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ORIGINAL CONTRIBUTIONS

A Novel Full Sense Device to Treat Obesity in a Porcine Model: Preliminary Results

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Abstract

Purpose To evaluate the technical feasibility, safety, and efficacy of a novel full sense device (FSD) for the treatment of obesity in a porcine model.

Materials and Methods The novel FSD comprised a self-expanding metallic esophageal stent connected to a star-shaped nitinol disk. Three types of FSD were used: fully covered (type A), fully covered with barbs (type B), and uncovered with barbs (type C). Nine juvenile pigs were divided into two groups: FSD ($n = 6$) and control ($n = 3$). FSD type A was placed in the FSD group. In case of migration, either FSD type B or type C was then randomly placed. Food intake was monitored daily. Weight changes and ghrelin hormone levels were monitored weekly for 12 weeks.

Results FSD placement was technically successful in all pigs. All FSDs except one migrated to the stomach within 1 week after placement. The pig in which the FSD was retained showed decreased food intake in the first week after FSD placement, and there was a difference in the final weight between the FSD pig and control pigs. The percentage of weight gain was 116.6% in the control group and 105.3% in the FSD pig.

Conclusion FSD placement under fluoroscopic and endoscopic guidance is technically feasible and safe in a porcine model. The uncovered FSD appears to decrease food intake and reduce the rate of weight gain. However, the high FSD migration rate is not encouraging.

Keywords Obesity · Weight loss · Ghrelin · Full sense device

Introduction

Bariatric surgical procedures, such as sleeve gastrectomy, Roux-en-Y gastric bypass, and laparoscopic adjustable gastric banding, are effective for the treatment of severe obesity [1, 2]. However, these procedures are associated with high costs, adverse events, and low patient acceptance [3]. Endoscopic bariatric therapies, including the use of intragastric balloons

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and duodenal–jejunal bypass sleeve (DJBS) (EndoBarrier Gastrointestinal Liner), provide a minimally invasive treatment approach to treat obesity, which could increase treatment options beyond surgery [3–5]. With the use of intragastric balloon, serious adverse events, such as balloon migration and gastric perforation, have been limited to rates of 1.4% and 0.1%, respectively [5]. Conversely, adverse events of DJBS use include migration (4.9%), gastrointestinal bleeding (3.86%), sleeve obstruction (3.4%), liver abscess (0.126%), cholangitis (0.126%), acute cholecystitis (0.126%), and esophageal perforation (0.126%) secondary to trauma from an uncovered barb during withdrawal [3].

Full sense device (FSD) is another reversible weight-loss device to overcome the problems associated with the use of intragastric balloons and DJBS [3, 6]. By placement in the cardia, the FSD can induce satiety and feelings of fullness. Unpublished human data have shown 28% excess weight loss (EWL) in 46 days with the use of FSD. Moreover, unpublished animal data have shown 20% weight loss in dogs. To our knowledge, although it is an interesting concept, clinical or experimental data in the literature are scarce. Therefore, we designed a device similar to the FSD and evaluated its effectiveness. The purpose of this study was to evaluate the technical feasibility, safety, and efficacy of the novel FSD in a porcine model.

Materials and Methods

Animal Study

This study was approved by the Institutional Animal Care and Use Committee of our institution and conformed to U.S. National Institutes of Health guidelines for humane handling of laboratory animals.

A total of 9 pigs weighing 33.6–45.2 kg (median, 40.5 kg) (Orient Bio, Seongnam, Korea) were randomized into two groups. Six pigs underwent FSD placement (FSD group). The remaining three weight- and age-matched healthy pigs were used as controls (control group). All pigs were fed a fixed amount of food (regular chow; 1 kg three times a day) and were maintained at 22 ± 2 °C.

Novel FSD and FSD Delivery System

Three types of FSDs (A, B, and C) were used in this study (Fig. 1). The FSD comprised two parts: a straight self-expanding metallic stent (SEMS) for the lower esophagus and a nitinol disk for the fundus of the stomach. The esophageal SEMS part was knitted from a 0.229-mm nitinol wire into a tubular configuration. When fully expanded, the SEMS part was 24 mm in diameter and 60 mm in length. Four flaps were attached to the upper end of the esophageal SEMS part to prevent migration. To make the FSD removable, a drawstring of nylon monofilament was attached to the upper inner margin of the SEMS. The disk part was designed to be in direct contact with the fundus of the stomach to apply continuous pressure. It was a star-shaped flat mesh made from a 0.254-mm nitinol wire (diameter, 7 cm) and perpendicularly connected to the esophageal SEMS part by a single pillar of nitinol wire and a nylon string.

Type A FSD was fully covered: the esophageal SEMS part was lined with polytetrafluorethylene membrane covering the inner side and the disk part was covered with silicon membrane using the dip-coating method. Type B FSD was similar to type A, but barbs were added to the lower part of the esophageal SEMS to prevent migration. Type C FSD was designed the same as types A and B, but it was totally uncovered. The FSD delivery system comprised a Teflon sheath (outer diameter, 9.3 mm; inner diameter, 8.3 mm; length, 70 cm) and a pusher catheter with a guiding olive tip. The total introducer length was 120 cm. Retrieval set comprised a 13-Fr sheath, a 10-Fr dilator, and a hook wire [7]. First, type A FSD was placed in the FSD group. In case of migration, either type B or C FSD was randomly placed immediately after the removal of the migrated FSD.

Techniques of FSD Placement and Removal

After 8 h of fasting and under the supervision of a veterinarian, the pigs were premedicated with 50 mg intramuscular ketamine. An endotracheal tube was placed, and anesthesia was administered by inhalation [0.5–2% isoflurane (Ifran®; Hana Pharm. Co., Seoul, Korea) with oxygen (510 mL/kg per min) at 1:1]. All procedures were performed in the left decubitus position. An overtube was placed through the mouth into the esophagus. An endoscope (CF-H260AI; Olympus Inc. Tokyo, Japan) was introduced through the overtube into the stomach, and the suction of gastric secretions was performed by a gastroenterologist. A 0.035-in. guidewire (Radifocus M; Terumo, Tokyo, Japan) was passed through the working channel of the endoscope into the stomach. The endoscope was removed while retaining the guidewire, and the FSD delivery system was passed over the guidewire into the stomach by an interventional radiologist. Under fluoroscopic guidance, the pusher catheter was held in place with one hand, while the sheath was slowly withdrawn in a continuous motion with the other hand. The disk part was placed in the gastric fundus, and the connection part was placed in the lower esophagus, bridging the gastroesophageal junction. After FSD deployment, its position was assessed by endoscopic examination. Two endoscopic clips (Hemoclip, Olympus Inc.) were applied to the esophageal mucosa at the proximal end of the FSD to prevent migration (Fig. 2). Antibiotics (cefazolin,

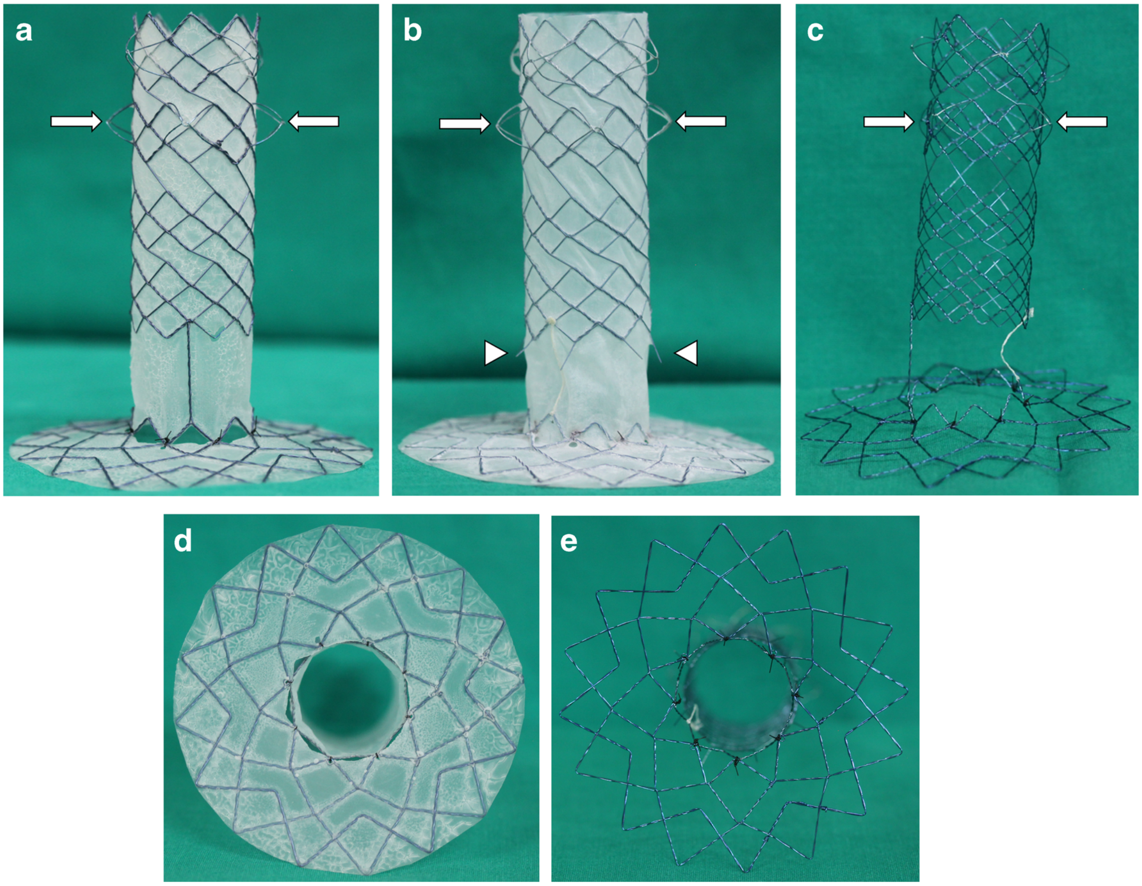

Fig. 1 Photographs showing the three prototypes of the FSD. **a** Type A (fully covered). **b** Type B (fully covered with barbs). **c** Type C (uncovered). Note the anti-migration flaps (arrows), and the barbs (arrowheads). The disk part is shown in the photograph **d** covered and **e** uncovered. FSD, full sense device

15 mg/kg) and analgesia (alfentanil, 0.5 mg) were administered for 3 days after the procedures.

For the removal of the FSD, the drawstring was grasped and pulled into the sheath, and the entire device was collapsed by withdrawing the hook wire using fluoroscopic monitoring [7]. If the FSD had migrated to the stomach, removal was performed under endoscopic and fluoroscopic guidance.

Follow-Up

After FSD placement, the pigs could eat after recovery from the anesthesia. The amount of food intake was monitored three times per day. Weight and behavioral changes were monitored at 1-week intervals. The percentage of weight gain was calculated according to the following formula: percentage

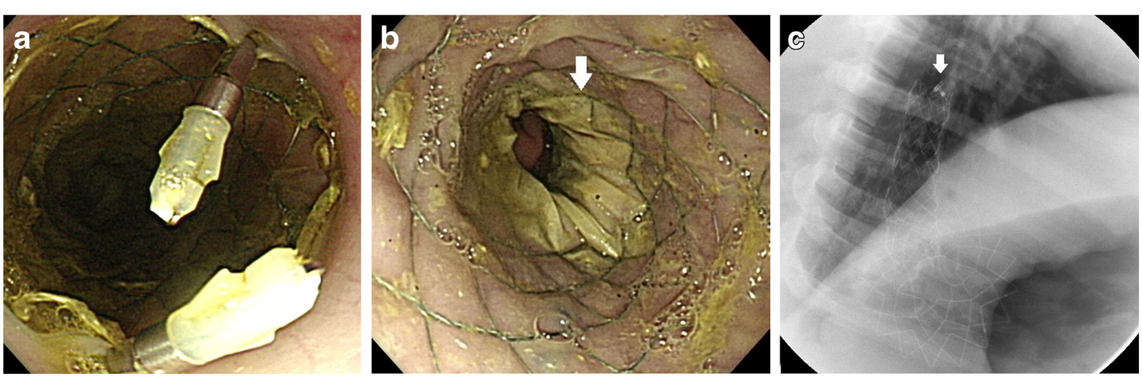

Fig. 2 **a** Endoscopic image showing the proximal end of the FSD fixed to the wall of the esophagus by two clips. **b** Endoscopic image showing the distal end of the esophageal SEMS part of the FSD (type A) with the connection part placed across the gastroesophageal junction (arrow). **c** Lateral radiograph showing the FSD after placement; note the metallic endoscopic clips (arrow). FSD, full sense device; SEMS, self-expanding metallic stent

of weight gain = (final weight − initial weight) / initial weight × 100. Plain radiographs of the abdomen were obtained at 1-week intervals to assess the FSD position. Blood ghrelin levels were assessed at 1-week intervals, and total (acyl and des-acyl) ghrelin levels were measured before the morning meal at 8 am at 1-week intervals [8]. Endoscopic examination was performed 8 weeks after FSD placement to evaluate the FSD position and FSD-related side effects.

All pigs were euthanized by the administration of an overdose of xylazine hydrochloride (Rompun; Bayer, Seoul, Korea) 12 weeks after placement. Surgical exploration of the esophagus and stomach was followed by gross examination to evaluate the degree of granulation tissue formation and to determine possible esophageal and/or gastric injury after FSD placement.

Statistical Analysis

Data are expressed as the mean ± standard deviation. The differences between the groups were analyzed using Mann–Whitney *U* test, as appropriate. A P value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (version 23.0; SPSS, IBM, Chicago, IL, USA).

Results

Technical Outcomes (Fig. 3)

FSD type A placement was technically successful in the FSD group ($n = 6$) without procedure-related side effects. FSD migration into the stomach occurred in all pigs within 1 week after the placement (6/6, 100%). All migrated FSDs were successfully removed under endoscopic and fluoroscopic guidance with no side effects. In the second trial, six pigs were randomly divided into two groups ($n = 3$, each). The first group received type B FSD, and the second group ($n = 3$) received type C FSD. In the first group, all FSDs migrated to the stomach within 1 week after the placement (3/3, 100%). In the second group, two FSDs migrated to the stomach (2/3, 66.7%). The remaining FSD did not migrate until the end of the study. All migrated FSDs were successfully removed under endoscopic and fluoroscopic guidance. One pig that retained type C FSD survived until the end of the study with no device-related side effects. All pigs in which FSDs migrated were excluded from this study.

Food Intake

In the FSD pig, food intake was interrupted 1 to 3 days after the placement. However, on day 7, the pig consumed all of the supplied food. Pigs in the control group consumed all of the food supplied every day. The amount of food intake of the FSD pig FSD (1.6 kg ± 0.9 kg per day) was lower than that of the control pigs (3.0 kg per day) in the first week after FSD placement. There was no remarkable difference in the following weeks between the FSD pig (2.9 kg ± 0.1 kg per day) and control pigs (3.0 kg per day). However, because FSD was retained in only one pig, statistical significance could not be confirmed.

Weight and Ghrelin Level Changes

There was no significant difference in the initial weight between the FSD pig and control pigs ($P = 0.95$). At the end of the 12-week follow-up, there was a difference in the final weight between the control pigs (92.7 ± 4.2 kg) and the FSD pig (86 kg) (Fig. 4). There was a difference in percentage weight gain between the control pigs (116.6%) and the FSD pig (105.3%). However, statistical significance could not be confirmed.

From weeks 1 to 7 after FSD placement, ghrelin level in the FSD pig was higher than that in control pigs (Fig. 5). From the seventh week until the end of the study, ghrelin level in the control pigs was higher than that in the FSD pig.

Endoscopic and Gross Findings

The FSD was observed in place with extensive granulation tissue formation through the mesh of the esophageal SEMS part of the FSD. The disk part was seen in the fundus of the stomach after the retroflexion of the scope and was in contact with the fundus of the stomach. There was no opposition of the esophageal and disk part because the connection part was weak. This resulted in deviation of the disk from the original position after FSD placement (Fig. 6).

Discussion

We developed a novel FSD to induce satiety and promote weight loss in a porcine model. FSD placement is technically feasible and safe when performed under combined endoscopic and fluoroscopic guidance, with no procedure-related side effects. The migration rate of the fully covered FSD with or without barbs is 100%; however, the migration rate for the uncovered FSD is 66.7%. The pig that retained the uncovered FSD till the end of the study has an initial decrease in food intake and a tendency to slower weight gain compared to the control.

Bariatric surgery produces long-term weight loss in obese patients, and it can improve some of the metabolic disorders associated with obesity [9]. These observations give rise to the concept that the interruption of the gut–brain signaling may be beneficial for treating obesity and that the development of

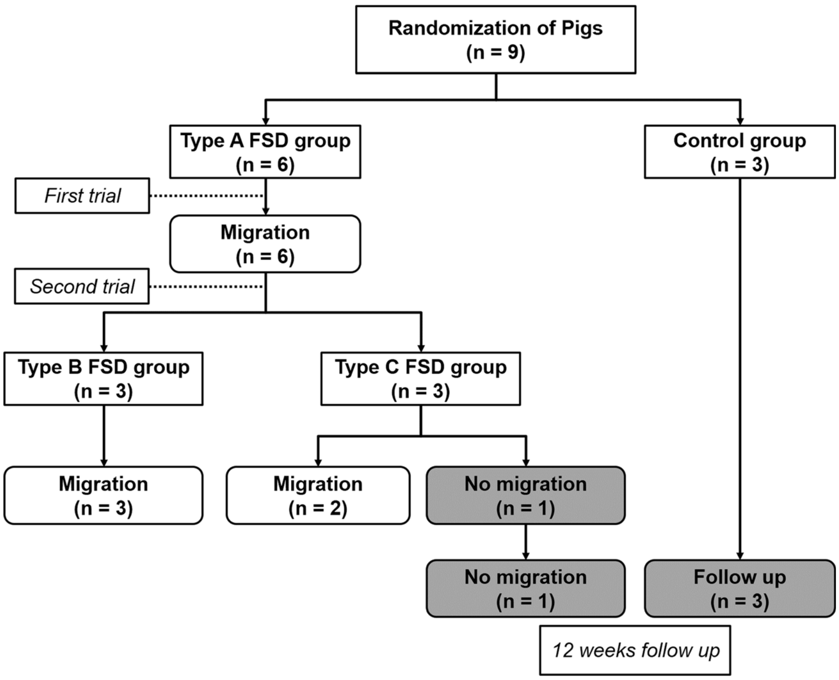

Fig. 3 Flow diagram showing the steps of FSD placement. FSD, full sense device

non-invasive approaches that mimic the effect of bariatric surgery may be valuable [10]. In 2009, a study group announced that they had developed a modified esophageal SEMS called the Full Sense™ Device (Baker, Foote, Kemmeter, Walburn [BFKW] LLC, Grand Rapids, MI, USA) for treatment of obesity [6]. The device comprised an esophageal SEMS connected to a gastric disk via a strut that was placed and removed endoscopically. The hypothesis behind the development of this device was that by applying pressure to the cardia and fundus of the stomach, satiety can be induced. They reported that unpublished human data with three subjects has shown 28% EWL in 46 days. A median of 80% EWL has been reported during a 6-month trial in an unknown number of subjects. These results were reportedly backed by a randomized trial and follow-up crossover trial design. Nevertheless, no peer-reviewed data (either animals or human) have been published until recently [5]. In our study, a similar FSD was developed to test the hypothesis in a porcine model. FSD placement was technically successful when performed under endoscopic and fluoroscopic guidance, with no procedure-related side effects. All FSDs that migrated to the stomach were removed uneventfully. Food intake and the rate of weight gain decreased in the FSD pig.

The theory behind the FSD is stretching the proximal stomach (cardia and fundus) as long as the device is retained in the stomach. The vagal nuclei and the vagus nerve innervates most of the gastrointestinal tract involved in food intake and satiety [9]. Vagal afferents are directly stimulated by changes in the wall tension when food passes through the gastrointestinal tract [9]. We believe that the disk part of the FSD can

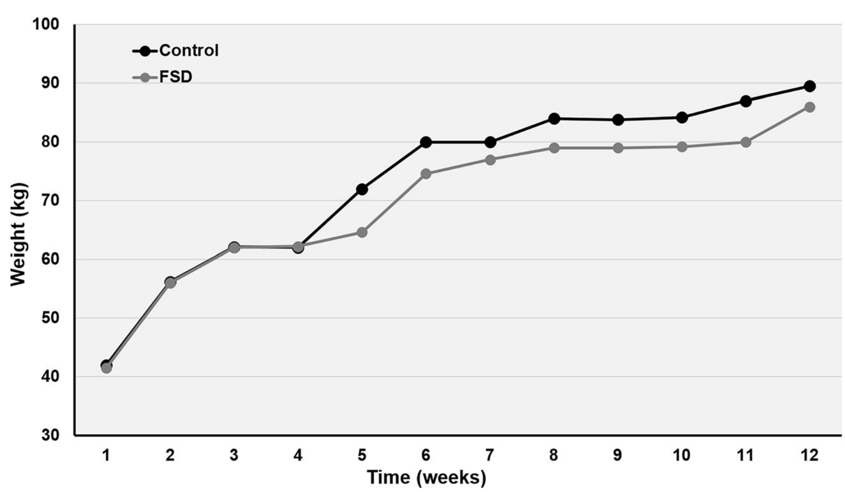

Fig. 4 Weight change in the FSD pig compared with the control pigs. FSD, full sense device

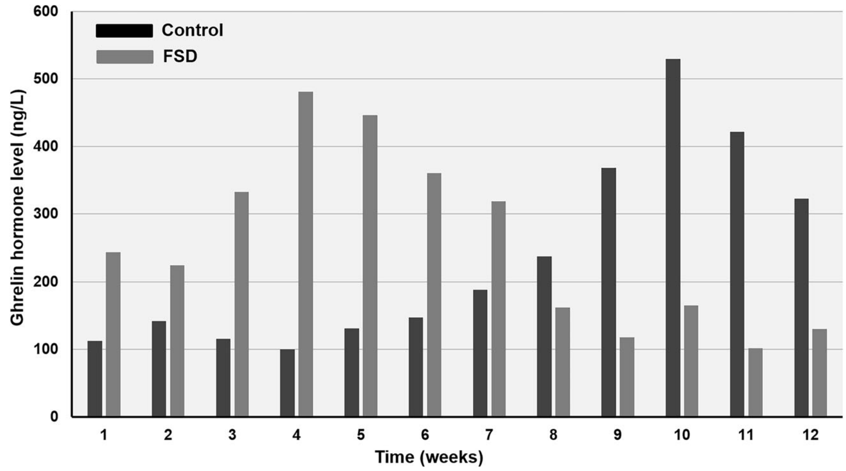

Fig. 5 Ghrelin level changes over 12 weeks in the FSD pig and control pigs. FSD, full sense device

induce a similar effect and can induce satiety. It should be noted that there are different types of sensory receptors that innervate the gastrointestinal tract [11]. The receptors' characteristics show marked plasticity, and their rates of adaptation and sensitivity to distention range from very low to very high [11]. We assume that these characteristics allow the disk part to continuously send signals to the brain to induce satiety.

The fundus of the stomach is the major site of production of the ghrelin hormone which is the main orexigenic hormone in the body [8]. Early studies on the ghrelin hormone found a strong relation between weight changes and ghrelin hormone levels. However, other studies found only a marginal role in the induction and maintenance of weight loss [12]. We tried to find if FSD has any effect on the ghrelin levels. Initially, the ghrelin hormone levels increased compared to the control for the first 6 weeks; however, the levels decreased afterwards. There was no clear relation between food intake and the hormone levels. We measured the serum ghrelin level at a fixed time before serving the breakfast and we measured the total level to decrease the errors during assessment. It is difficult though, to draw conclusions regarding the ghrelin hormone effect because of the small sample size in our study and fixed amount of food supplied to each animal.

The main drawback of the FSD in our study is the high migration rate. Migration of the esophageal SEMS is a known limitation especially with the fully covered SEMSs [13, 14]. The disk part of the FSD increases its weight, thereby increasing the migration rate. Anti-migration flaps, barbs, and endoscopic clips have been previously used to prevent migration of the esophageal SEMS [15]. Unfortunately, these methods were not effective to prevent FSD migration in our study. We have considered other methods for fixation, such as endoscopic suturing [16] and over-the-scope clips [17], but they are unavailable at our facility. Nonetheless, no further side effects were observed from the migrated FSDs (e.g., gastric outlet obstruction). Baker and colleagues have reported that they initially used barbs to prevent migration, which induced esophageal ulcers. Later, they used a laparoscopically sutured tether at the angle of His and reported the development of an endoscopic fixation method with no further details [6]. Measures to prevent FSD migration should be investigated in future studies.

There are several limitations in our study. First, the high migration rate indicates that relevant statistical conclusions cannot be drawn from our results. Second, we did not include an additional sham group to distinguish between the effects of

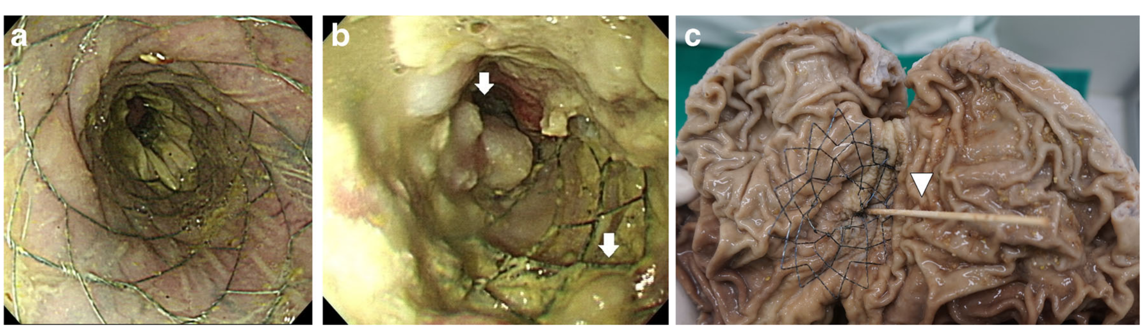

Fig. 6 **a** Endoscopic image showing the esophageal SEMS part of the FSD immediately after placement. **b** Endoscpic image showing granulation tissue formation (arrows) at the esophgaeal SEMS part 8 weeks after the placement. **c** Photograph after autopsy showing opened stomach with the retained FSD (the stick [arrowhead] is placed inside the esophagus passing through the gastroesophageal junction). FSD, full sense device; SEMS, self-expanding metallic stent

FSD from that of the procedure itself, especially the interruption of food intake in the first week after FSD placement. Third, limiting the amount of food to 3 kg every day in growing juvenile pigs may underestimate the effect of the FSD on food intake. Lastly, we did not perform histological evaluation to assess the effect of the FSD on the stomach. These limitations should be addressed in future studies.

In conclusion, FSD placement under fluoroscopic and endoscopic guidance is technically feasible and safe in a porcine model. The uncovered FSD appears to decrease food intake and reduce the rate of weight gain. However, the high FSD migration rate is not encouraging.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All applicable institutional and/or national guidelines for the care and use of animals were followed.

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References

1. Tammaro P, Hansel B, Police A, et al. Laparoscopic adjustable gastric banding: predictive factors for weight loss and band removal after more than 10 years' follow-up in a single university unit. World J Surg. 2017;41(8):2078–86.
2. Nguyen NT, Varela JE. Bariatric surgery for obesity and metabolic disorders: state of the art. Nat Rev Gastroenterol Hepatol. 2017;14(3):160–9.
3. Force ABET, Committee AT, Abu Dayyeh BK, et al. ASGE bariatric endoscopy task force systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting endoscopic bariatric therapies. Gastrointest Endosc. 2015;82(3):425–38 e5.
4. Saunders KH, Igel LI, Saumoy M, et al. Devices and endoscopic bariatric therapies for obesity. Curr Obes Rep. 2018;7(2):162–71.
5. Choi HS, Chun HJ. Recent trends in endoscopic bariatric therapies. Clin Endosc. 2017;50(1):11–7.
6. Myall P New endoscopic stent can lead to 100% EWL [Internet] London: Bariatric News; c2012 [updated 2012 Jun 5; cited 2018 july 7] Available from: wwwbariatricnewsnet/?q=node/102.
7. Na HK, Song HY, Yeo HJ, et al. Retrospective comparison of internally and externally covered retrievable stent placement for patients with benign urethral strictures caused by traumatic injury. AJR Am J Roentgenol. 2012;198(1):W55–61.
8. Steinert RE, Feinle-Bisset C, Asarian L, et al. Ghrelin, CCK, GLP-1, and PYY(3-36): secretory controls and physiological roles in eating and glycemia in health, obesity, and after RYGB. Physiol Rev. 2017;97(1):411–63.
9. Camilleri M. Peripheral mechanisms in appetite regulation. Gastroenterology. 2015;148(6):1219–33.
10. Dockray GJ. Gastrointestinal hormones and the dialogue between gut and brain. J Physiol. 2014;592(Pt 14):2927–41.
11. Brookes SJ, Spencer NJ, Costa M, et al. Extrinsic primary afferent signalling in the gut. Nat Rev Gastroenterol Hepatol. 2013;10(5):286–96.
12. Ionut V, Burch M, Youdim A, et al. Gastrointestinal hormones and bariatric surgery-induced weight loss. Obesity. 2013;21(6):1093–103.
13. Sharma P, Kozarek R. Practice Parameters Committee of American College of G. Role of esophageal stents in benign and malignant diseases. Am J Gastroenterol 2010;105(2):258–273; quiz 74.
14. Spaander MC, Baron TH, Siersema PD, et al. Esophageal stenting for benign and malignant disease: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. Endoscopy. 2016;48(10):939–48.
15. Kim KY, Tsauo J, Song HY, et al. Self-expandable metallic stent placement for the palliation of esophageal cancer. J Korean Med Sci. 2017;32(7):1062–71.
16. Yang J, Siddiqui AA, Kowalski TE, et al. Esophageal stent fixation with endoscopic suturing device improves clinical outcomes and reduces complications in patients with locally advanced esophageal cancer prior to neoadjuvant therapy: a large multicenter experience. Surg Endosc. 2017;31(3):1414–9.
17. Watanabe K, Hikichi T, Nakamura J, et al. Feasibility of esophageal stent fixation with an over-the-scope-clip for malignant esophageal strictures to prevent migration. Endoscopy International Open. 2017;5(11):E1044–E9.