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A new obesity treatment method that does not require restriction in food intake and organ resection

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The study was approved by the Experimental Animals Local Ethics Committee of Bezmialem Vakif University (April 2021/no: 21-046).

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Abstract

Background/Aim: There are numerous treatment methods available for obesity, with bariatric surgery being the most effective. However, these techniques come with the risk of serious complications. This study presents a novel obesity treatment device that can shorten the length of the small intestine without the need for surgical intervention.

Methods: Our new device comprises three main components: a 25 cm long rope, with one end attached to a 1 cm diameter plastic ring and the other end attached to a 2 mm diameter, 5 g sphere. Twenty-one male Wistar albino rats (6 months old, mean weight 400 g, outbred) were divided into three equal groups. Laparotomy and gastrotomy were performed on the subjects in Group 1, and all three parts of the device were placed into the gastrointestinal tract. In Group 2, only the plastic ring was placed in the stomach, and in Group 3, only a gastrotomy was performed. All subjects were followed for 3 months, during which their body weight, serum ghrelin, leptin, and nesfatin-1 levels were recorded, and the amount of food they consumed was measured. After sacrificing the animals, the stomach, proximal, and distal intestines were resected for histopathological evaluation.

Results: The subjects in Group 1 experienced weight loss, whereas those in Groups 2 and 3 showed statistically significant weight gain (P<0.001 and P=0.022, respectively). Serum ghrelin levels were significantly increased in Groups 1 and 3 (P=0.015 and 0.031, respectively), while serum leptin levels were significantly decreased in Group 1 (P=0.015). Plasma nesfatin-1 levels were significantly higher in Group 1 compared to the other groups (P=0.014). There was no statistically significant difference in feed consumption between the groups. Histopathological examination revealed significantly higher fibrosis and inflammation scores in the proximal small intestine of Group 1 compared to the other groups (P=0.008 and P=0.005, respectively).

Conclusions: This new device facilitates rapid and effective weight loss without the need for restricting oral food intake or organ resection. Changes in serum ghrelin, leptin, and nesfatin-1 levels did not affect these results. We hypothesize that the effective weight loss is linked to the shortening of the small intestine length. Our future plans involve modifying the device for endoscopic application in humans.

Keywords: obesity, treatment, new, medical device, endoscopy, bariatric

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Introduction

According to data from the World Health Organization (WHO) [1], obesity is recognized as the most serious health problem affecting humanity. It is a critical risk factor for cardiovascular diseases, diabetes, and cancer. Additionally, obesity reduces life expectancy by 5–20 years [2]. Various treatment options exist for combating obesity, ranging from dietary interventions to radical organ resections [3]. The primary approach to obesity treatment involves limiting calorie intake orally. A weight loss of 5–10% achieved through diet has been shown to reduce disease risk and have positive effects on health for individuals who are overweight or obese [4,5]. However, many individuals struggle to adhere to diets due to individual, medical, or psychological factors. In such cases, endoscopic or surgical interventions have been employed [6]. Surgical techniques can be classified as restrictive, malabsorptive, or a combination of both [7-9].

Due to its ability to deliver faster results compared to other treatment options, obesity surgery has become the method of choice in contemporary practice [1,10]. However, like any surgical procedure, it carries inherent risks of complications, some of which can be life-threatening. Additionally, obesity surgery is a costly treatment option [10]. This study introduces a novel obesity treatment approach that has not been previously described in the literature. Notably, this treatment can be administered endoscopically without the need for surgical intervention when applied to human subjects.

Materials and methods

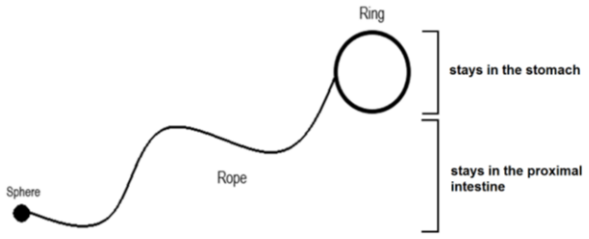
Consent was obtained from the Experimental Animals Local Ethics Committee of Bezmialem Vakif University (April 2021, no: 21-046). For the power analysis, we determined a sample size of 21 male Wistar albino rats (mean weight: 400 g), which were randomly assigned to three equal groups (n = 7). This allocation ensured a 95% confidence interval and a significance level of $P<0.05$. The rats were fed a standard pellet feed specifically designed for small experimental animals and were housed in cages made of plastic with stainless steel wire ceilings. The cages were layered with wood shavings and maintained on a 12-h light-dark cycle. Prior to surgery, all subjects underwent an overnight fasting period and were weighed. Additionally, 2 ml of blood was collected from each rat to measure serum levels of ghrelin, leptin, and nesfatin-1.

A new medical device (Figure 1) was utilized in this study, which was designed and patented by our team (Turkish Patent Institute Application No: 2019/00613). Our device comprises three main components: a 25 cm long rope, with one end connected to a plastic ring measuring 1 cm in diameter, and the other end attached to a 5 g sphere with a diameter of 2 mm.

The device structure consists of three main parts:

- **The stomach ring:** This ring is made of biologically inert plastic, measuring 2 mm in thickness and 10 mm in diameter. Its thinness ensures it does not impede the passage of food from the stomach to the duodenum, while its diameter is sufficiently large to prevent it from passing through the pylorus. The ring is connected to the rope, which in turn is attached to the sphere located in the small intestine.
- **The connecting rope:** A 25 cm long surgical rope, 3/0 in thickness, made of polypropylene, serves as the connection between the ring and the sphere. One end of the rope is connected to the ring inside the stomach, and the other end is attached to the sphere in the small intestine.
- **The small intestine sphere:** Constructed from stainless steel, this sphere has a diameter of 2 mm and weighs 5 g. It features a central hole for attaching the rope. The sphere is designed with a small diameter and a smooth surface to prevent the passage of food through the small intestine and to minimize any potential damage to the mucosa.

Figure 1: Graphical view of the device



All rats in the study underwent a midline abdominal incision while under general anesthesia. A 10 mm incision was made on the anterior surface of the stomach (gastrotomy). In Group 1 (n = 7), the ring, sphere, and rope were inserted into the stomach through this incision. The sphere was then carefully guided through the pylorus into the second part of the duodenum using forceps. Subsequently, the gastrotomy incision was sutured using 3/0 vicryl, and the abdominal incision was closed with 3/0 polypropylene. In Group 2 (n = 7), the same procedures were performed, but only the ring was placed into the stomach. In Group 3 (n = 7), only the gastrotomy procedure was carried out, with nothing inserted into the stomach.

Following the surgery, the subjects were provided with standard pellet food, and their daily food intake was measured. Weekly weight measurements were taken for all subjects. After a three-month follow-up period, the subjects were euthanized, and their stomachs and small intestines were excised for histopathological examinations. Blood samples were collected from all subjects on both day 0 (before surgical operations) and day 90 (after euthanization) to measure serum ghrelin, leptin, and nesfatin-1 levels.

Statistical analysis

The parameters of the rats included in the study were reported as mean (SD), and statistical analyses were conducted using GraphPad Prism 8.0 statistical software. Non-parametric evaluations between groups were performed using the Kruskal-Wallis test, and for determining statistical significance, Dunn's multiple comparison tests were applied. In-group statistical analysis of non-normally distributed groups was carried out using the Wilcoxon signed-rank test. For comparisons of data with normal distribution between the groups, the One-Way analysis of variance (ANOVA) test was utilized, and Tukey's post-hoc test was applied to determine statistical significance. The paired t-test was used for the statistical analysis of groups with a normal distribution. Histopathological examinations involved comparisons between groups using the Kruskal-Wallis test, and subgroup analyses were performed using the Mann-Whitney test to assess differences between the groups.

Results

Weights increased in Groups 2 and 3 but decreased in Group 1 (Table 1). The differentiation between Group 1 and Group 3 was statistically significant (P<0.001). Food consumption was not statistically different among all groups during the 3-month follow-up period: Group 1 consumed 59.02 g/day, Group 2 consumed 63.81 g/day, and Group 3 consumed 69.03 g/day.

Table 1: In-group and intergroup weight changes in the preoperative and postoperative periods. (SD: Standard derivation, *: <0.05).

	Group 1	Group 2	Group 3	*P*-value (0ne way ANOVA)
Preoperative weight mean (SD)	427.70 (49.75)	387.40 (54.16)	389.00 (56.83)	0.305
Postoperative weight mean (SD)	366.40 (71.34)	408.70 (70.39)	413.30 (49.32)	0.347
Weight differences (%)	-14.3%	+5.4%	+6.1%	
***P*-value (paired T-Test)**	<0.001*	0.079	0.022*	

Postoperative ghrelin values significantly increased in both Group 1 and Group 3 compared to their respective preoperative values (Table 2). A significant difference in plasma leptin levels was observed during the preoperative period (P=0.010). Subgroup analysis revealed that this difference was primarily attributed to variations between Group 2 and Group 3 (P=0.008). Only Group 1 exhibited a significant decrease in postoperative plasma leptin levels (P=0.015) (Table 3). Plasma nesfatin-1 levels were significantly higher in Group 1 compared to the other groups (P=0.014). In the group analysis, no changes were observed between the preoperative and postoperative periods in any of the groups (Table 4).

Table 2: Preoperative and postoperative in-group and intergroup plasma ghrelin changes. (SD: Standard derivation, *: <0.05).

	Group 1	Group 2	Group 3	*P*-value (Kruskal-Wallis)
Preoperative ghrelin mean (SD)	11.27 (2.35)	22.74 (18.63)	10.62 (5.81)	0.524
Postoperative Ghrelin mean (SD)	44.17 (22.66)	31.18 (25.21)	23.30 (10.94)	0.202
***P*-value (Wilcoxon)**	0.015*	0.937	0.031*	

Table 3: Preoperative and postoperative in-group and intergroup plasma leptin changes. (SD: Standard derivation, *: <0.05).

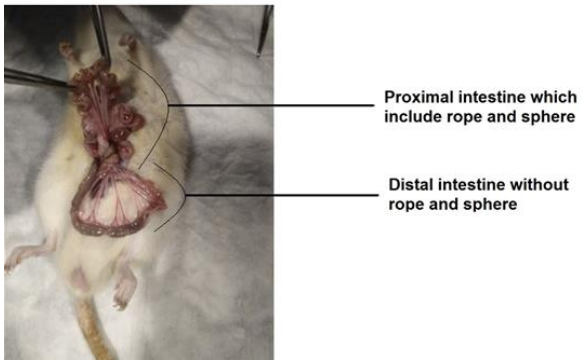
	Group 1	Group 2	Group 3	*P*-value (Kruskal-Wallis)
Preoperative Leptin mean (SD)	3.07 (1.08)	4.12 (1.06)	2.19 (0.87)	0.010*
Postoperative Leptin mean (SD)	1.48 (0.76)	2.97 (1.61)	1.62 (0.85)	0.129
***P*-value (Wilcoxon)**	0.015*	0.296	0.375	

Table 4: Preoperative and postoperative in-group and intergroup plasma nesfatin changes (SD: Standard derivation, *: <0.05).

	Group 1	Group 2	Group 3	*P*-value (Kruskal-Wallis)
Preoperative Nesfatin mean (SD)	204.70 (60.46)	259.10 (101.50)	178.70 (34.20)	0.277
Postoperative Nesfatin mean (SD)	259.3 (94.78)	156.50 (63.40)	107.6 (86.39)	0.014*
***P*-value (Wilcoxon)**	0.296	0.078	0.156	

Macroscopic examination showed that the small intestines in Group 1 exhibited folding and shortening, while no changes were observed in the other groups (Figure 2). None of the subjects displayed signs of intestinal obstruction, such as kinking, dilatation, or peritoneal adhesion.

Figure 2: Laparotomy image of any Group 1 animal. The upper part of the image belongs to proximal and the lower part of the image belongs to the distal small intestine. It is obvious that the proximal small intestine is shortened and folded like an accordion over the intraluminal.



Histopathological evaluation of the stomach, proximal, and distal small intestines was conducted to assess fibrosis (Table 5) and inflammation (Table 6). The histopathological examination of gastric and distal small intestine specimens across all subjects revealed no significant differences in fibrosis and inflammation scores (P=0.061 and P=0.183, respectively, for fibrosis; P=0.424 and P=0.165, respectively, for inflammation). However, a significant difference was observed between the groups regarding fibrosis and inflammation in the proximal small intestine (P=0.001 and P=0.002, respectively). Subgroup analyses indicated that Group 1 had significantly higher fibrosis and inflammation scores than the other groups (P=0.008 and P=0.005, respectively).

Table 5: Classification of fibrosis histopathologically

Grade 0	No fibrosis (no fibroblast and / or collagen fibers)
Grade 1	Minor fibrosis (few fibroblasts and / or collagen fibers)
Grade 2	Moderate fibrosis (more fibroblast and / or collagen fibers)
Grade 3	Advanced fibrosis (many fibroblasts and / or collagen fibers present)

Table 6: Classification of inflammation histopathologically

Grade 0	A few lymphocytes and plasmacytic cell in the mucosa
Grade 1	Increased number of mononuclear inflammatory cell infiltrations in the submucosa and lamina propria as a fallout
Grade 2	Increased number of mononuclear inflammatory cell infiltrates in the submucosa, lamina propria, and superficial muscular tissue, with partially aggregate-forming
Grade 3	Intense mononuclear inflammatory cell infiltration in all transmural layers

Discussion

Lifestyle regulation, diet, exercise, drug treatment, psychological, familial, and social support, as well as surgical interventions, are utilized in the current treatment of obesity [11]. Typically, obese patients can lose a significant amount of weight with an energy-restricted diet; however, they struggle to maintain this success in the long term [12,13]. Research shows that obese patients who lose weight through dieting tend to regain approximately 70% of the lost weight within 2 years [6,14]. Consequently, surgical treatment has become a frequently chosen option. Various techniques, such as organ resections, diversions, or bypass procedures, are employed in obesity surgery. However, these procedures come with serious complications and risks, including gastrointestinal tract disruption, anastomosis leakage, hemorrhage, pulmonary emboli, stenosis, infection, and sepsis, as well as bowel, liver, or major vessel injuries [15-20].

In this study, we evaluated a new patented medical device developed by our team, which primarily functions through the malabsorptive mechanism but possesses distinct characteristics. It is well-known that various types of food, particularly those high in sugar, are absorbed in the proximal small intestine. The extent of the small intestine's surface area

directly affects food absorption. Previous research has demonstrated that patients who undergo small bowel resection experience increased weight loss in relation to the length of the resected segment [21,22]. In this project, we aimed to decrease the surface area of the proximal small intestine without resorting to surgical intervention. We hypothesized that peristaltic movements would attempt to propel the sphere distally. However, the sphere is tethered to the ring by a rope, preventing the ring from passing through the pylorus. Consequently, tension arises between the ring and the sphere, causing the proximal small intestines to fold in a manner resembling an accordion around the intraluminal rope (see Figure 2). As a result, the absorptive area of the proximal small intestine is significantly reduced, even though oral food intake continues, leading to weight loss.

According to our hypothesis, we observed a statistically significant increase in weight among participants in Groups 2 and 3, whereas Group 1 showed a significant decrease in weight. It is important to note that food consumption among the study participants remained similar across all groups.

We assessed the changes in serum levels of three hormones (ghrelin, leptin, and nesfatin-1) associated with obesity before and after the intervention. Ghrelin is a hormone that typically rises during fasting, suppressing the postprandial period, and is considered a target in obesity treatment [23,24]. Increased basal ghrelin levels have been linked to increased eating behavior [25]. In this study, we observed elevated serum ghrelin levels in Groups 1 and 3. Consequently, despite participants in Group 3 gaining weight due to increased food intake, those in Group 1 experienced weight loss despite consuming comparable amounts of food. This finding aligns with the expected effects of elevated ghrelin levels.

Leptin is a hormone that typically suppresses appetite and food intake in individuals with normal weight, but in overweight and obese individuals, it can actually stimulate an increase in oral food intake [26-28]. Nesfatin-1, on the other hand, is an anorexigenic hormone that has been shown to reduce oral food intake by interacting with dopaminergic neurons [29,30]. Nesfatin-1 plays a role in maintaining body weight balance by reducing both oral food intake and gastrointestinal peristalsis [31]. In our study, we observed a decrease in serum leptin levels in Group 1, while Nesfatin-1 levels remained similar across all groups. However, when we analyzed the hormonal changes collectively among all subjects, we found that these hormonal changes did not significantly contribute to the mechanisms of weight loss.

In our view, the main mechanism behind the observed weight loss in this study is the reduction in the length of the proximal intestine, which leads to a decreased absorption area in the proximal small intestine. Our opinion is further supported by the results of the histopathological evaluation, which revealed significantly higher scores for fibrosis and inflammation in the proximal small intestine of Group 1.

The technique employed in this study offers a notable advantage in terms of its reversibility without the need for surgical intervention. If required, the rope can be cut endoscopically, allowing the rope and sphere to pass through the anus, while the ring can be removed endoscopically through the mouth. Furthermore, the amount of weight loss can be individually adjusted by modifying the length of the rope.

A significant limitation of this study was that due to the small size of the rats, we could not perform the procedures endoscopically and instead had to resort to laparotomy and gastrotomy. This limitation arises from the fact that our study subjects were small animals, and if larger animals were available for endoscopic procedures, it would have allowed for more precise interpretations regarding the applicability of our findings to humans.

Another limitation of this study is that we could not observe the potential diarrhea-inducing effect of the device in rats, as their defecation is continuous. However, it is important to note that the application of this device in humans may lead to diarrhea due to the shortened length of the small intestine.

The future research proposal for this study entails the development of biocompatible materials specifically designed for human anatomy, allowing for their endoscopic application. Once these materials are successfully produced, a phase 1 study can be initiated involving a limited number of morbidly obese patients, following the approval of the human ethics committee.

Conclusion

In conclusion, we have demonstrated the effectiveness of a novel obesity treatment technique that eliminates the need for surgical intervention, does not compromise gastrointestinal integrity, and does not impose restrictions on oral food intake. Our hypothesis regarding the weight loss outcomes being associated with the shortening of the small intestine length is supported by these promising results. However, to advance this device toward clinical applicability in humans, further development is required to create an endoscopically suitable form. Subsequently, small-scale studies should be conducted to evaluate its efficacy and safety in human subjects.

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