-tubes were replaced directly into the ice bath and cooled for another 15 min. Samples were then ultracentrifuged for 15 min at 4° C at 3,000 revolutions min^{-1}. Plasma was withdrawn directly after centrifugation, aliquoted into two samples of 500 μl, and returned to the ice bath immediately. Samples were frozen at less than −70° C until time of analysis. GLP-1 analysis was conducted using a Radioimmunoassay (GLP1T-36HK, Millipore, Billerica, MA, USA) on a Beta-Counter (Berthold).

Statistics Randomization was 2:1 for device vs. controls. Case number calculation was initially based on an expected 15 vs. 5 % EWL after 3 months for endoluminal mechanical device controls. Sixty patients were considered sufficient to reach statistical significance in a two-sided analysis at the 5 % significance level. Ninety-five percent confidence intervals of the treatment difference will be presented to illustrate the precision of the study. However, recruitment was stopped due to the high number of adverse events after randomizing 38 and actually including 31 patients (see below). We therefore, conducted an interim analysis of the patients that were included in the study. Post hoc power analysis of the completers group revealed that sample sizes of 12 and 10 achieve 59 % power to detect a difference of 14.0 between the null hypothesis that in both group means are 18.4 and the alternative hypothesis that the mean of group 2 is 4.4 with estimated group standard deviations of 19.4 and 6.3 and with a significance level (alpha) of 0.05000 using a two-sided two-sample *t* test. Statistical calculations for all analysis were performed by using SPSS version 19. A *p* value of less than 0.05 was considered statistically significant

Results

Patient Inclusion

The study was prematurely terminated due to high migration rates (see below) after randomizing 38 patients; 26 to the device, and 12 to the control group. After withdrawal of consent of 7 patients before the actual study start, 5 in the treatment group (4 before device insertion and 1 after the second month after implantation) and 2 in the control group, 21 and 10 patients were left for analysis in the treatment and control group, respectively. Baseline characteristics of these included patients are shown in Table 1. Endoscopic implantation was performed in an average time of 18 min and ranged from 11 to 40 min including sedation, diagnostic endoscopy, and device insertion.

Results of Weight Loss

Average weight loss was 4.6 kg in the intention to treat (ITT) treatment group (n=21), 6.7 kg in the completers group (n=12), and 2.2 kg in the control group after 3 months (Table 2). Corresponding reduction of BMI was 1.6 (ITT), 2.4 (completers), and 0.6 kg/m^2 (control) (graph 2). Although patients in the treatment group lost more weight, statistical significance was not reached for the ITT group. However, study completers lost significantly more weight than patients in the control group (p=0.02).

Excess weight loss was 12.2 (ITT) and 18.4 % (completers) in the device group compared to 4.4 % in the

Table 1 Baseline characteristics of all patients

		Control group		Treatment group	
		Mean	Number	Mean	Number
Age (years)		41.7		43.5	
Sex	Female		7		13
	Male		3		8
BMI (kg/m^2)		41.2		41.3	
Weight (kg)		118.5		123.8	
Height (m)		169		173	

Table 2 Weight loss, reduction of BMI, and excess weight loss; $p=0.02$ if calculated for completers vs. control group. No significant reductions for ITT vs. control group.

	Intention to treat analysis ($n=21$)	Completers ($n=12$)	Control group ($n=10$)
Reduction of BMI (kg/m^2)	1.6	2.4	0.6
Reduction of weight (kg)	4.6	6.7	2.2
Excess weight loss (%)	12.2	18.4	4.4

control group ($p=0.02$ for completers vs. control group). Compared to the control group in patients, the ITT treatment group EWL did not exceed 10 %, whereas EWL was greater than 10 % in the completers group (Fig. 2).

Complications

Migration of the endoluminal mechanical device, even when the device was spontaneously excreted with no need for endoscopy or hospitalization, was considered a potentially serious adverse event. 10 migrations occurred and were managed in different ways depending on the localization of the device: three devices were excreted spontaneously without causing any damage to the intestine, one was removed by upper gastrointestinal (GI) endoscopy including enteroscopy, and four by colonoscopy, while two had to be operated laparoscopically. In one of these patients, following an unremarkable device removal by jejunostomy 22 days after placement, an insufficiency of the intestinal anastomosis occurred which required further treatment on an intensive care unit and consecutive surgical interventions including hemicolectomy. Therefore, serious adverse events occurred in 10 out of 21 patients in the treatment group compared to 0 of 10 patients in the control group.

Patient Assessment

When asked 1 month after device insertion for any positive or negative symptoms possibly related to the endoluminal mechanical device, one patient described an easier defecation, one reported eating smaller portions, one reported earlier satiety, and one claimed a lack of appetite. After 2 months, one patient complained about abdominal pain, one patient reported about smaller food portions, one patient noted earlier satiety, and one patient reported of a lack of appetite. No patient complained about nausea or vomiting or bothering flatulence as a symptom. After 3 months neither positive nor negative symptoms were reported.

Hormone analysis in subgroup

Baseline characteristic of the seven patients undergoing mixed-meal tests for investigation of GLP-1, glucose, and insulin are summarized in Table 3. The reduction of weight and BMI in subgroup patients were 4.8 and 1.68 kg/m^2, respectively. However, reduction of BMI and weight after 3 months compared to baseline did not reach statistical significance in *t* test.

Mixed-meal test was performed in order to measure glucose and insulin levels and to assess changes in GLP-1 profiles. Glucose and insulin-level measurements after 20, 60, 90 and 120 min of food intake revealed no statistically significant differences in patients with or without having the endoluminal mechanical device in place. Figure 3 illustrates glucose, insulin, and GLP-1 levels after meal tolerance test. Maximal values of glucose and insulin after food ingestion are very similar in patients with and without duodenal device in place, but differ markedly in the instance of time when the maximum is achieved: While peak values of glucose and insulin are achieved after 20 min in patients without the device in place, the maximum peek is reached after 60 min with the device.

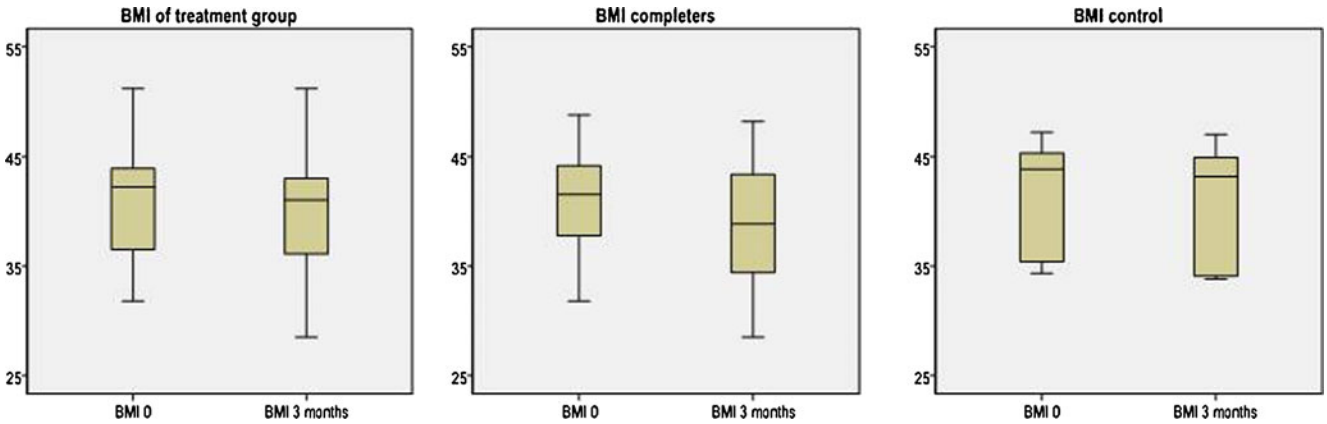

Fig. 2 Reduction of BMI in the control group ($n=10$), ITT group ($n=21$), and study completers ($n=12$; $p=0.02$ for completers vs. control group); see also text.

Table 3 Baseline characteristics of the subgroup of patients with hormone measurements (n=7).

		Mean	Standard deviation	Number
Age (year)		43.55	7.98	
Sex	Female			3
	Male			4
Weight (kg)		127.3	27.1	
BMI (kg/m^2)		41.30	5.58	

Laboratory analysis revealed a typical GLP-1 curve following ingestion of nutrients in patients without the device. In patients who had the device in place, GLP-1 levels did not increase after food intake. Additionally, basal GLP-1 levels were slightly higher (Fig. 1). However, difference of baseline GLP-1 levels with and without device did not reach statistical significance.

Discussion

Even though bariatric surgery is an effective treatment option with a limited rate of complications, there is a perceived need for nonsurgical interventional treatment options. Following intragastric balloon implantation which was introduced many years ago and failed to show consistent benefit over controls [9], several new endoscopic procedures have been tested recently [7]: They either aim at a restrictive effect such as TOGA [19], or the trans-oral endoscopic restrictive implant system (TERIS) [20], or try to mimic gastric bypass by inducing malabsorption such as the duodenal-jejunal-bypass-sleeve

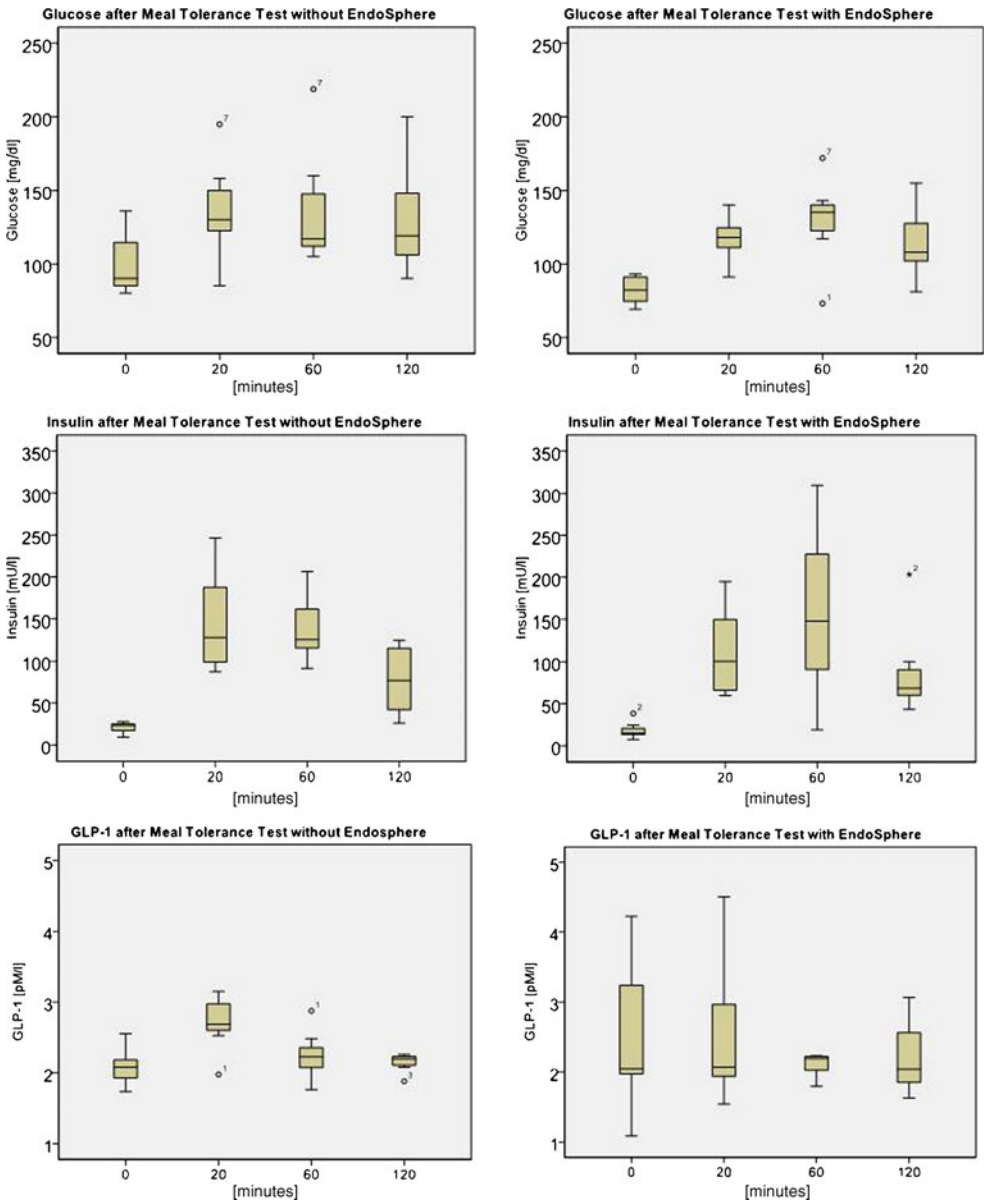

Fig. 3 Glucose, insulin and GLP-1 levels after meal tolerance test with and without the SatiSphere in place

(EndoBarrier) [10]. The new device which was tested in this study follows the opposite principle and was designed to delay transit time of nutrients through the duodenum. However, 10 out of 21 patients in the treatment group had a serious adverse event due to spontaneous migration of the device. In two cases, surgical intervention was necessary; in one case, as emergency procedure followed by postoperative complication. Therefore, there is clearly a need for improvement of the device; this could be an improved anchoring mechanism of the endoluminal mechanical device or—as opposite solution—it could be made more flexible to avoid entrapment in case of migration or both. The study was therefore prematurely terminated.

Notwithstanding this very high migration rate, the device might be effective once it remains in place in the stomach and along the duodenal C. Excess weight loss in the treated group (ITT analysis) exceeded that of the control group by 7.7 % at the 3-month control, when the device had to be removed as per protocol. Therefore, comparison with other endoscopic devices for weight loss and diabetes control is currently difficult, since most clinical trials exceed 12 weeks in duration. In addition, BMI is often not comparable between studies; in one sham-controlled study on the intragastric balloon, it was removed after 3 months, and there was significantly greater weight loss in the balloon group (7.3 kg) compared with the sham group (3.3 kg) [21]. In a sham-controlled trial using the Endobarrier system, excess weight loss was 11.9 and 2.7 % for treated and sham group, respectively, after 12 weeks. However, even in this CE-marked device, severe complications such as gastrointestinal bleeding, abdominal pain, nausea, and vomiting occurred [10]. In summary, all currently available endoscopic procedures are limited with respect to the time of devices staying in place and thus the lack of long-term data. Even more importantly, there is no information on what happens long-term after device removal in any of the implanted antiobesity devices. Therefore, there is a clear need for further studies which may help to select patients in whom endoscopic procedures will lead to a long-lasting weight reduction and improvement of metabolic comorbidities without serious complications. A rebound effect after device removal, however, remains likely, so that long-term placement and/or easy regular exchanges would be another way to go for endoscopic antiobesity methods. Thus, in summary, none of these clinically very important questions can as yet be answered for the endoluminal mechanical device, since this was the first pilot trial in man. Further studies will only be conducted after the device has been modified to reliable stay in place and/or migrate safely without impaction.

In order to shed some light on the possible underlying mechanisms of action of the endoluminal mechanical device implant leading to weight loss, we also analyzed GI hormones to further investigate the physiology of GLP-1 secretion in the gastrointestinal tract. In principle, the endoluminal mechanical device was constructed to slow alimentary flow and to present nutritional remains to the duodenum even at times when patients are fasting, possibly leading to higher levels of satiety signaling gastrointestinal peptides such as GLP-1. Apart from playing a major role for insulin secretion, GLP-1 is responsible for slowing gastric emptying [22]; a further effect of GLP-1 on satiety might be mediated directly via stimulation of the GLP-1-receptor in the hypothalamus. Drucker and Nauck postulated a sustained-weight loss that is maintained as long as increased GLP-1 levels are present [23]. Beglinger and Degen support the role of gastrointestinal peptides as regulators of satiety [24].

Dynamic in GLP-1 secretion revealed a typical shape in the curve of GLP-1 after food intake with a peak value about 30 min after food intake [25]. In our study, although the median GLP-1 level in patients with the device in place was not significantly higher, we saw a wider range of results. However, in patients with the device in place, glucose absorption and insulin secretion were delayed. Peak values for glucose and insulin were reached after 60 min, while in the same patients without the device maximum levels for glucose and insulin were documented after only 30 min. In addition, GLP-1 levels remained almost entirely stable with the endoluminal mechanical device in place. Our observations thus indicate that delaying duodenal transit time prolongs glucose absorption and insulin secretion. This might affect GLP-1 secretion in a way that leads to a continuous GLP-1 production rather than a dynamic secretion following nutrient intake. Therefore, the device resembles exogenous GLP-1 application and this effect might be, at least in part, responsible for the observed weight loss. Hypothetically, this effect might be enhanced if in future devices, duodenal transit time could be delayed further.

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