ORIGINAL ARTICLE

EARLY METABOLIC DISORDERS AND MORPHOLOGICAL CHANGES OF INTERNAL ORGANS AFTER GASTRIC BYPASS WITH ONE ANASTOMOSIS. EXPERIMENTAL STUDY

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ABSTRACT

The aim: To investigate morphofunctional changes in bone tissue, mucous membranes of different parts of the intestine, parathyroid glands, as well as changes in blood biochemical parameters depending on the length of the common loop in modeling gastric bypass with one anastomosis within 60 days.

Materials and methods: Modeling of obesity in males of white outbred rats (n = 50) which were induced high-calorie diet with high animal fat content. Weight was measured before the induced diet, 1,2,3 months after the start of the induced diet and 2 months after surgery to assess the dynamics of excess weight loss. Rats were divided into three groups: control group - 5 rats, 1st group - 10 rats, 2nd group - 10 rats, 25 rats were removed from the experiment.

Results: The average weight of rats before introduction into the diet was 180.5 grams, after 3 months of induced diet reached 256.7 grams, the average weight gain was 76.2 grams (42.2%). 1 group of rats had a weight loss of -16.2% (41.7 grams), Second group had a weight loss of -20.6% (53.2 grams) 60 days after gastric bypass surgery.

Conclusions: The average statistical indicators of blood tests of the second group of animals in comparison with the first group show lower levels of iron phosphorus?magnesium, total protein and albumin. The average body weight loss of the first group was -16.2% (41.7 grams), the second -20.6% (53.2 grams) with a difference of 11.7 grams, which is not significant.

KEY WORDS: obesity, weight loss, gastric bypass surgery

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INTRODUCTION

The mechanisms that provide metabolic control after gastric bypass surgery with a single anastomosis remain completely unexplored [1, 2]. It is proved that the use of animal models is an important tool for studying the physiological processes that underlie long-term surgical practice. A large number of experimental studies not only in general but also in bariatric surgery have been performed on rodents and have helped to understand many physiological processes after combined and gastrorestrictive surgeries. Nevertheless, the data obtained from experimental animal studies should always be critically evaluated and carefully compared with human physiology. Modeling of obesity and gastric bypass with a single anastomosis in laboratory rats with different lengths of biopancreatic and common loops can study the metabolism of trace elements and morphological changes in internal organs, bone tissue at different times after surgery.

THE AIM

The aim is to investigate morphofunctional changes in bone tissue, mucous membranes of different parts of the intestine, parathyroid glands, as well as changes in blood biochemical parameters depending on the length of the common loop in modeling gastric bypass with one anastomosis within 60 days.

MATERIALS AND METHODS

STATISTICAL METHODS

Average statistical indicators of blood tests are presented in table I with indicators of standard deviation (σ). Statistical analysis and processing of the results were carried out using the IBM SPSS Statistics 20 Integrated Software Package.. The nonparametric Mann-Whitney U test was used as a criterion for the significance of differences between groups 1 and 2.

ANIMALS

Males of white outbred rats (n = 50) were induced high-calorie diet with a high content of animal fat, which was 45% of the main diet for 3 months to simulate obesity. 5 rats (control group) with simulated obesity were withdrawn from the experiment by intrapleural administration of 1 ml of 10% sodium thiopental solution.

Animal weight was measured before the induced diet at 1, 2, 3 months, and 2 months after surgery to further

Table I. Changes in mineral and protein metabolism in experimental animals.

Indexes	Average biochemical parameters of rat blood			
	Control group of rats treated with ID before surgery (n = 5), σ	2 group of animals with a length of alimentary loop, which was 1/2 of the total length of the small intestine 60 days after surgery (n = 17) , σ	3 group of animals with a length of alimentary loop that was 1/3 of the total length of the small intestine 60 days after surgery. (n = 18) , σ	p
Iron, μmol / l	26,4 ± 11,3	5,45 ± 15,3	3,4 ± 5,8	<0,05*
Phosphorus, mmol / l	1,8 ± 0,04	1,22 ± 0,6	1,15 ± 0,42	<0,05*
Total calcium, mmol /l	2,6 ± 0,17	2,26 ± 0,89	2,1 ± 1,29	>0,05*
Magnesium, mmol / l	0,71 ± 0,004	0,67 ± 0,085	0,65 ± 0,07	>0,05*
Total protein, g / l	62,3 ± 5,8	44,9 ± 268,3	42 ± 305,5	>0,05*
Albumin, g / l	29,5 ± 4,5	25,2 ± 69,3	23 ± 51,6	<0,05*

* - The nonparametric Mann-Whitney U test.

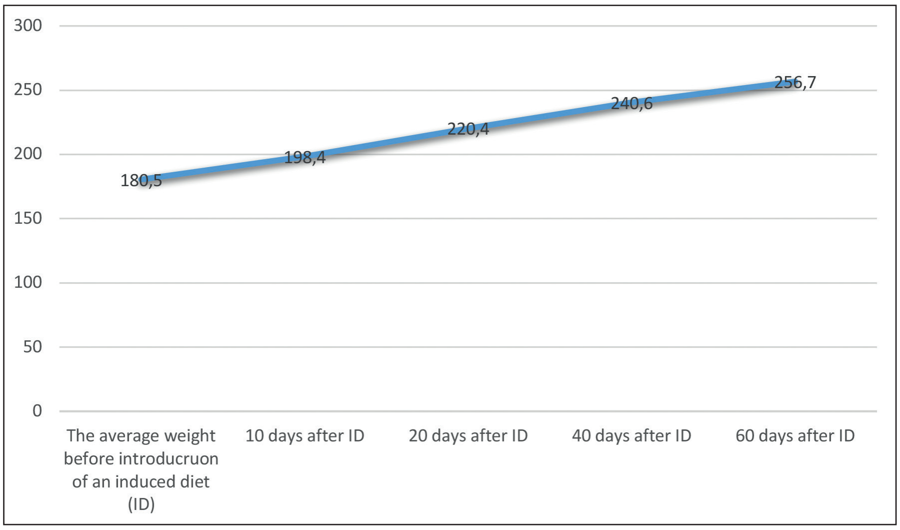

Fig. 1. Weight gain after introduction of animals into the induced diet.

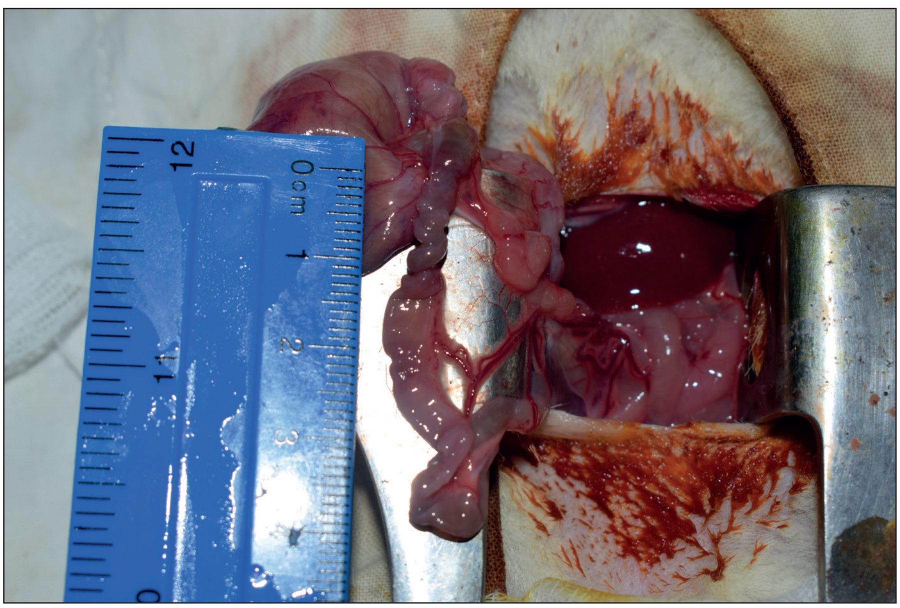

Fig. 2. Measuring the total length of the small intestine.

assess the dynamics of excess weight loss. Weight change was analyzed using the percentage according to the weight change formula (% WE) (actual weight - initial weight / initial weight) × 100. The induced nutrition did not change after surgery. 2 months after surgery, the animals were removed from the experiment. Examination and sampling of the spine (thoracic and lumbar regions), metaepiphysis of the femur and femoral neck with the

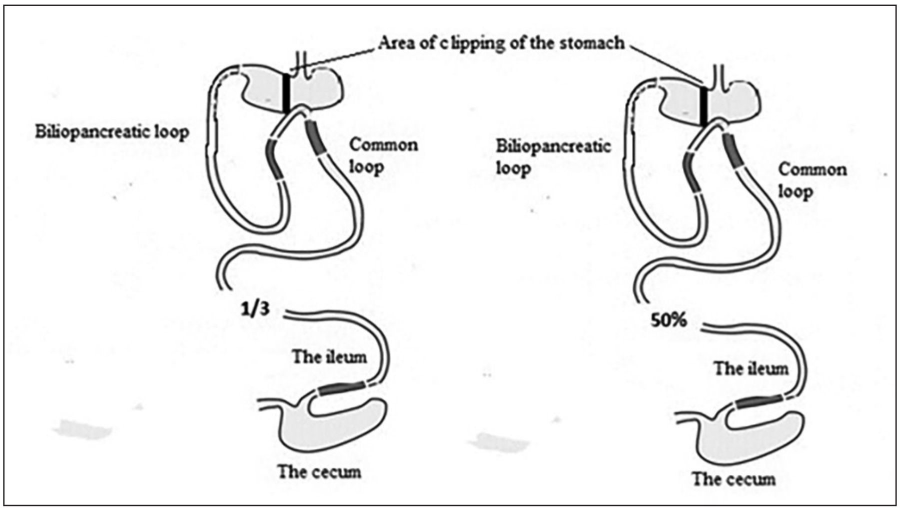

Fig. 3. Scheme of surgical intervention in the first and second groups of rats.

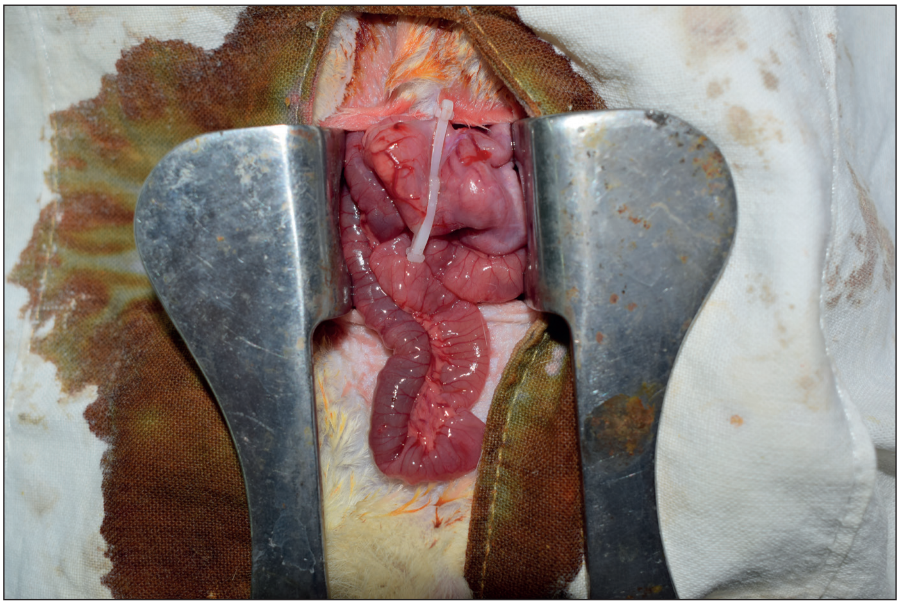

Fig. 4. View of the paired Haem-o-lock clip and the clipped area between the body and the antrum of the stomach.

hip joint, parathyroid glands, tissues of the common and biopancreatic loop, liver.

SURGICAL MODEL

The first group of animals (10 obese rats) underwent gastric bypass with one anastomosis with a total loop length equal to 50% of the total length of the small intestine. The second group of animals (10 obese rats) performed gastric bypass with one anastomosis with a total loop length equal to one third of the total length of the small intestine. Narcotic sleep was administered by intraperitoneal injection of 2% sodium thiopental solution using an insulin syringe with a needle length of 6 mm at a dose of 25 mg / kg. Twenty-five rats with signs of postoperative complications (intestinal, gastric obstruction, esophageal perforation, peritonitis due to failure of anastomotic sutures) were excluded from the experiment.

All manipulations and withdrawals of experimental animals from the experiment were performed in accordance with bioethical standards of humane treatment of laboratory animals in accordance with international and national regulations for experiments involving animals: "European Convention for the protection of vertebrates used for research and other scientific purposes" (Strasbourg, 1986); "General ethical principles of animal experiments" (Ukraine, 2001), the Law of Ukraine "On protection of animals from cruel treatment" 3447-IV, 2006.

BLOOD TESTS

5 control rats and rats of the first and second groups blood was taken 60 days after surgery by tail vein puncture to determine total protein, albumin, total calcium, phosphorus, magnesium, iron, potassium using EasyLytePlus analyzers (MedicaCorp., USA) , and Prestige 24 (PZCOR-MAYS.A, Poland).

PREPARATION FOR SURGERY AND POSTOPERATIVE MANAGEMENT

All rats that underwent surgery were transplanted into dry cages the day before with free access to 5% glucose solution.

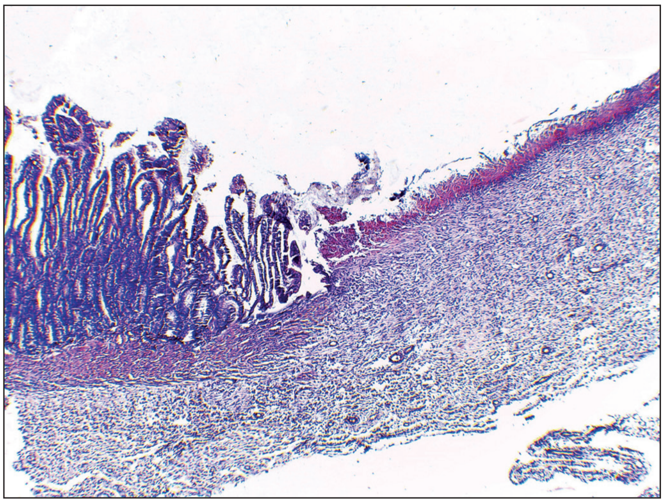

Fig. 5. Area of the complete destruction of the intestinal villi of the biliopancreatic loop. Hematoxylin and eosin staining. Increase 40.

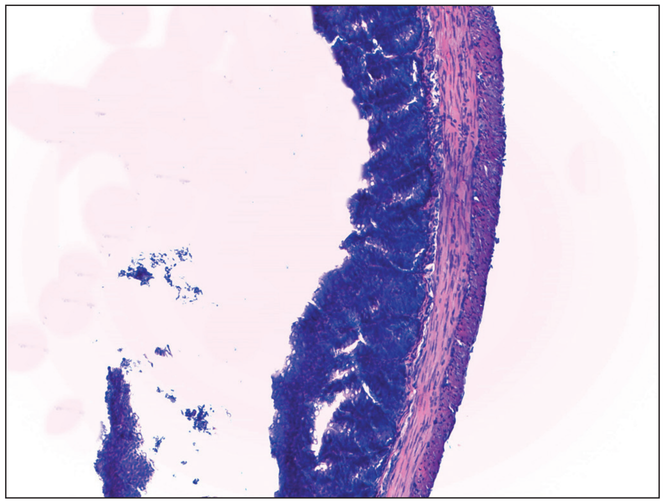

Fig. 6. The cecum is atonic, dilated. Destruction of the surface layer of the mucous membrane, epithelium is preserved in the crypts, dystrophically changed. Hematoxylin and eosin staining. Increase 100.

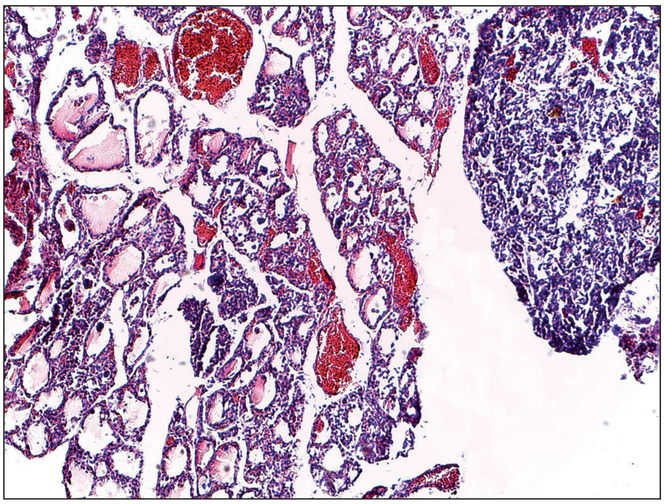

Fig. 7. Severe fullness of HMCB vessels, moderate dystrophic changes of parathyrocytes. Staining with picrofuxin by van Gizon. Increase 400.

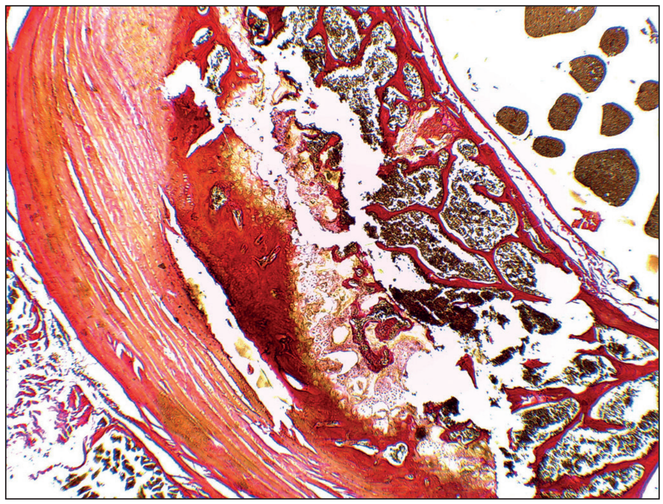

Fig. 8. Lumbar spine with signs of demineralization, picrinophilia of the osteomatrix. Staining with picrofuxin by van Gizon. Increase 40.

After surgery, the animals received meloxicam (5 mg / kg), ceftriaxone (20 mg / kg) and 10 ml of isotonic sodium chloride solution by subcutaneous injection. On the second day after the operation, liquid food was administered (not more than 20 ml per day of a balanced mixture for enteral nutrition PeptamenAF with a neutral taste and subsequent return to induced 4 days after the intervention.

HISTOLOGICAL EXAMINATION OF ORGANS

5 control rats and rats of the first and second groups 60 days after gastric bypass surgery and blood tests were removed from the experiment with subsequent collection of organs and fixation of the selected material in 10% buffered neutral formalin for 24 hours. Areas of the thoracic, lumbar spine of the femoral epiphysis underwent an additional stage of decalcification for 6 days, followed by sealing with paraffin. Tissue sections were stained with picrofuxin according to van Gizon, hematoxylin and eosin. Sections of the thyroid and parathyroid glands, areas of the excluded stomach, common and biliopancreatic loop of the small intestine, proximal stump of the stomach with anastomosis, esophageal-gastric junction, cecum were also stained with picrofuxin by van Gizon and hematoxylin and eosin.

45 gastric bypass operations with one anastomosis were performed. The average duration of the operation was 50 ± 5 minutes The overall mortality rate was 44.4% (n = 25). In both groups there were cases of peritonitis due to necrosis of the gastric wall (n = 2), perforation of the esophagus (n = 3), failure of the sutures of the anastomosis (n = 5), stenosis of gastroenteroanastomosis with acute expansion of the proximal stump (n = 15), which occurred in the first postoperative week and were directly related to the performance curve of microsurgical techniques. A total of 20 rats had a full observation period of 60 days and were included in the analyzes.

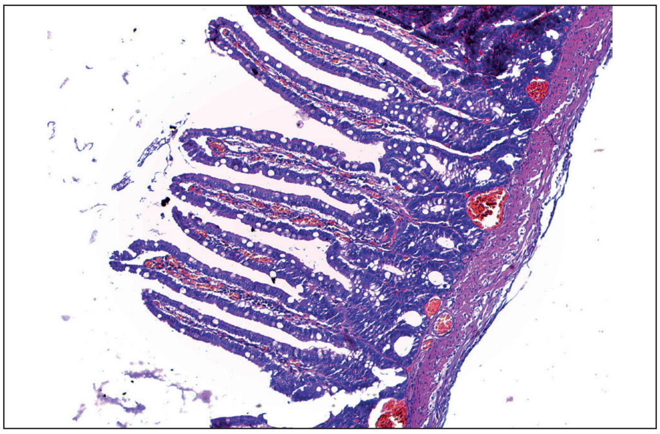

Fig. 9. More pronounced demineralization of the vertebral osteomatrix, loss of osteomatrix structure in the second group of animals 60 days after surgery. Hematoxylin and eosin staining. Increase 400.

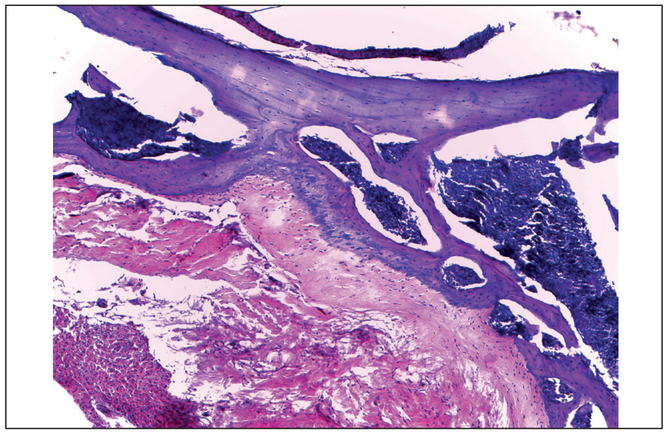

Fig. 10. Normal mucosa of small intestine. Hematoxylin and eosin staining increase 100.

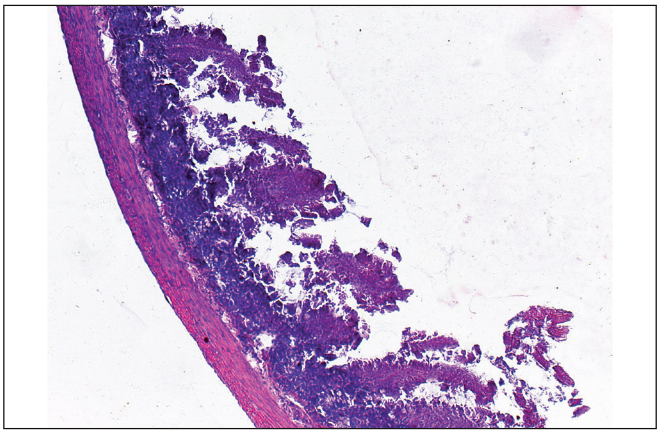

Fig. 11. Morphometric changes biliopancreatic loop 60 days after surgery. The length of the total loop, which was 50% of the total length of the small intestine. (1 group).

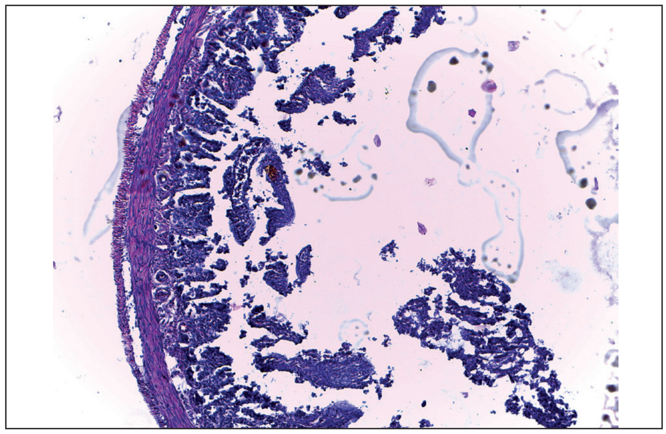

Fig. 12. Morphometric changes biliopancreatic loop 60 days after surgery. The length of the total loop, which was one third of the total length of the small intestine. (group 2). Hematoxylin and eosin staining increase.

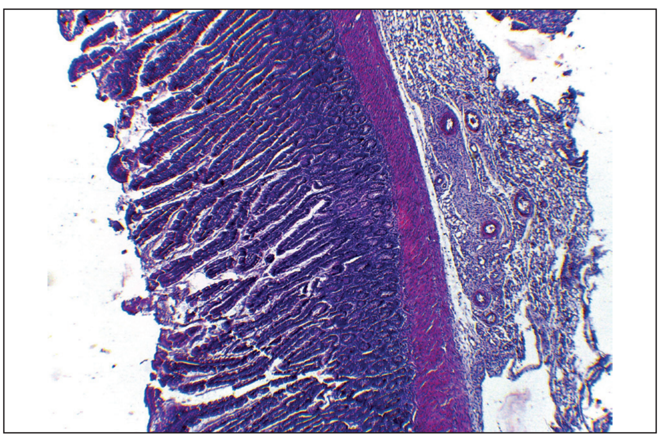

Fig. 13. Morphometric changes common loop 60 days after surgery. The length of the total loop, which was 50% of the total length of the small intestine. (1 group) Hematoxylin and eosin staining increase 100.

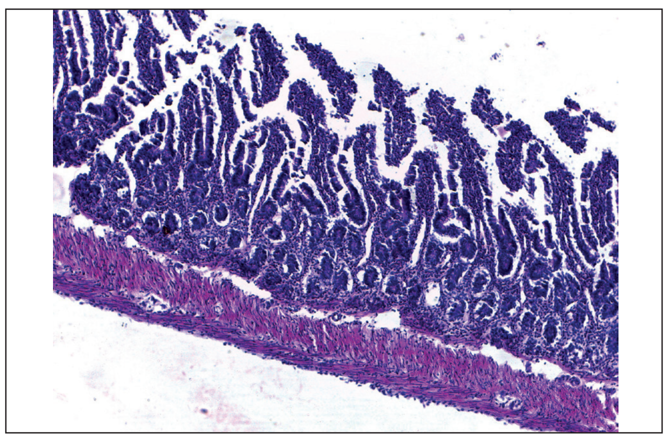

Fig. 14. Morphometric changes common loop 60 days after surgery. The length of the total loop, which was one third of the total length of the small intestine. (group 2) Hematoxylin and eosin staining increase 100.

TECHNIQUE OF SURGICAL INTERVENTION

After processing of the operating field, an upper-middle laparotomy was performed. The cecum was removed into the laparotomy wound, followed by a complete measurement of the small intestine with a ruler against the mesenteric edge of the intestine in parts of 5 centimeters from the ileocecal angle to the duodenojejunal junction, which corresponded to 100% (Fig. 2). The length of the total loop, which corresponded to 50% of the total length of the small intestine and 1/3, respectively, was determined intraoperatively. In their study, Cavin, J.-B. Et al. showed that the total length of the small intestine in rats varies from

90 to 120 cm. In our case, the total length of the intestine varied from 85 to 110 cm.

The first group consisted of animals in which the length of the alimentary loop was 1/3 of the total length of the small intestine, the second - 1/2 of the total length of the small intestine (Fig. 3).

The most well-known methods of forming the proximal stump by stitching the stomach wall at the border of the body and the antrum with staplers TA-DST 30-mm-3.5 - 3.5mm [2, 3, 4], which provide a tight separation of the stomach, which is confirmed by tomodensitometry, but are more expensive and require a more careful surgical approach.

The use of gastric clipping significantly reduced the number of failures of the distal and proximal gastric stump and also provided a tight separation of the stomach and reduced the average operation time (Fig. 4). Mobilization of a large gastric curvature, perigastric dissection of a small gastric curvature distal to the left gastric artery and conduction of two paired polymer clips hem-o-lock through a technological orifice in small seal and compression of the gastric wall at the border of the stomach were performed. Resection of the bottom of the stomach in our case was not performed.

In this way, the antrum of the stomach, duodenum and proximal parts of the hungry intestine were excluded (Fig. 4).

Gastroenteroanastomosis (GEA) with a width of about 1 cm in diameter was formed by a continuous suture on the large curvature of the stomach proximal to 1 cm from the clipping site using monofilament thread Prolene 8-0 (Ethicon, Somerville, NJ, USA). Gastro- and enterotomy were performed using a monopolar knife. In cases of detection of gastric remnants, they were evacuated through the gastrotomy hole until complete clearance of the proximal stump of the stomach. Mandatory technique for the prevention of anastomosis and the development of acute obstruction of the proximal stump of the stomach was marginal resection of the gastric mucosa after gastrotomy. The afferent loop of the small intestine was also fixed along the large curvature of the stomach proximal to 1.5-2 cm from the GEA site. Abdominal suturing was performed in 2 layers using Vicryl-Rapid 4-0 (Etikon).

RESULTS

EFFECT ON BODY WEIGHT OF A HIGH-FAT DIET BEFORE AND AFTER SURGERY

The average weight of rats before induction was 180.5 grams, after 3 months of induced diet reached 256, 7 grams, the average weight gain was 76.2 grams (42.2%). According to the formula for weight change (% WE) 1 group of rats had a weight loss of -16.2% (41.7 grams), Second group had a weight loss of -20.6% (53.2 grams) 60 days after gastric bypass surgery.

SURGICAL EFFECTS ON MINERAL AND PROTEIN METABOLISM

In both groups there was a decrease in mineral and protein metabolism compared with preoperative parameters, which are presented in table I.

HISTOLOGICAL EXAMINATIONS

After the loss of the functioning area of the small intestine by surgical exclusion of the biliopancreatic loop from the passage in the common loop, a functional and morphological compensatory adaptive reaction occurs. Increased epithelial proliferation in the crypts leads to an increase in intestinal villi height, arch depth and villi hyperplasia, accompanied by increased absorption of nutrients, fluid and electrolytes and fat-soluble vitamins, which may explain the reduction of malabsorption and loss of body fat recurrence of obesity after bypass surgery. Clinical observations suggest that functional adaptation occurs not only in humans but also in rats with experimental models of gastric bypass and short bowel syndrome [6,7]. In the immediate postoperative period, patients with significant small bowel resection were observed massive fluid and electrolyte losses with reduced nutrient uptake.

For many patients, the adaptive response can reduce the dose of supplement therapy after shunt surgery. However, other patients with the same total loop length receive supplemental therapy for life and have some malabsorption complications. When simulating short bowel syndrome, the number of goblet cells on villi and Panet cells in crypts increased as early as 12 hours after resection, the number of absorbing enterocytes per villi begins to increase 36 hours after resection, but the percentage of enterocytes on villi does not increase even after surgery. [8]. Given the functional significance of the absorptive enterocyte, the study of early adaptive response in humans at an early stage after gastric bypass surgery may be crucial to determine future malabsorption complications. Studies in rats [9] have shown that intestinal exclusion increases the expression of proapoptotic genes, thereby increasing the number of apoptoses in crypt cells and persists [10]. Vitamin A deficiency inhibits intestinal adaptation and leads to decreased crypt proliferation and increased apoptosis [11].

According to our experimental study, the adaptive response in the general loop was observed for 20 days of the postoperative period in rats of both groups, which were confirmed morphometrically.

MORPHOLOGICAL CHANGES OF THE MUCOUS MEMBRANE OF THE BILIOPANCREATIC AND COMMON LOOP

In both groups of experimental animals, areas of complete destruction of intestinal villi and atony of the muscular membrane were noted against the background of edema of the submucosal membrane of the initial parts of the biopancreatic loop. Epithelial cells were stored only in the crypts, or on the lateral surfaces of the intestinal villi. In the proximal parts of the biliopancreatic loop closer to the GEA there was swelling of the mucosal plate, signs of increased desquamation of the epithelium from the apex of the villi, the epithelial cells themselves showed signs of dystrophic changes (expressed basophilia of the cytoplasm, The muscular membrane is moderately atonic, neurons of the intermuscular plexus with signs of dystrophic changes.

In the general loop, the pathological manifestations were less pronounced: less swelling of the mucous membrane, less manifestations of dystrophy, epitheliocytes are more functionally active, desquamation is increased, but there was no significant exposure of the villi. The mucous membrane's own plate was infiltrated mainly by lymphocytes, lymphocytes in the muscular membrane were also noted, the serous membrane was infiltrated unevenly, and contained foci of lymphocytic infiltration.

BILIOPANCREATIC LOOP

More significant areas of destruction of intestinal villi, pronounced atony of the muscular layer, dystrophic changes of intestinal epithelium and its desquamation from the tips of villi, the absence of the latter in the crypts in the studied areas of the biopancreatic loop were observed in the small intestine of animals of the second group (Fig.11, 12). All animals of the second group (100%) had areas of complete destruction of the mucous membrane of the biliopancreatic loop (Fig.5). Only 2 (11.7%) animals from the first group had similar changes. Macroscopically, these areas of thinning of the intestinal wall during organ harvesting were so pronounced and transparent that bile was visually determined through them.

COMMON LOOP

Manifestations of atony of the muscular membrane are less pronounced, in the mucosa there is a slightly increased desquamation of epitheliocytes from the tips of the villi and areas of destruction of the tips of the villi and more pronounced in the second group (17 of 18) (94%) versus 10 of 17 animals of the 1st group (58%). The epithelial plate is better preserved in both groups when comparing them with the state of the biliopancreatic loop. The epithelium is preserved on the lateral surfaces of the villi and in the crypts in both cases (Fig. 13, 14).

BONE AND PARATHYROID CHANGES

Vitamin D deficiency is widespread in obese people due to insufficient intake in food supplements containing this vitamin. Secondary hyperparathyroidism on the background of vitamin D deficiency is common in obesity, despite eating high-calorie foods.

The mesenchymal origin of osteoblasts and adipocytes may explain one of the mechanisms of low bone mineral density in obese people [12]. Visceral and subcutaneous fat have completely opposite properties of impact on bone strength, as visceral fat can adversely affect the formation, structure and strength of bones, while subcutaneous fat performs a "protective function". Decreased gastric juice production due to the restrictive component of surgery and hypoacidity with proton pump inhibitors taking impair calcium absorption by up to 80% in the duodenum, which is excluded from the passage in conventional shunt surgery. Analysis of the literature data shows that dystrophic changes in bone tissue were observed after gastric bypass surgery for Ru as early as 3 months after surgery. Such changes were caused by calcium malabsorption and low levels of vitamin D before surgery. Low values of vitamin D observed before surgery are difficult to correct in the remote postoperative period, which is almost non-existent after gastro-restrictive surgery [13]. On the seventh day after gastric bypass surgery in the parathyroid gland was observed enlightenment of the cytoplasm of parathyrocytes, which are located mainly under the capsule. At 60 days, there was a pronounced fullness of the blood vessels of the HMCB, moderate dystrophic changes of parathyrocytes (Fig.7). Increased number of cells with enlightened cytoplasm.

In animal experiments, dystrophic changes were observed in the bone tissue of the lumbar vertebrae in both groups of animals. In animals of the group 1 and 2 in the lumbar spine there were pronounced signs of demineralization. Osteomatrix acquired picrinophilia, became less dense, in the fibrous cartilage of intercartilaginous discs there were foci of dystrophic changes (Fig.8).

More pronounced changes in bone tissue were observed in the second group of animals (18 of 18 versus 1 of 17): bone thinning, dystrophic changes in bone tissue, more pronounced demineralization of the osteomatrix of the vertebrae. Osteomatrix in some areas lost structure: there were no lines of cementation, he himself became homogeneous. The decrease in fuchsinophilia of the matrix and its liquefaction indicated changes in collagen fibers (Fig.9).

DISCUSSION

The results of animal experiments do not make sure that the effect on the human body will have the same effect, because it is impossible to completely reproduce the technique of surgery. In studies conducted by other authors who simulated mini-shunting of the stomach with a single anastomosis, researchers limited the imposition of an anastomosis between the small intestine and esophagus, so it was not possible to assess the effect of bile reflux on the stomach stump [13]. Cavin et al. presented the results of the modification of such surgery, which left the stump of the stomach, thereby bringing the experimental model closer to the surgery performed in the clinic [4]. In their models, they used the length of the intestine to apply an anastomosis from 60 to 80 cm with the length of the biopancreatic loop 35 cm. Comparison of the direct dependence of the length of the biopancreatic loop allows us to study the metabolic effects on the body, thus approaching the standardization of modeling. Also one of the options is the developed technique of surgery on rats by Siebert MA et al. [2]. A method of excluding a part of the stomach from the passage by the method of applying a modified Hem-o-lock clip has been developed. There are no publications in which the results of the use of gastric clipping are given. Clipping, in contrast to stitching the stomach wall with staplers, avoids injury to the walls of the organ, which significantly reduces the likelihood of surgical complications (bleeding, perforation of the gastric wall, recanalization of the staple suture with subsequent formation of gastro-gastric fistula in the long term), and if necessary allows to restore gastric patency at an early terms. Many previous experiments by other authors allow us to correlate the trend of exposure to laboratory animals with similar effects on the human body. Thus, after conducting this experiment, we assume that exclusion from the passage of more than 1/2 of the small intestine will not have the advantage of losing excess weight compared to exclusion from the passage of less than ½ small intestine, but will lead to more significant metabolic disorders. Thus, in the future, bariatric surgery will be able to calculate the length of the small intestine to exclude from the passage to obtain on the one hand a satisfactory effect on weight loss, on the other - to minimize the manifestations of malnutrition disorders.

CONCLUSIONS

Chronic malabsorption always leads to bone demineralization. In the lumbar vertebrae in both groups of animals, dystrophic changes were observed already after 60 days, there were pronounced signs of demineralization - osteomatrix picrinophilia with loss of density.

More pronounced changes in bone tissue were observed in the second group of animals. All animals of the second group had more pronounced demineralization of the osteomatrix of the vertebrae. In some areas, the osteomatrix lost its structure: there were no cementation lines, it itself became homogeneous. A decrease in the fuchsinophilia of the matrix and its liquefaction indicated a change in collagen fibers.

The reaction of the parathyroid gland was observed already on the seventh day after gastric bypass surgery in the parathyroid gland, the cytoplasm of parathyrocytes, located mainly under the capsule, was cleared. On the 60th day, there was a pronounced plethora of blood vessels of the HMCB, moderate dystrophic changes in parathyrocytes. Increase in the number of cells with clear cytoplasm. We did not find any differences in the histological examination of the parathyroid gland between groups 1 and 2. Histological signs of atrophy of the mucous membrane of the small intestine were observed in both groups of animals, atonic, dilated. Destruction of the surface layer of the mucous membrane of the cecum with preservation of the dystophically altered epithelium in crypts was observed in animals of both groups. More pronounced desquamation of the epithelium was characteristic of the biliopancreatic loop in comparison with the common loop. Areas of complete destruction of the mucous membrane of the biliopancreatic loop were observed in all animals of the second group, only 2 animals of the first group (11.7%) had these changes.

The average statistical indicators of blood tests of the second group of animals in comparison with the first group show lower levels of iron 3.4 ± 5.8 versus 5.45 ± 15.3, $p < 0.05$, phosphorus 1.15 ± 0.42 versus 1, 22 ± 0.6, $p < 0.05$, calcium 2.1 ± 1.29 versus 2.26 ± 0.89 $p > 0.05$, magnesium 0.65 ± 0.07 versus 0.67 ± 0.085, $p > 0.05$, total protein 42 ± 305.5 versus 44.9 ± 268.3, $p > 0.05$ and albumin 23 ± 51.6 versus 25.2 ± 69.3, $p < 0.05$. The average body weight loss of the first group was -16.2% (41.7 grams), the second -20.6% (53.2 grams) with a difference of 11.7 grams, which is not significant.

Disorders of protein and mineral metabolism can be observed not only with massive resection of the small intestine, but also with the exclusion of 1/2 or more of the small intestine from the passage by gastric bypass, which does not have a significant advantage in reducing excess body weight, but leads to deeper metabolic disorders due to atrophy of the gastrointestinal tract.

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