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Intragastric satiety-inducing device reduces food intake and suppresses body weight gain in a rodent model

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Abstract

Background An intragastric satiety-inducing device (ISD) (Full Sense Device; Baker, Foote, Kemmeter, Walburn, LLC, Grand Rapids, MI) is a novel weight-loss device, which may induce satiety by applying continuous pressure on the gastric cardia. This study investigated the effect of the ISD on food intake and body weight gain in a rodent model.

Methods Thirty-two male Sprague–Dawley rats (weight, 250–300 g) were randomly divided into four groups of eight individuals. Single-disk (SD) and double-disk (DD) group animals underwent peroral placement of a single- or double-disk ISD, respectively, under fluoroscopic guidance. The ISD comprised a 4 mm × 1.5 cm nitinol stent placed in the lower esophagus and one (single-disk) or two (double-disk) 2.5-cm-diameter star-shaped nitinol disks placed in the gastric fundus. Esophageal stent (ES) and sham-operated (SO) group animals underwent peroral placement of the ES part of the ISD and a sham operation, respectively.

Results Food intake was significantly different among the four groups over the 4-week study period ($P < 0.001$); food intake was significantly lower in the SD and DD groups than in the SO group ($P = 0.016$ and $P = 0.002$, respectively) but was not significantly different between the SD and DD groups ($P > 0.999$) and between the ES and SO groups ($P = 0.677$). Body weight was significantly different among the four groups by the end of the study period ($P < 0.001$); body weight was significantly lower in the DD group than in the SD, ES, and SO groups ($P = 0.010$, $P < 0.001$, and $P < 0.001$, respectively) and in the SD group than in the SO group ($P = 0.001$), but it was not significantly different between the ES and SO groups ($P = 0.344$).

Conclusion ISD reduced food intake and suppressed body weight gain in a rodent model.

Keywords Bariatric medicine · Bariatrics · Obesity · Obesity management · Weight loss · Self-expandable metallic stents

Abbreviations

BMI	Body mass index
ISD	Intragastric satiety-inducing device
SD	Single-disk
DD	Double-disk
ES	Esophageal stent
SO	Sham-operated

Obesity (body mass index [BMI] ≥ 30 kg/m^2) has become a health epidemic involving 650 million people worldwide as of 2016 [1]. Obesity is a major risk factor for many noncommunicable diseases, such as cardiovascular diseases, diabetes, musculoskeletal disorders, and several types of cancers [2]. For severely obese patients (BMI ≥ 35 kg/m^2), lifestyle modification and pharmacotherapy have limited effectiveness [3]; only bariatric surgery (e.g., Roux-en-Y gastric bypass, sleeve gastrectomy, and adjustable gastric banding)

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has resulted in both clinically meaningful and sustained weight loss [4]. However, < 1% of eligible patients receive bariatric surgery annually due to poor access to care, high surgical costs, and perception of major risk [5]. Therefore, minimally invasive interventions to bridge the gap in the management of obesity have been a growing interest [6].

The intragastric satiety-inducing device (ISD) (Full Sense Device; Baker, Foote, Kemmeter, Walburn, LLC, Grand Rapids, MI) is a novel weight-loss device modified from an esophageal stent [7, 8]. Unlike intragastric balloons, which work by occupying space in the stomach, the ISD works by applying continuous pressure on the gastric cardia, which may stimulate the vagal afferent receptors and the vagus nerve distributed around the cardia, thereby inducing satiety [9]. In addition, the ISD may also induce satiety by suppressing ghrelin secretion since ghrelin-producing cells are predominately distributed in the gastric fundus, which is near the cardia [10–12]. However, clinical data associated with this device are lacking, and experimental evidence is limited [13]. The purpose of this study was to investigate the effect of the ISD on food intake and body weight gain in a rodent model.

Materials and methods

Study design

The Animal Care and Use Committee of our institute approved this study. All animals were maintained according to the Guide for the Care and Use of Laboratory Animals. Thirty-two male Sprague-Dawley rats weighing between 250 and 300 g were randomly divided into four groups of eight individuals. Single-disk (SD) and double-disk (DD) group animals underwent peroral placement of a single- or double-disk ISD, respectively. Esophageal stent (ES) and sham-operated (SO) group animals underwent peroral placement of the ES part of the ISD and a sham operation, respectively. After the operation, the animals were housed individually in cages with a 12 h light/dark cycle in a temperature-controlled room (24 ± 2 °C) and were supplied with food and water ad libitum the next day. Food intake and body weight were monitored at 1-week intervals. Fasting serum ghrelin was measured at 2-week intervals. Radiographs were taken at 1-week intervals to monitor device migration in the SD, DD, and ES groups. All rat behaviors and complications after the operation were properly recorded. The animals were euthanized 4 weeks after the operation by administrating inhalable pure carbon dioxide.

ISD construction

The ISDs used in this study were constructed in-house and comprised two parts: a stent and a disk (Fig. 1). The former was braided from a 0.12 mm nitinol wire into a tubular configuration and was 4 mm in diameter and 15 mm in length, whereas the latter comprised one (single-disk) or two (double-disk) 25-mm-diameter star-shaped disks constructed from 0.10 mm nitinol wires. The stent was perpendicularly connected to the disk with 5–0 nylon sutures. One and two radiopaque markers were attached to each end of the stent and the disk, respectively. The purpose of the disk was to apply continuous pressure on the gastric cardia, and the purpose of the stent was to maintain the position of the ISD. The ISD was compressed and loaded with a 6-Fr stent delivery system (S&G Biotech, Yongin, Korea).

ISD placement operation

After 8 h of fasting, the rats were anesthetized with an intramuscular injection of a mixture of 50 mg/kg zolazepam and tiletamine and 10 mg/kg xylazine. Under fluoroscopic guidance, the stent delivery system was inserted perorally into the stomach with a 0.018-inch guidewire (Transcend; Boston Scientific, Natick, MA), and a single- or a double-disk ISD was deployed across the esophagogastric junction with the disk situated in the gastric cardia and the stent situated in the lower esophagus (Fig. 2). In the ES group, an esophageal stent was deployed in the lower esophagus, with the lower

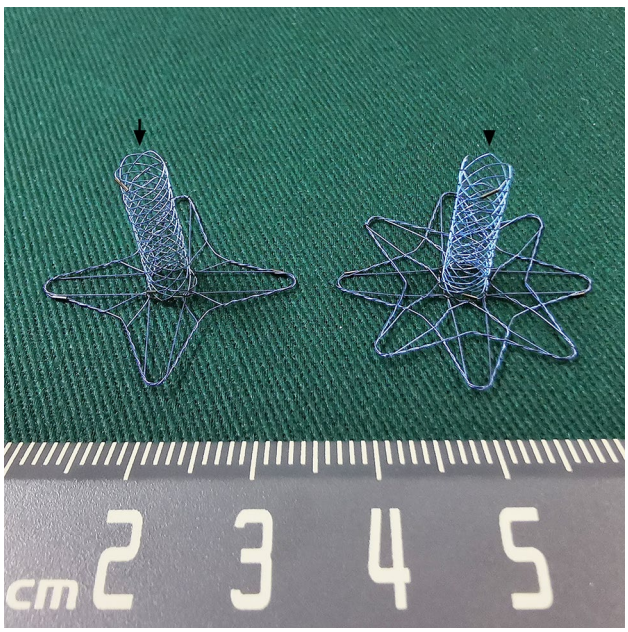

Fig. 1 A photographs show a single- (arrow) and a double-disk (arrowhead) ISD (both constructed in-house)

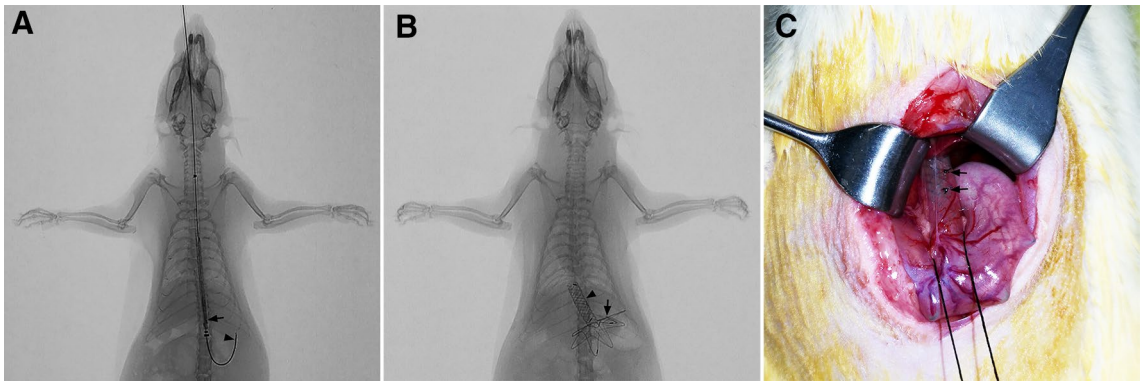

Fig. 2 Double-disk ISD placement. **A** A radiograph showing the 6-Fr delivery system (S&G Biotech, Yongin, Korea) (arrow) inserted perorally into the stomach with a 0.018-inch guidewire (Transcend; Boston Scientific, Natick, MA) (arrowhead). **B** A radiograph showing the double-disk ISD (constructed in-house) deployed across the esophagogastric junction with the disk situated in the gastric fundus (arrow) and the stent situated in the lower esophagus (arrowhead). **C** A photograph showing the stent of the ISD sutured at two points to the lower esophageal wall (arrows) with 5–0 silk sutures via laparotomy

margin of the stent situated in the esophagogastric junction. To prevent device migration, the stent in the SD, DD, and ES groups was sutured at two points to the lower esophageal wall with 5–0 silk sutures via laparotomy. SO group rats underwent peroral insertion of the stent delivery system into the stomach under fluoroscopic guidance without placement of any device, and two sutures were made to the lower esophagus via laparotomy.

Ghrelin analysis

After the rats were fasted overnight, blood samples were drawn from the tail vein and quiesced for 6 h at 4 ℃. Serum was separated from the blood samples by centrifugation at 8000 × g for 10 min and stored at − 80 ℃ until assayed. The ghrelin concentration in the serum samples was determined by a commercially available rat ghrelin enzyme-linked immunosorbent assay kit (ImmunoWay, Plano, TX) according to the manufacturer's instructions.

Histologic analysis

The stomach and the lower esophagus of the rats were removed *en bloc* from the abdominal cavity and opened along the greater curvature of the stomach. The excised tissue samples were then fixed by immersion in 10% buffered formalin for 24 h, embedded in paraffin, sectioned at a 4-μm thickness, and stained with hematoxylin and eosin.

Statistical analysis

The overall comparison between groups was made using a repeated measures analysis of variance. Post hoc pairwise comparisons between groups were made using the Bonferroni method to correct for multiple comparisons. $P < 0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed with SPSS software (version 22; SPSS, Chicago, IL).

Results

The designated operation was technically successful in all 32 rats. One animal in the double-disk group died 2 weeks after the operation due to gastric perforation. The remaining animals survived until the end of the 4-week study period without any adverse events. The radiographs showed no signs of device migration in the SD, DD, and ES group animals.

Food intake

Food intake significantly decreased from baseline in all four groups at week 1 (all $P < 0.001$) (Fig. 3). In the ES and SO groups, food intake returned to baseline at week 2 ($P = 0.603$ and $P > 0.999$, respectively) and remained unchanged from baseline at weeks 3 and 4 (all $P > 0.05$). Similarly, in the SD group, food intake returned to baseline at week 2 ($P = 0.546$) and remained unchanged from baseline at weeks 3 and 4 ($P > 0.999$ and $P > 0.999$, respectively). In the DD group, however, food intake remained significantly decreased from baseline at week 2 ($P = 0.035$), but returned to baseline at week 3 ($P = 0.205$), and remained unchanged from baseline at week 4 ($P = 0.756$). Food intake was significantly different among the four groups over the 4-week study period ($P < 0.001$) and was significantly lower in the SD and DD groups than in the sham groups ($P = 0.016$ and $P = 0.002$, respectively); it was not significantly different between the SD and DD groups ($P > 0.999$) and between the ES and SO groups ($P = 0.677$).

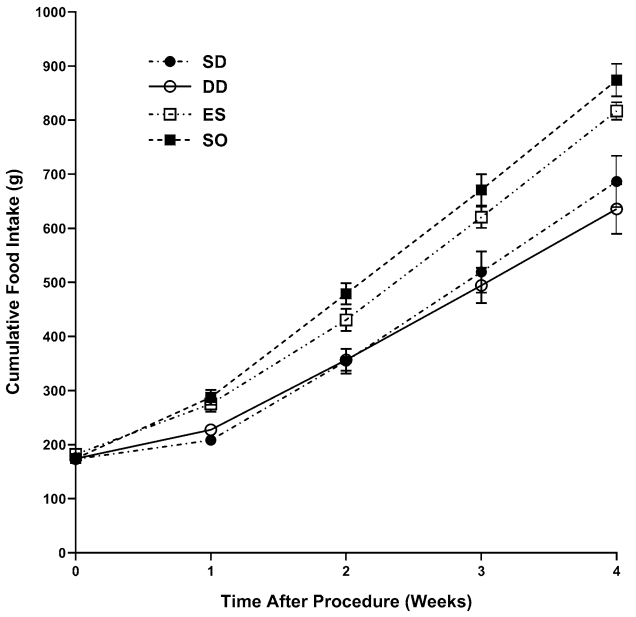

Fig. 3 A dotted line graph showing the cumulative food intake for the total 4-week study period. Note: dot = mean; range of error bar = standard error of the mean (SEM); *SD* single-disk, *DD* double-disk, *ES* esophageal stent, *SO* sham-operated

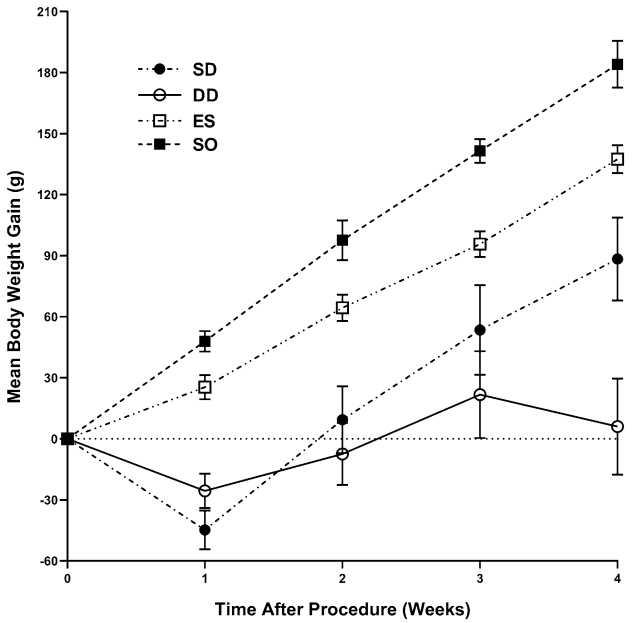

Fig. 4 A dotted line graph showing the changes in body weight from baseline. Note: dot = mean; range of error bar = standard error of the mean (SEM); *SD* single-disk, *DD* double-disk, *ES* esophageal stent, *SO* sham-operated

Body weight

Body weight steadily increased in the ES and SO groups after the operation, with a significant increase from baseline at week 1 through week 4 (all $P < 0.05$) (Fig. 4). In the SD group, body weight significantly decreased from baseline at week 1 ($P < 0.001$) but returned to baseline at week 2 ($P > 0.999$) and steadily increased thereafter, with a significant increase from baseline at week 3 and week 4 ($P = 0.01$ and $P < 0.001$, respectively). In contrast, in the DD group, body weight significantly decreased from baseline at week 1 ($P = 0.037$) and remained unchanged from baseline at week 2 through week 4 (all $P > 0.999$). Body weight was significantly different among the four groups by the end of the 4-week study period ($P < 0.001$); it was significantly lower in the DD group than in the SD, ES, and SO groups ($P = 0.01$, $P < 0.001$, and $P < 0.001$, respectively) and in the SD group than in the SO group ($P = 0.001$), but it was not significantly different between the ES and SO groups ($P = 0.344$).

Fasting serum ghrelin

Fasting serum ghrelin remained unchanged from baseline until the end of the 4-week study period in all four groups (all $P > 0.05$) and was not significantly different among the four groups over time ($P = 0.308$) (Fig. 5).

Gross inspection and histologic analysis

Gross inspection showed mild luminal strictures near the esophagogastric junction in all 23 rats in the SD, DD, and ES groups (Fig. 6). In these animals, histologic analysis confirmed that the strictures were caused by granulation tissue formation. Gross inspection also showed that some of the disk protrusions were embedded in the gastric wall in all 15 animals in the SD and DD groups. In these animals,

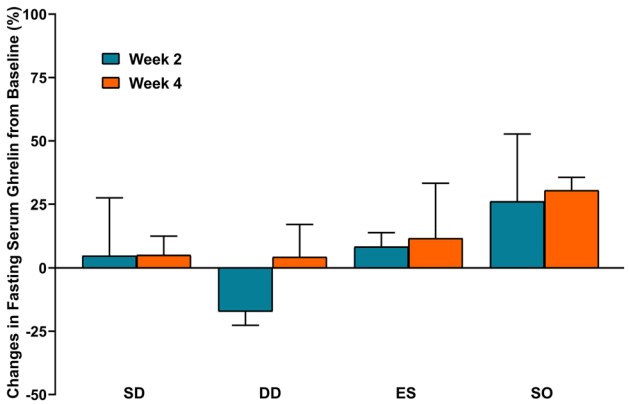

Fig. 5 A bar graph showing the changes in fasting serum ghrelin from baseline. Note: bar = mean; range of error bar = standard error of the mean (SEM); *SD* single-disk, *DD* double-disk, *ES* esophageal stent, *SO* sham-operated

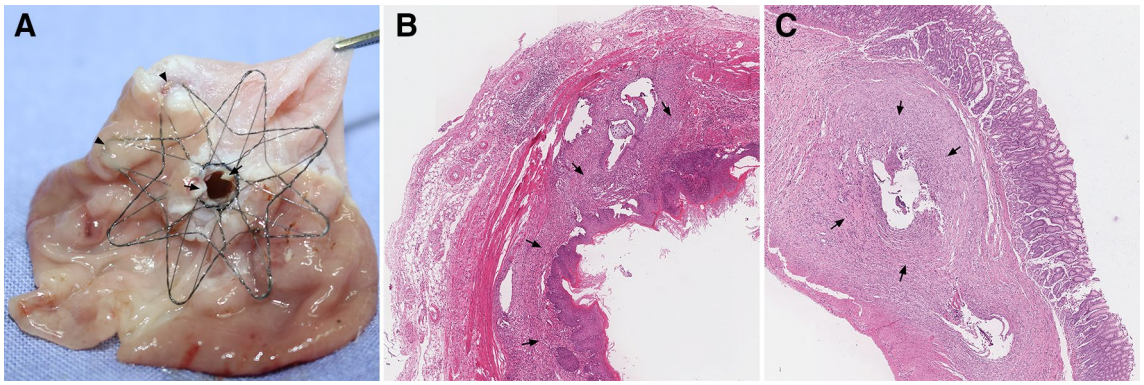

Fig. 6 Gross inspection and histologic analysis 4 weeks after double-disk ISD placement. **A** A photograph showing mild luminal strictures near the esophagogastric junction (arrows) and two of the protruding areas where the disk became embedded in the gastric wall (arrowheads). **B** A hematoxylin and eosin-stained section of the lower esophagus near the esophagogastric junction showing granulation tissue formation (arrows). Note: original magnification = ×20. **C** A hematoxylin and eosin-stained section of the stomach at the site of one of the protruding areas of the disk showing granulation tissue formation (arrows). Note: original magnification = ×20

histologic analysis showed granulation tissue formation but no perforation or ulceration in these areas.

Discussion

The ISD was developed as a minimally invasive treatment option for severe obesity, but it may also be used in a relatively large segment of the population with moderate obesity. In this study, we found that both SD and DD ISDs significantly reduced food intake and suppressed body weight gain in a rodent model. In 2009, a group announced that the Full Sense Device resulted in a 28.5% excess weight loss (EWL) in three patients over 6 weeks [7]. Furthermore, they announced that an 80% EWL was achieved during a 6-month trial in an unknown number of subjects, without any significant adverse events. Moreover, they claimed these results were backed by a randomized trial and follow-up crossover trial design. However, no peer-reviewed human data have been published until now. Recently, Park et al. [13] reported their preliminary results regarding three types of ISDs (constructed in-house) in a porcine model. They confirmed that ISD placement was technically feasible and safe, but they could not report definite conclusions with regard to the effect of an ISD on food intake and body weight gain due to a small sample size. In addition to confirming the effect of an ISD on food intake and body weight gain in a rodent model, we found that a double-disk ISD was more effective than a single-disk ISD. This suggests that the degree of pressure applied to the gastric cardia by the ISD is correlated with its effect on food intake and weight loss.

The safety and retrievability of ISDs must be assured before clinical usage. In this study, one rat in the double-disk group died due to gastric perforation. In addition, granulation tissue formation occurred in all animals in both ISD groups. These results were most likely attributed to the traumatic tips of the disk part and the bare design of the ISD. Therefore, the disk part of the ISD should be redesigned to make the tips less traumatic, and the ISD should be fully covered. The retrievability of the ISD would also improve as a result of the covering membrane, but at the cost of increasing the risk of device migration. Park et al. [13] showed that a fully covered ISD without barbs, a fully covered ISD with barbs, and an uncovered ISD with barbs presented device migration rates of 100%, 100%, and 67%, respectively, despite endoscopic clipping. Surgical fixation by means of open or laparoscopic sutures could prevent device migration but would increase the invasiveness of the procedure. Alternatively, less invasive options, such as endoscopic and gastropexy sutures, could be used to prevent device migration [14, 15]. However, these methods would affect the retrievability of the ISD, and therefore, biodegradable ISDs may be preferred over fully covered ISDs.

Bariatric surgery was initially believed to induce weight loss by mechanical restriction and malabsorption, but it is now evident that physiological alterations in hormone regulation, gut neuroendocrine signaling, gastrointestinal motility, and autonomic nervous system signaling also play an important role [16–18]. In this study, the animals in the ISD groups had significantly reduced food intake; the causes of this may include the following: (i) stimulation of the vagal afferent receptors and the vagus nerve distributed around the cardia; (ii) suppression of ghrelin secretion; and (iii) pain caused by continuous pressure applied to the gastric cardia. Given that no animals in the ISD groups showed any signs of pain (e.g., arched back posture or dysphoria), it is unlikely that food intake decreased due to pain only. Ghrelin has been recognized as the only hormone that potently stimulates appetite [19–21]. Although we found no significant change in fasting serum ghrelin from baseline in the ISD groups, it remains unclear whether ISD affected

ghrelin secretion because ghrelin levels were based on several single time points rather than time course data. Further studies (e.g., vagal activity assessment, time course serum ghrelin, and 24-h metabolic measurement) are necessary for elucidating the mechanisms by which ISDs work (e.g., vagal- or ghrelin-mediated satiety or hunger).

This study has several limitations to note. First, growing rats were used instead of obese rats, but it is much more difficult to suppress body weight gain in growing rats than in obese rats. Second, the follow-up period was limited to 4 weeks. Third, other hormones involved in energy homeostasis, such as gastrin, glucagon-like peptide-1, peptide YY, and leptin, were not assessed [22, 23]. Fourth, a meal test or a 24-h metabolic measurement was not performed. Finally, the effects of the ISD on the gastric neuro-feedback system and motility were not evaluated.

In conclusion, the ISD reduced food intake and suppressed body weight gain in a rodent model. In addition, the degree of pressure applied to the gastric cardia by the ISD was correlated with its effect on food intake and weight loss. Further studies are warranted to confirm the results of this study in obese rats and elucidate the mechanisms by which ISDs work.

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Compliance with ethical stanadrds

Disclosures Yingen Luo, Xiaowu Zhang, Jiaywei Tsauo, Hwoon-Yong Jung, Ho-Young Song, He Zhao, Jingui Li, Tao Gong, Peng Song, and Xiao Li have no conflicts of interest or financial ties to disclose.

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

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