

Original Article

Effect of left or right gastric artery interventional embolization on obesity and ghrelin/leptin expression in pigs

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Received December 29, 2020; Accepted January 27, 2021; Epub May 15, 2021; Published May 30, 2021

Abstract: Objective: To investigate the effect of left or right gastric artery interventional embolization on obesity and ghrelin/leptin expression in pigs. Methods: Thirty-two female Wuzhishan pigs aged 3-4 months were randomly divided into four groups, with eight pigs in each group: obesity + left gastric artery embolization group, obesity + right gastric artery embolization group, obesity + sham surgery group and healthy control group. The body weight and serum levels of ghrelin, leptin, interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) before the operation, one month and three months after the operation, and the gastric pathology three months after the operation were compared. Results: The preoperative body weight, ghrelin level, leptin level, IL-6 level and TNF- α level of the obesity + sham surgery group, obesity + left gastric artery embolization group and obesity + right gastric artery embolization group were higher than those of the healthy control group (all $P < 0.05$). One month after the operation, the body weight, ghrelin level, leptin level, IL-6 level and TNF- α level of the obesity + sham surgery group, obesity + left gastric artery embolization group and obesity + right gastric artery embolization group were higher than those of the healthy control group. The body weight, ghrelin level, IL-6 level and TNF- α level of the obesity + sham surgery group were higher than those of the obesity + left artery embolization group and obesity + right gastric artery embolization group (all $P < 0.05$). Three months after the operation, the body weight, ghrelin level, leptin level, IL-6 level and TNF- α level of the obesity + sham surgery group were higher than those of the obesity + left artery embolization group, obesity + right artery embolization group and the healthy control group (all $P < 0.05$). Conclusion: Left or right gastric artery interventional embolization in pigs can effectively reduce body weight, which may be related to the reduced secretion of ghrelin, leptin and inflammatory factors. However, the clinical application and safety of left or right gastric artery embolization still need further study.

Keywords: Gastric artery embolization, pigs, intervention, obesity, ghrelin/leptin, inflammatory factors

Introduction

Obesity is a medical condition where patients have a body mass index of ≥ 28 kg/m². The incidence of obesity worldwide has increased with the increase of high-calorie intake and the decrease in exercise. Obesity has become a global public problem and has been on the rise in China [1]. Previous studies have found that the changes in the internal environment of the obese patients cause an increased burden of heart and kidney and gastrointestinal flora imbalance, which clinically manifests as obesity combined with hypertension, diabetes, nephropathy and gastrointestinal diseases relat-

ed to intestinal flora imbalance [2-4]. Abnormal hormone secretion and metabolic indexes can be found in obese patients, among which ghrelin and leptin are the most relevant indicators. Ghrelin can promote gastrointestinal motility, increase the feeling of hunger and increase food intake, while leptin is another obesity-related hormone [5]. A previous study showed that bariatric surgery might act through the reduction of ghrelin and leptin levels [6]. Studies have found that the chronic inflammatory response in adipose tissue is also an essential factor to promote the occurrence and development of obesity, which may be related to the secretion of inflammatory factors after adipo-

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cyte hypertrophy [7-9]. The production of inflammatory factors not only promotes obesity but also induces complications [10].

For the treatment of obesity, weight loss is particularly critical, and diet control and exercise are the most effective ways for obese patients to control their weight [4]. For obese patients who still have poor weight control after diet and exercise, drugs targeting related weight loss mechanisms can be used [11]. The above treatment plans are sufficient for most obese patients, but some patients still have low efficacy after diet, exercise and drug intervention. Therefore, gastric surgical intervention has become the treatment scheme for these obese patients. A study showed that gastric surgical intervention had a better effect on obese patients with diabetes mellitus and could effectively reduce cardiovascular events [12]. Although the effect of surgical treatment is significant, the trauma after surgery is extensive and postoperative complications often occur. Ghrelin is mainly secreted by the gastric fundus [13]. The blood supply of the gastric fundus is mostly from the left and right gastric arteries. A study showed that embolization of the left gastric artery could inhibit the secretion of ghrelin at the gastric fundus to achieve weight loss [14]. However, a study found that nearly half of the experimental animals had ulcers in the gastric body and antrum after left gastric artery surgery, which may be related to ectopic embolism or stress ulcer. Despite the curative effect of left gastric artery embolization, its safety still needs further study [15].

The right gastric artery is also the main branch of the gastric fundus blood supply. We determined whether the right gastric artery could be embolized, so the left gastric artery could be preserved to reduce the blood supply to the gastric fundus, and whether the goal of weight loss could also be achieved. We also compared its postoperative safety of left gastric artery embolization. Wuzhishan pigs are similar to humans in genes, gastric artery distribution and gastric ghrelin level. Highly homozygous Wuzhishan pigs can be used as animal models of multiple human diseases, so we selected Wuzhishan pigs as the experimental animal object of gastric artery embolization [16]. There is no experimental study on the efficacy and safety of left or right gastric artery embolization

on obesity. In this study, we observed the effect of left and right gastric artery embolization on obesity and ghrelin/leptin expression in Wuzhishan pigs.

Materials and methods

Establishment of the obesity model of Wuzhishan pigs

This study was approved by the animal ethics committee of our hospital. Thirty-two healthy female Wuzhishan pigs aged 3-4 months were randomly divided into four groups with eight pigs in each group: obesity + left gastric artery embolization group, obesity + right gastric artery embolization group, obesity + sham surgery group and healthy control group. The healthy control group was fed a normal diet, and the three obesity groups were fed a high-fat diet (the normal diet and high-fat diet were both provided by Institute of Animal Science and Veterinary Medicine, Hainan Academy of Agricultural Sciences). The obesity model standard: the pig's weight exceeded the standard weight by no less than 30% [16].

Interventional operation

Femoral artery catheterization: The obesity model pigs were treated with interventional embolization and fasted for 12 hours before the operation. The operation procedures included anesthesia, preoperative preparation, femoral artery puncture angiography and angiographic drug embolization. Atropine (Wuhu Kangqi Pharmaceutical Co., Ltd., China) was injected intramuscularly with a dose of 0.03 mg/kg to the buttock muscles of the 24 Wuzhishan pigs in the obesity groups. About 10 minutes later, a dose of 0.05 mL/kg Sumianxin injection (Institute of Animal Science and Veterinary Medicine, Hainan Academy of Agricultural Sciences) was intramuscularly injected. After the drug took effect, pigs were in a quiet state, and a dose of 7 mg/kg ketamine (Zhejiang Jiuxu Pharmaceutical Co., Ltd., China) and a dose of 0.3 mg/kg diazepam injection (National Pharmaceutical Group Rongsheng Pharmaceutical Co., Ltd, China) were intravenously injected until the pigs were in an entirely sleep state. The pig's right femoral artery was selected as the routine puncture artery. The pig was fixed supine on the interventional operating table. The operation area was shaved, and

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the local disinfection was carried out. The surgical towel was covered, and a transverse incision with a length of 2 cm was made at about 4-5 cm above the knee joint. The subcutaneous tissue was separated bluntly until the superficial branch of the femoral artery was dissociated about 3-4 cm, and the distal end of the femoral artery was ligated. The forearm of the femoral artery was punctured with a fine needle. After the puncture, a guide wire was inserted, and a 4F arterial sheath (Oriental Medical Equipment Co., Ltd.) was inserted along the guide wire with a proximal direction, and the arterial sheath was fixed after insertion. A 4F catheter was inserted along the arterial sheath for celiac arteriography. The 4F catheter was then changed to a 3F microcatheter (Minimally Invasive Medical Devices Co., Ltd, Shanghai, China). The 3F microcatheter was inserted into the left or right gastric artery to complete the angiography. Then, 500 μ m polyvinyl alcohol (PVA) particles (Hangzhou Ailikang Medical Technology Co., Ltd., China) were injected into the left or right gastric artery for embolization. Normal saline was respectively injected into the left and right gastric arteries in the sham-operated group. The embolization standard was that the left and right gastric arteries were completely occluded. After the operation, the catheter and the arterial sheath were pulled out, and the proximal end of the femoral artery was ligated. Sutures were made to the outermost skin layer by layer. The pigs were orally given metoclopramide tablets (Sichuan Dazhong Pharmaceutical Co., Ltd., China; 1 tablet/time) and amoxicillin (Harbin Pharmaceutical Group Pharmaceutical General Factory, China; 2 tablets/time), once a day for 10 days. The suture was removed 10 days after the operation.

Outcome measures

Primary outcome measures: Weight measurement. The fasting weight of pigs was measured, and 5 milliliters of venous blood were collected from the dorsal superficial vein of the forelimb at 08:00 am before the operation, seven days and one month after the operation. Serum ghrelin/leptin levels were detected by enzyme-linked immunosorbent assay (ELISA; Shanghai Enzyme Technology Co., Ltd., China).

Secondary outcome measures: Five milliliters of venous blood were collected from the fore-

limb's dorsal superficial vein at 08:00 am before the operation, one month and three months after the operation. IL-6 and TNF- α levels were detected by the enzyme-linked immunosorbent assay (ELISA).

Three months after the operation, 32 pigs were injected with 100 mg of excessive pentobarbital sodium (Shanghai Shangyao Xinya Pharmaceutical Co., Ltd., China) and killed. Their stomachs were opened, and pathological sections were made from different parts of the stomachs to observe the effect of left and right gastric artery embolization on the gastric mucosa.

Statistical analysis

SPSS 17.0 software was used for statistical analysis. Continuous variables were expressed as mean \pm standard deviation ($\bar{x} \pm sd$). One-way ANOVA was used to detect the differences among groups, and the Turkey method was used to compare the differences between the two groups. $P < 0.05$ was considered significantly different.

Results

Comparison of the body weight changes among four groups of experimental pigs

The body weight of the obesity + sham surgery group, obesity + left gastric artery embolization group and obesity + right gastric artery embolization group was higher than that of the healthy control group before the operation (all $P < 0.001$). The body weight of the obesity + sham surgery group, obesity + left gastric artery embolization group and obesity + right gastric artery embolization group was higher than that of the healthy control group one month after the operation, and the body weight of the obesity + sham surgery group was higher than that of the obesity + left gastric artery embolization group and obesity + right gastric artery embolization group (all $P < 0.05$). Three months after the operation, the body weight of the obesity + left gastric artery embolization group and obesity + right gastric artery embolization group decreased significantly ($P < 0.001$), and the body weight of the obesity + sham surgery group was higher than that of the obesity + left gastric artery embolization group, obesity + right gastric artery embolization group, and healthy control group

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Table 1. Comparison of the body weight changes among four groups of experimental pigs ($\bar{x} \pm sd$)

Weight	Before operation (kg)	One month after operation (kg)	Three months after operation (kg)
Obesity + sham surgery group (n=8)	12.45±0.89***	13.72±0.93***,#	13.95±0.99***,###,@@
Obesity + left gastric artery embolization group (n=8)	12.54±0.91***	10.96±0.86***	10.61±0.71
Obesity + right gastric artery embolization group (n=8)	12.61±0.97***	11.21±0.87***	10.91±0.71
Healthy control group (n=8)	9.52±0.53	9.68±0.59	10.01±0.61
F	25.611	33.741	15.692
P	<0.001	<0.001	<0.001

Note: Compared with the healthy control group, ***P<0.001; compared with obesity + left gastric artery embolization group, #P<0.05, ###P<0.001; compared with obesity + right gastric artery embolization group, @@P<0.01.

Table 2. Comparison of serum ghrelin levels among four groups of experimental pigs ($\bar{x} \pm sd$)

Ghrelin (pg/mL)	Before operation	One month after operation	Three months after operation
Obesity + sham surgery group (n=8)	1413.63±116.21***	1437.52±124.37***,##	1458.71±122.48***,###,@@
Obesity + left gastric artery embolization group (n=8)	1429.34±121.37***	1297.72±115.39**	1192.11±107.67
Obesity + right gastric artery embolization group (n=8)	1428.74±119.47***	1349.37±116.73**	1267.26±119.13
Healthy control group (n=8)	1102.23±95.34	1124.43±102.49	1131.36±98.14
F	16.081	10.512	12.841
P	<0.001	<0.001	<0.001

Note: Compared with the healthy control group, **P<0.01, ***P<0.001; compared with obesity + left gastric artery embolization group, *P<0.05, **P<0.01; compared with obesity + right gastric artery embolization group, #P<0.05, ##P<0.01.

(all P<0.01), but there was no difference in the body weight among the obesity + left gastric artery embolization group, obesity + right gastric artery embolization group and healthy control group (P>0.05). See **Table 1**.

Comparison of serum ghrelin levels among four groups of experimental pigs

The ghrelin level of the obesity + sham surgery group, obesity + left gastric artery embolization group and obesity + right gastric artery embolization group was higher than that of the healthy control group before the operation (all P<0.001). One month after the operation, the ghrelin level of the obesity + sham surgery group, obesity + left gastric artery embolization group and obesity + right gastric artery embolization group was higher than that of the healthy control group, and the ghrelin level of obesity + sham surgery group was higher than that of obesity + left gastric artery embolization group and obesity + right gastric artery embolization group (all P<0.05). Three months after the operation, the ghrelin level of the obesity + sham surgery group was higher than that of obesity + left artery embolization group and

healthy control group (both P<0.01), but there was no difference in ghrelin level among the obesity + left gastric artery embolization group, obesity + right gastric artery embolization group and healthy control group (P>0.05). See **Table 2**.

Comparison of serum leptin levels among four groups of experimental pigs

The leptin level of the obesity + sham surgery group, obesity + left gastric artery embolization group and obesity + right gastric artery embolization group was higher than that of the healthy control group before the operation (all P<0.01). One month after the operation, the leptin level in the obesity + sham surgery group, obesity + left gastric artery embolization group and obesity + right gastric artery embolization group was higher than that in the healthy control group (all P<0.05). Three months after the operation, the leptin level of the obesity + sham surgery group was higher than that of obesity + left gastric artery embolization group, obesity + right gastric artery embolization group and healthy control group (all P<0.05), but there was no difference in leptin level among obesity

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Table 3. Comparison of serum leptin levels among four groups of experimental pigs ($\bar{x} \pm sd$)

Leptin ($\mu\text{g/L}$)	Before operation	One month after operation	Three months after operation
Obesity + sham surgery group (n=8)	5.92±0.96**	5.96±0.94**	6.02±0.98**,#,@
Obesity + left gastric artery embolization group (n=8)	5.87±0.93**	3.71±0.84*	2.72±0.56
Obesity + right gastric artery embolization group (n=8)	5.94±0.78**	3.89±0.69*	3.09±0.54
Healthy control group (n=8)	2.31±0.42	2.32±0.43	2.41±0.45
F	40.331	23.031	50.081
P	<0.001	<0.001	<0.001

Note: Compared with the healthy control group, *P<0.05, **P<0.01; compared with obesity + left gastric artery embolization group, ##P<0.01; compared with obesity + right gastric artery embolization group, @P<0.05.

Table 4. Comparison of IL-6 levels among four groups of experimental pigs ($\bar{x} \pm sd$)

IL-6 (pg/mL)	Before operation	One month after operation	Three months after operation
Obesity + sham surgery group (n=8)	223.82±7.71***	217.23±7.32***,###,@@@	219.26±7.56***,###,@@@
Obesity + left gastric artery embolization group (n=8)	220.45±7.54***	159.73±4.92***	143.23±4.56
Obesity + right gastric artery embolization group (n=8)	219.23±7.22***	168.47±5.27***	146.23±4.82
Healthy control group (n=8)	131.23±3.43	133.23±3.82	134.36±4.23
F	359.81	327.61	420.12
P	<0.001	<0.001	<0.001

Note: Compared with the healthy control group, ***P<0.001; compared with obesity + left gastric artery embolization group, ###P<0.001; compared with obesity + right gastric artery embolization group, @@@P<0.001.

Table 5. Comparison of TNF- α levels among four groups of experimental pigs ($\bar{x} \pm sd$)

TNF- α (pmol/L)	Before operation	One month after operation	Three months after operation
Obesity + sham surgery group (n=8)	558.23±78.82***	556.62±77.34***,###,@@@	551.19±76.87
Obesity + left gastric artery embolization group (n=8)	551.23±75.82***	403.16±61.37***	279.28±53.22
Obesity + right gastric artery embolization group (n=8)	561.11±79.72***	431.23±65.18***	285.18±55.27
Healthy control group (n=8)	224.22±47.81	234.23±48.21	236.23±49.12
F	42.991	34.531	46.582
P	<0.001	<0.001	<0.001

Note: Compared with the healthy control group, ***P<0.001; compared with obesity + left gastric artery embolization group, ###P<0.001; compared with obesity + right gastric artery embolization group, @@@P<0.001.

+ left gastric artery embolization group, obesity + right gastric artery embolization group and healthy control group (all P>0.05). See **Table 3**.

Comparison of IL-6 levels among four groups of experimental pigs

The IL-6 level of the obesity + sham surgery group, obesity + left gastric artery embolization group and obesity + right gastric artery embolization group was higher than that of the healthy control group before the operation (all P<0.001). One month after the operation, the IL-6 level in the obesity + sham surgery group,

obesity + left gastric artery embolization group and obesity + right gastric artery embolization group was higher than that in the healthy control group (all P<0.001). Three months after the operation, the IL-6 level of the obesity + sham surgery group was higher than that of obesity + left gastric artery embolization group, obesity + right gastric artery embolization group and healthy control group (all P<0.001), but there was no difference in IL-6 level among obesity + left gastric artery embolization group, obesity + right gastric artery embolization group and healthy control group (all P>0.05). See **Table 4**.

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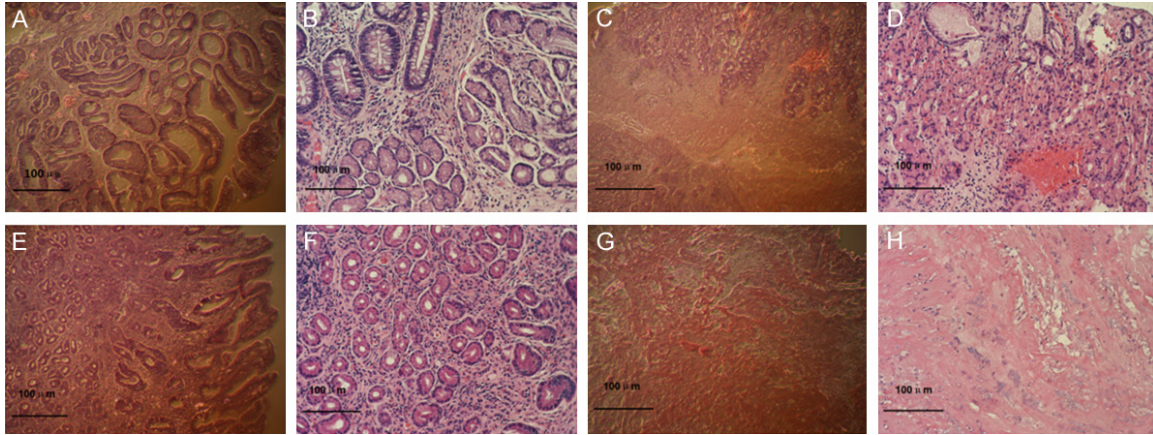


Figure 1. Pathological pictures of the stomach. A and B: Superficial gastritis (100×); C and D: Superficial gastritis with erosion (100×); E and F: Ulcer (100×); G and H: Ischemic necrosis (100×).

Comparison of TNF- α levels among four groups of experimental pigs

The TNF- α level of the obesity + sham surgery group, obesity + left gastric artery embolization group and obesity + right gastric artery embolization group was higher than that of the healthy control group before the operation (all $P < 0.001$). One month after the operation, the TNF- α level in the obesity + sham surgery group, obesity + left gastric artery embolization group and obesity + right gastric artery embolization group was higher than that in the healthy control group (all $P < 0.001$). Three months after the operation, the TNF- α level of the obesity + sham surgery group was higher than that of obesity + left gastric artery embolization group, obesity + right gastric artery embolization group and healthy control group (all $P < 0.001$), but there was no difference in TNF- α level among obesity + left gastric artery embolization group, obesity + right gastric artery embolization group and healthy control group (all $P > 0.05$). See **Table 5**.

Comparison of postoperative safety

The gastric pathological sections of the four groups of experimental pigs showed that the gastric mucosa in the healthy control group was basically normal. In the obesity + sham surgery group, there was one case of superficial gastritis. In the obesity + right gastric artery embolization group, there were two cases of superficial gastritis with erosion, one case of ulcer and one case of ischemic necrosis. In the obesity + left gastric artery embolization group,

there were two cases of superficial gastritis with erosion, one case of ulcer and two cases of ischemic necrosis. See **Figure 1**.

Discussion

Obesity causes inconvenience to patients' movement, affects the quality of life and induces a series of complications, which has become a public problem all over the world [17]. With the research on the pathogenesis of obesity, diet and exercise control, drug therapy and surgical treatment have become more mature. With the in-depth study of stomach anatomy and related hormones, minimally invasive techniques have become possible to treat obesity. Minimally invasive surgery has the characteristics of less trauma than traditional surgical treatments [14].

In this study, we found that the body mass index and the levels of ghrelin, leptin, IL-6 and TNF- α of the pigs decreased significantly after left or right gastric artery embolization. The clinical embolization technique of left gastric artery interventional therapy is mainly used in gastric bleeding diseases and has a significant effect on hemostasis under the microscope. A study found that in gastric hemorrhage patients treated with left gastric artery embolization or abdominal aorta embolization, weight loss both occurred during postoperative follow-up, especially in patients treated with left gastric artery embolization [18]. After clinical observation of the above phenomenon, some scholars put forward the idea of using gastric artery interventional embolization technology

to treat obesity. To further confirm the effect of gastric artery embolization on obesity, an animal experiment study was performed on pigs whose left gastric artery was embolized with sodium morrhuate or normal saline. Four weeks after the operation, the weight loss effect of the sodium morrhuate group was better than that of the normal saline group. This experiment proved that left gastric artery interventional embolization was beneficial to weight loss [19]. With the development of interventional embolization technology, different embolization dosage forms are used clinically. An experimental study found that after embolizing the left gastric artery with different dosage forms, the dogs' weight at 4 weeks after the operation was reduced to varying degrees, and the differences were statistically significant compared with the control group using normal saline embolization. The experiment also studied the relevant mechanism and found that the weight loss of dogs was accompanied by a significant decrease in ghrelin level and fat area [20]. In a clinical study, 5 obese patients were treated with left gastric artery embolization. After the operation, the body weight and leptin levels of the patients decreased significantly. In contrast, the ghrelin level increased slightly, which may be related to the activation of the negative feedback mechanism caused by left gastric artery embolization [21]. A previous study showed that inflammatory factors played an important role in the development of obesity, and it has been confirmed that adipose stem cells in obese rats can secrete a large number of inflammatory factors [22]. In another study involving obese patients and healthy volunteers, it was found that the levels of IL-6 and TNF- α in obese patients were significantly higher than those of healthy volunteers, which further confirmed the existence of a chronic inflammatory state in obese patients [23]. However, there are no reports on the treatment of obesity by right gastric artery embolization.

In a study on the safety of gastric artery embolization, one, two and four gastric vessels were embolized in three embolization groups respectively, and a gastric mucosal protective agent was used to compare the safety of the embolization groups and the un-embolized control group. Compared with the control group, the ghrelin in the four gastric vessels embolization group was significantly lower, and the level of ghrelin in one gastric artery embolization group was higher. Gastric ulcers occurred

in three of the six experimental pigs in the four gastric vessels embolization group (3/6), and two pigs in the two and one gastric vessels embolization groups (2/6) [24]. Another study showed that nearly half of the experimental pigs undergoing left gastric artery embolization developed gastric ulcers [15]. In this study, almost half of the experimental pigs had gastric lesions after left gastric artery embolization. Further research in this study found that the incidence of gastric lesions after right gastric artery embolization did not significantly decrease.

Shortcomings and prospects. This is an experimental study, and the sample size is small. We did not conduct clinical studies to further prove the effectiveness and safety of the left or right gastric artery embolization in obese patients. In the future study, the sample size should be expanded, and clinical research should be conducted to confirm the effect of left or right gastric artery embolization on obesity.

To sum up, the interventional embolization of the left or right gastric artery in pigs can effectively reduce weight, which may be related to the reduced secretion of ghrelin, leptin and inflammatory factors. However, the clinical application and safety of left or right gastric artery embolization still need further research.

Acknowledgements

This work was supported by Hainan Provincial Natural Science Foundation of China in 2018 (818MS135).

Disclosure of conflict of interest

None.

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