MEDICAL SCIENCE MONITOR

ANIMAL STUDY

e-ISSN 1643-3750
© Med Sci Monit, 2020; 26: e924097
DOI: 10.12659/MSM.924097

Received: 2020.03.07
Accepted: 2020.04.13
Available online: 2020.04.17
Published: 2020.04.23

Effect of Sleeve Gastrectomy on Bone Metabolism and Serum 5-Hydroxytryptamine in Obese Rats

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Source of support: This study was financially supported by the National Natural Science Foundation of China (Grant No. 81873650), the Shandong Medical and Health Technology Development Project (Grant No. 2014WS0148), and the Qilu Hospital of Shandong University Scientific Research Fund (Grant No. 2019QLQN08)

Background: Studies have shown that bariatric surgery, such as sleeve gastrectomy (SG), has an adverse effect on bone, including decreased bone mineral density (BMD) and bone metabolism. Peripheral 5-hydroxytryptamine (5-HT) has an adverse regulatory effect on bone formation. Here, we assessed changes in bone metabolism and whether 5-HT is involved in the effect of SG on bone metabolism.

Material/Methods: A rat model of obesity was established using Wistar rats. After successful modeling, rats were randomly assigned to 2 groups – the SG group and the Sham group – with 10 rats in each group. We then performed sleeve gastrectomy or sham operation. Bone metabolic markers and BMD of rats were measured at 2 and 16 weeks after the operation and the level of 5-HT in serum was determined. Rats were killed at 16 weeks after the operation, and bones of the hind limbs were harvested to measure 5-HT by immunofluorescence.

Results: BMD was decreased and bone metabolism demonstrated a trend of bone destruction in the rats after SG. A significantly increasing trend in the level of serum 5-HT was found, and bone immunofluorescence showed increased expression of 5-HT.

Conclusions: BMD was decrease and bone metabolism demonstrated a trend of bone destruction after SG. SG can affect the level of 5-HT in serum or bone tissue and the 5-HT may be involved in the process through which SG affects bone metabolism.

MeSH Keywords: **Bone Density • Gastrectomy • Metabolism • Receptor, Serotonin, 5-HT1A**

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/924097

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Background

The incidence of obesity is steadily increasing, making it a serious human health problem [1,2]. China has one of the largest populations of obese people in the world. Obesity can cause many related complications, such as type 2 diabetes mellitus, cerebrovascular diseases, and cardiovascular diseases [2,3]. Bariatric surgery, including sleeve gastrectomy (SG), has been proven to be a widely applicable surgery for obesity and it has been accepted by the medical community. Bariatric surgery can continuously reduce the weight of obese people, and it can improve many obesity-related complications [4–6]. Studies have shown that bariatric surgery has a negative impact on bone, including increased postoperative bone resorption, decreased BMD, and increased risk of fracture [7–9]. A wide array of studies confirms that there is an increased risk of bone fracture after bariatric surgery [7,10–14]. The activity of osteoblasts in bone and the formation and destruction of bone can be judged by 4 related indicators of bone metabolism [15]. Serum calcium is an important bone nutrient, levels of which reflect changes in bone metabolism. Osteocalcin (OC) can regulate bone calcium and decrease bone mass, and the loss of calcium in bone decreases OC. High levels of bone isoenzyme of alkaline phosphatase (BALP) indicate insufficient calcium deposition. N-terminal pro-peptide of type 1 collagen (P1NP) is a marker used in the diagnosis of osteoporosis, and increased levels of P1NP are common in osteoporosis caused by some factors and other diseases. C-terminal telopeptide (CTX) is a marker of bone resorption, and high levels of CTX reflect increased degradation of bone matrix, suggesting that the rate of bone resorption is increased [16]. Generally speaking, OC, BALP, and P1NP are markers of bone formation, while CTX is a marker of bone absorption. Recent research shows that the neurotransmitter 5-HT is involved in bone metabolism, including bone formation and bone resorption [17,18]. Bone formation can be inhibited by peripheral 5-HT, which can block the link between the transcription factor FOXO1 and the cyclic adenosine response element binding protein (CREB), inhibiting bone formation [19–21]. However, whether 5-HT plays a role in the process of SG affecting bone metabolism has not been studied. Based on the above research, our group made assumptions and proposed that SG can regulate bone metabolism and reduce BMD by affecting the level of peripheral 5-HT, and we sought to assess the effect of SG on bone metabolism and BMD. We also explored whether SG affects serum 5-HT level and whether 5-HT participates in bone metabolism. Our goal was to help prevent development of osteopenia and fracture by providing data to guide comprehensive clinical monitoring of bone health and treatment in people who underwent bariatric surgery. We assessed the relationship between 5-HT and bariatric surgery to provide a theoretical basis and scientific evidence for further research.

Material and Methods

Animals and experimental group

Wistar rats were used as experimental animals. These rats are easy to breed and are sensitive to changes in levels of various nutrients, making them suitable for the study of nutritional and metabolic diseases. Wistar rats are large, which makes them easier to perform surgery on. We purchased 40 male Wistar rats (age 4 weeks, weight 200 g) from Shandong University's Laboratory Animal Center in Jinan. These animals had not been used in other experimental studies, and had not been administered any drugs. They were housed individually in separate cages with good ventilation, temperature 24–26°C, and 50–60% humidity, with a 12/12 h light/dark cycle [22]. Rats were randomly assigned to 2 groups: a normal-diet group (20 rats) and a high-fat diet group (20 rats). The normal-diet group was fed a normal diet and the high-fat diet group was fed a high-fat diet (Huafukang Biotech, China) for 8 weeks. All rats were given tap water to drink. When the rats in the high-fat diet group were 20% heavier than those in the normal-diet group, they were considered to be obese and the model was regarded as successfully established [23–25]. The obese rats were randomly assigned to 2 groups, the sleeve gastrectomy (SG) group and the Sham surgery group, with 10 rats in each group. Rats in the SG group underwent sleeve gastrectomy, while rats in the Sham group underwent a sham operation. Rats in the normal-diet group underwent continued feeding for other experimental studies. All animal research was approved by the Laboratory Animal Ethics and Welfare Committee of Shandong University, Cheeloo College of Medicine.

Process of surgery

All rats were fed with a residue-free diet for 48 h and fasted for 16 h before surgery. During the operation, rats were anesthetized with 10% chloral hydrate. The dosage of anesthetics for each rat was calculated according to the body weight (3 ml/kg). The anesthetic dosage, anesthetic time, and surgery time were recorded. Rats were fed with free access to water at 24 h after the operation. Three days later, rats were given a dregs-free liquid diet for 3 days. After 7 days, a high-fat diet was given to all rats.

SG

Rats were anesthetized after weighing. An upper-abdominal longitudinal incision was made to enter the abdomen. Then, the greater curvature of the stomach was freed from the cardia to the pylorus. The left gastroepiploic vessel, short gastric vessel, and posterior gastric vessel were cut off and ligated. The greater curvature of the stomach and fundus of the stomach were completely dissociated, then were removed

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longitudinally. Approximately 70–80% of gastric volume was removed. After hemostasis and alcohol disinfection, the gastric stump was sewn shut with intermittent sutures. The belly was continuously closed layer-by-layer with sutures. The stomach was adequately freed and vessels were ligated in large curves to reduce bleeding [26,27]. We were careful to remove an appropriate volume of the stomach because if the volume removed is too large, it will affect eating and reduce survival after surgery, but if the volume is too small it will reduce the effectiveness of bariatric surgery.

Sham operation

The preoperative preparation and anesthesia in the sham group was the same as in the SG group. After performing laparotomy from the midline abdominal incision, the ligaments and blood vessels of the greater curvature of the stomach were cut off, but the greater curvature of the stomach was not removed. The exposure time and anesthetic dosage of the sham group were the same as in the SG group. Then, we closed the abdominal cavity and disinfected it. We compared the SG group with the Sham group to eliminate the influence of some factors on the experimental results, such as the effect of anesthetics on rats or the stress response of rats caused by surgery [28,29].

Measurement of basic data and collection of blood samples

The success of modeling was estimated according to rat body weight. The basic data measured were body weight and daily food intake, measured about 3 days before the operation. After the surgery, we monitored basic data of rats at various time points. At 2 and 16 weeks after surgery, fasting blood samples were collected from a tail vein after a 12-h fast, then centrifuged at 3000 rpm for 15 min at 4°C. The supernatant was collected and stored in a freezer at –80°C.

Determination of BMD and body fat

BMD and body fat of rats were measured at 2 and 16 weeks after the operation in the Endocrine Laboratory at Qilu Hospital of Shandong University, using a GE Lunar Prodigy X-ray Tube Bone Densitometer for measurement and Prodigy software for data analysis. During the measurement, the rats were anesthetized with an appropriate amount of inhalation anesthesia to keep the body stable.

Retention of bone

The rats were killed 16 weeks after surgery. Then, specimens were harvested, bones of hind limbs were harvested for immunofluorescence analysis, and other specimens were stored in a freezer at –80°C.

Enzyme-linked immunosorbent assay

Blood samples were centrifuged at 3000 rpm for 15 min at 4°C in a tabletop centrifuge (TGL-16C). Then, the supernatant was put into a refrigerator at 4°C. The specific operations are performed according to the instructions of the ELISA kit (Huamei Biology). We determined detection indexes for serum calcium, OC, BALP, P1NP, CTX, and 5-HT.

Immunofluorescence

Bones were decalcified by EDTA (Google Biology) decalcification solution at room temperature for 1 month, then underwent dehydration and embedding to make paraffin sections. Sections were dewaxed and placed in a repair box filled with citric acid antigen repair buffer (G1202, Google Biology) for antigen repair. The slides were washed in phosphate-buffered saline (PBS, pH7.4, G0002, Google Biology) and sealed at room temperature for 30 min after drying. After we discarded the blocking solution, the primary antibody, anti-5-HT (1: 50, 10443-1-AP, Wuhan Three Eagles) was added to the slices and incubated overnight at 4°C. The slides were washed in PBS, then dripped with the second antibody, cy3-goat anti-rabbit (1: 300, GB21303, Google Biology), and incubated at room temperature for 50 min. The slides were then washed in PBS, dripped with 4',6-diamidino-2-phenylindole (DAPI) (G1012, Google Biology) solution, then incubated for 10 min at room temperature. After slides were washed in PBS, they were sealed with anti-fluorescence quenching tablets (G1401, Google Biology). We obtained images of immunofluorescence under a Nikon inverted fluorescence microscope with a camera (Nikon DS-U3) at 40× magnification, and then were analyzed using ImageJ software to assess the positive signals in the of immunofluorescence images. We evaluated the expression of 5-HT by calculating the average optical density (AOD) of immunofluorescence images. Three areas were selected randomly from each image for measurement, and then the results were averaged.

Statistical analysis

We used SPSS 22.0 (IBM, Chicago, IL, USA) software for data analysis and GraphPad prism 7.0 software to draw curves. The Shapiro-Wilk test was used to check whether the measured data were normally distributed. Normally distributed measurement data were assessed using the independent-samples *t* test. Results are presented as mean±standard deviation (x±s). $P<0.05$ was considered to indicate a statistically significant difference.

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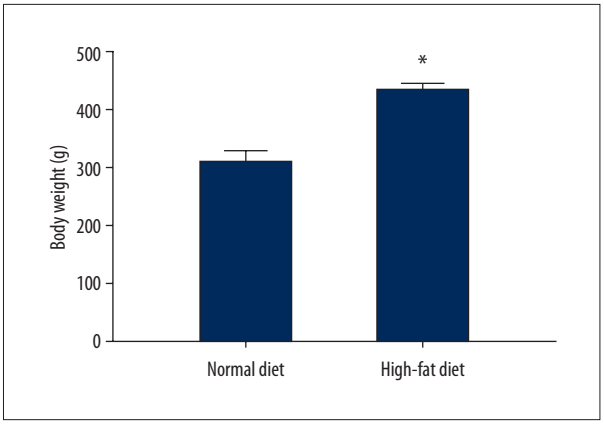

Figure 1. Body weights of normal-diet rats and high-fat diet rats (20 rats in each group). Rats in the high-fat diet group were significantly heavier than those in the normal-diet group, and were considered to be obese (* $P<0.05$).

Results

Obese rat model

Rat weights were used to determine whether the obese rat model was constructed successfully (Figure 1). None of the rats died during the modeling process, and none died due to surgery or postoperative complications. All the rats in the study survived until they were killed.

Weight and food intake

Figure 2 shows that the body weights in the SG and Sham groups both decreased during the first week after surgery, then they both increased gradually, but the body weights of rats in the Sham group increased faster than in the SG group. Weights in the 2 groups were significantly different at 2 weeks after surgery (* $P<0.05$). In the first week after the operation, food intake decreased in all rats, then the daily food intake increased and gradually stabilized at about 4 weeks after the operation. The numerical value in the SG group was significantly lower than in the Sham group 2 weeks after the operation (* $P<0.05$).

Effect of surgery on BMD and body fat rate

At 2 weeks after the operation, the BMD measured in the SG group was not significantly difference from the Sham group, and at 16 weeks after the operation, in the SG group, the BDM of rats was lower than in the Sham group (* $P<0.05$) (Figure 3). In addition, in the SG group, the BMD measured at 16 weeks was lower than at 2 weeks (* $P<0.05$), while in Sham group the difference was not significant (Figure 3). At 16 weeks after the operation, the body fat rate of rats in the SG group was lower than in the Sham group, and there was no significant difference in body fat rate between the SG group and Sham group at 2 weeks after the operation (Figure 4A). The body fat rate at 16 weeks after the operation in the SG group was lower than at 2 weeks after the operation, while in Sham group it was higher (Figure 4B).

Effect of operation on serum calcium, OC, BALP, P1NP, CTX, and 5-HT

Bone metabolism markers and 5-HT measured at 2 weeks after surgery were not significantly different between the SG group and Sham group. At 16 weeks after the operation, the following indexes in serum in the SG group were significantly different (* $P<0.05$) compared to Sham group: the level of serum calcium and OC were lower, while the levels of BALP, P1NP, CTX, and serum 5-HT were higher (Figure 5). In the SG

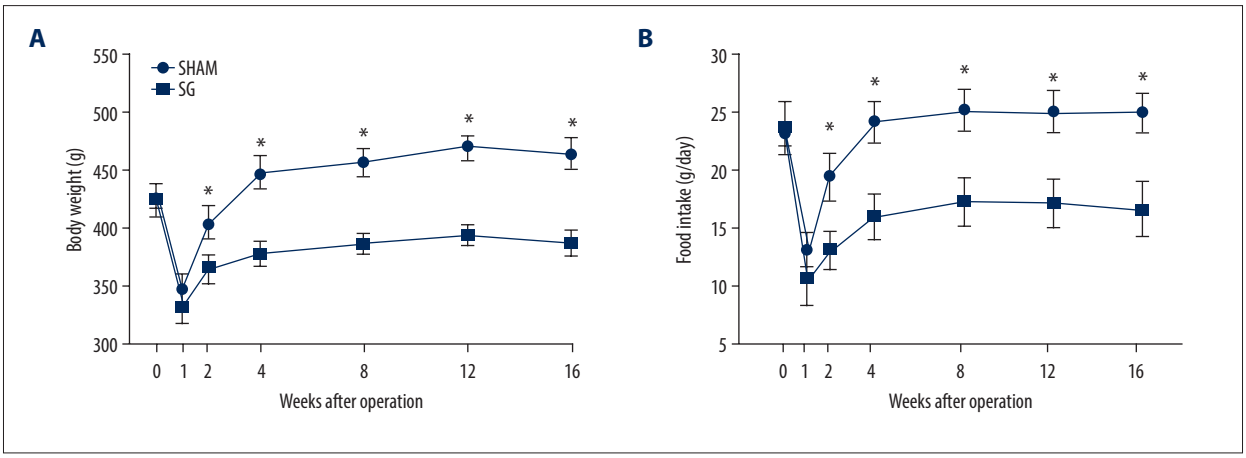

Figure 2. (**A**) Body weight in Sham group and SG group before and after surgery at different timepoints. (**B**) Daily food intake of rats before and after surgery at different timepoints. Body weight and food intake in the SG group were lower than in the Sham group (* $P<0.05$).

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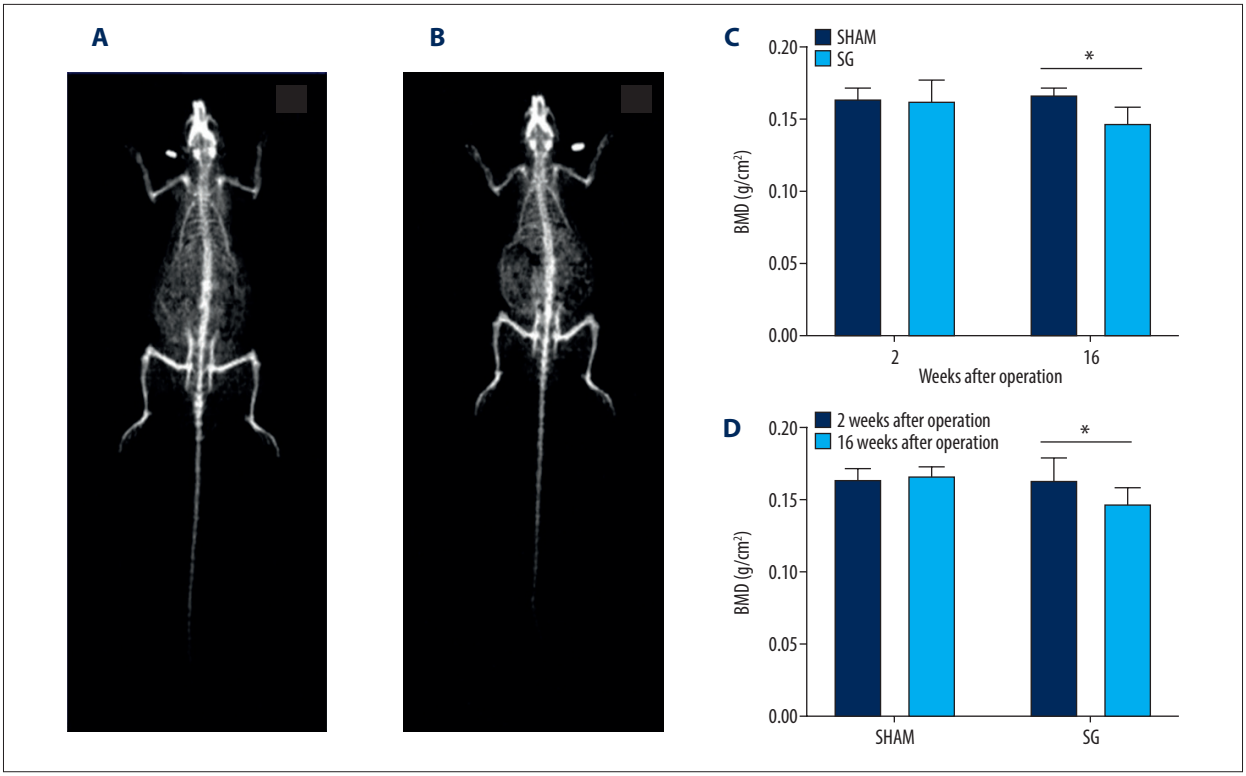

Figure 3. (**A**) X-ray of whole-body BMD in Sham group. (**B**) X-ray of whole-body BMD in SG group. They were both measured at 16 weeks postoperative. (**C**) BMD compared between the Sham and SG groups in 2 weeks after surgery and 16 weeks after surgery (* *P*<0.05). (**D**) Sham group and SG group compared with themselves at different timepoints (* *P*<0.05).

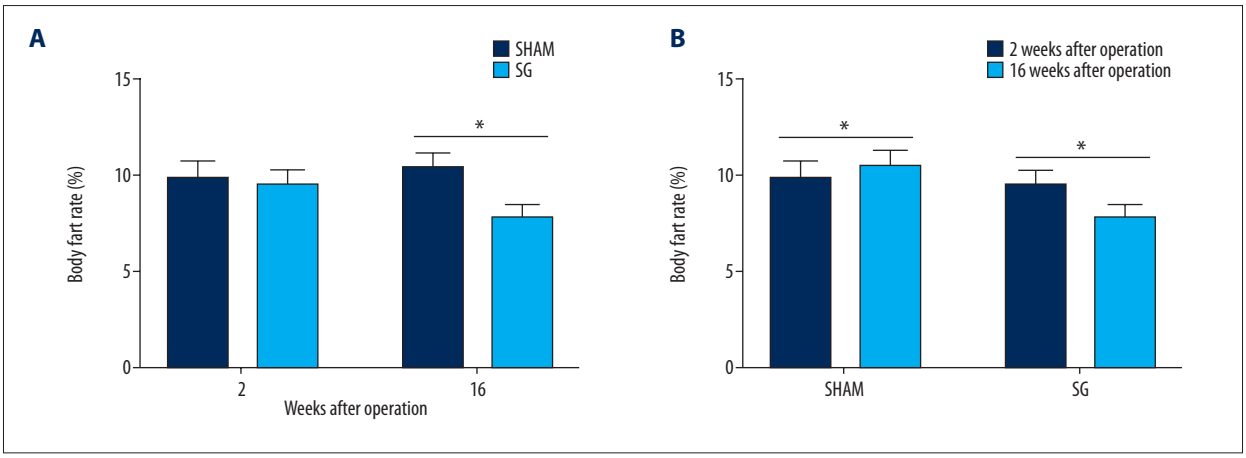

Figure 4. (**A**) Body fat measured at 2 and 16 weeks after surgery in Sham and SG group (* *P*<0.05). (**B**) Body fat rate measured at different timepoints in the 2 groups (* *P*<0.05).

group, the level of serum calcium and OC at 16 weeks after the operation were lower than at 2 weeks, while BALP, P1NP, CTX, and 5-HT levels were higher. In the Sham group, the differences between levels at 2 weeks *vs.* 16 weeks was not significant (Figure 6).

Immunofluorescence

Levels of 5-HT in bones of hind limbs were assessed by immunofluorescence (Figure 7). We used ImageJ software to determine the AOD in immunofluorescence images, which showed higher expression of 5-HT in SG group rats than in the Sham group (* *P*<0.05).

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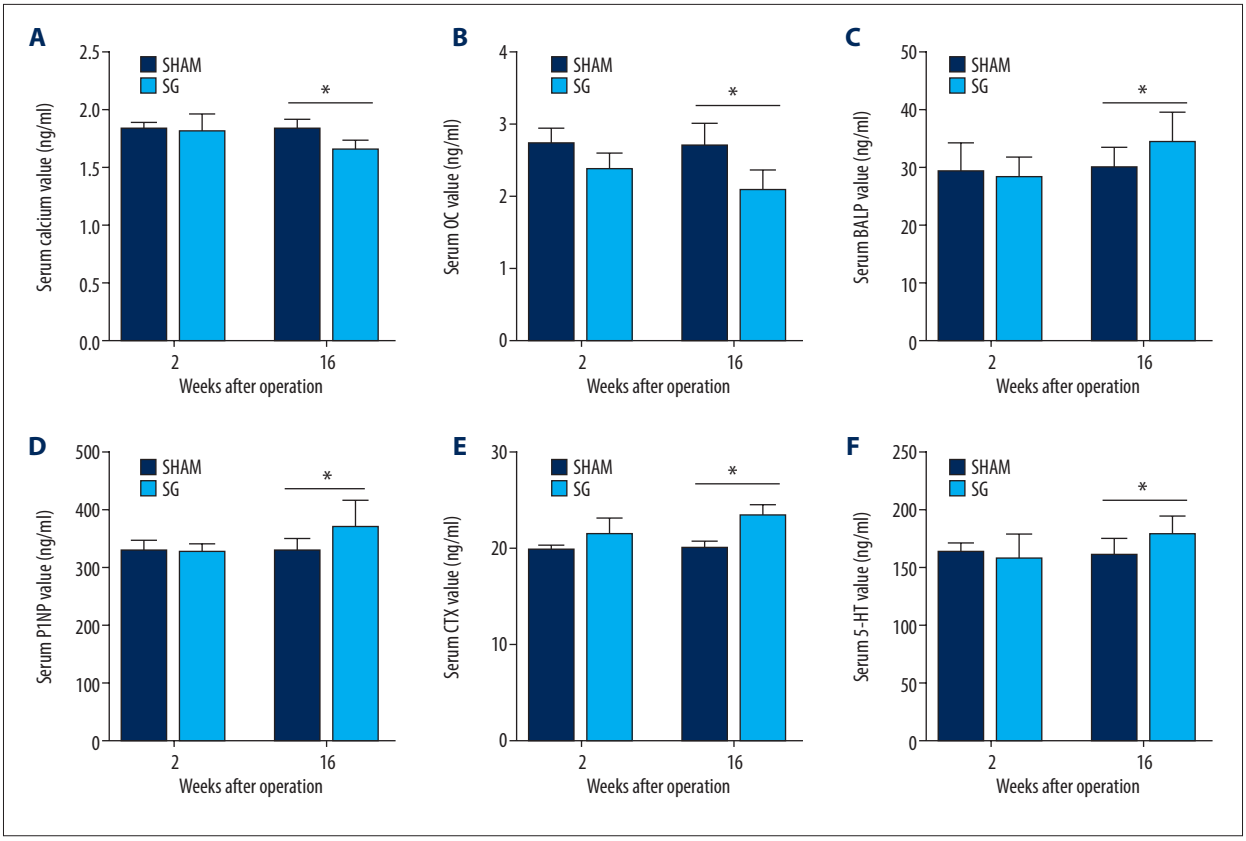

Figure 5. (**A**) Level of serum calcium. (**B**) OC. (**C**) BALP. (**D**) P1NP. (**E**) CTX. (**F**) 5-HT BALP measured at different timepoints after surgery in the 2 groups (* $P<0.05$).

Discussion

Numerous studies have shown that bariatric surgeries, such as SG, can result in weight loss [4–6], and our study supports this. We established an obese rat model based on relevant research and literature [23–25]. We found that the weight of rats fed a high-fat diet *vs.* those fed a normal diet were significantly different after 2 months. The obesity model was successfully established in all rats fed a high-fat diet. Based on the monitoring of body weight after surgery, we found that the weight of rats in both groups decreased at an earlier date due to gastrectomy, food restriction, and surgical stress. Subsequently, rats in both groups gained weight, and, compared to Sham group, the weights in the SG group increased more slowly. After 2 weeks, the rats' weights gradually stabilized. In the SG group, the rats' weights were significantly lower than in the Sham group, showing that the weight-loss surgery was successful.

The mechanism underlying the effect of SG on human organs is not completely understood. Some clinical studies have shown that bariatric surgery has a negative effect on bone, including increased bone resorption, decreased BMD, and increased risk of fracture, and BMD showed a downward trend for a longer period after surgery [7–9]. Recent studies have shown an increased risk of postoperative fracture [11–14]. Based on the effect of bariatric surgery on patients' BMD, whether SG will increase the risk of fracture in patients has become a topic of concern in the clinical setting. Some scholars have proposed that bone metabolism is changed in patients after bariatric surgery [15], and our data confirm this view. The mechanism by which bariatric surgery affects bone metabolism is not clear. Some studies [17–21] have found that 5-HT is involved in bone resorption and bone remodeling as a neurotransmitter, and reported that peripheral 5-HT inhibits bone formation. In the present study, we focussed on peripheral 5-HT and hypothesized that SG affects BMD and bone metabolism by affecting peripheral 5-HT levels.

The human skeleton has an active metabolism, and like other tissues and organs, it features some biological phenomena such as growth, aging, and disease [30]. Bone tissue produces many metabolites in the process of synthesis and catabolism, and these products are distributed in bone, blood, urine, or other body fluids in various concentrations and structures. A variety of hormones that regulate bone metabolism not only affect bone remodeling, but also provide feedback via multiple links of bone metabolism to maintain bone metabolism balance and internal environment stability [31]. Therefore, various

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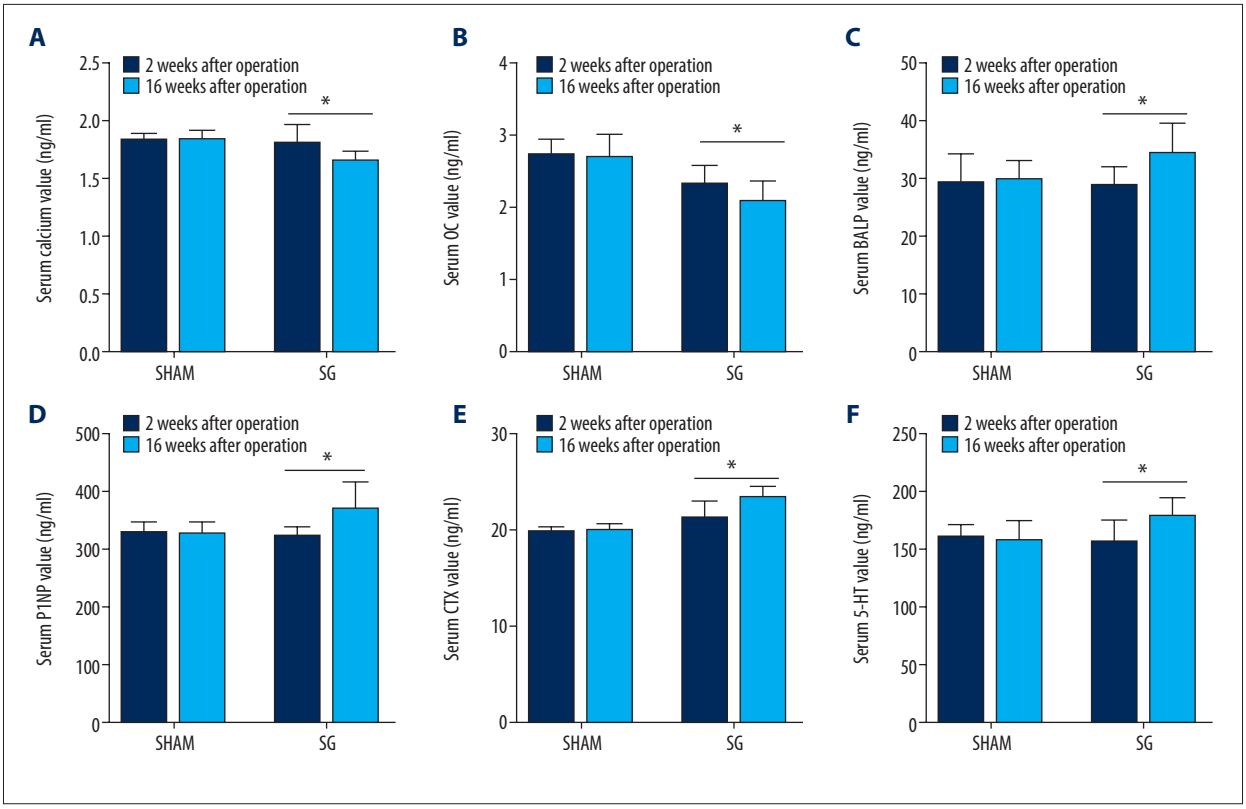

Figure 6. (**A**) Level of serum calcium. (**B**) OC. (**C**) BALP. (**D**) P1NP. (**E**) CTX. (**F**) 5-HT in 2 groups at different timepoints (* $P<0.05$).

metabolic states of bone can be inferred indirectly by detecting bone metabolites or related hormones in the blood. Bone formation and destruction are reflected by levels of bone metabolic markers, which we assessed in the present study. Serum calcium is one of the most important substances involved in bone formation. As an important bone nutrient, calcium is the basis of preventing and treating osteoporosis. Although serum calcium cannot be used as a diagnostic criterion for osteoporosis, it has reference value in preventing osteoporosis [32]. Bone alkaline phosphatase is an enzyme protein secreted by osteoblasts. BALP is a specific marker of differentiation of osteoblasts, and the level of BALP expressed in cells can reflect the degree of differentiation and functional status of cells [33]. P1NP enters the blood and urine as a metabolite, and P1NP level can reflect bone formation [34]. OC is mainly synthesized by osteoblasts, odontoblasts, and proliferative chondrocytes, and it has a strong effect on regulating bone calcium metabolism and is negatively correlated with age [35]. CTX is the most abundant form of collagen in the human body and is the only collagen component in bone, accounting for more than 90% of bone matrix. CTX plays an important role in osteoporotic fracture and has a high predictive value for osteoporotic fracture; therefore, it is used as a marker of bone resorption [36]. In the present study, various indicators in serum were detected. Bone metabolism indicators measured at 2 weeks after surgery were not significant different between the SG group and Sham group. At 16 weeks after surgery, compared to the Sham group, the level of serum calcium and OC in the SG group were lower, and the levels of BALP, P1NP, CTX were higher. In the SG group, serum calcium and OC measured at 16 weeks were lower than at 2 weeks, while BALP, P1NP, and CTX levels were higher. Between 2 weeks and 16 weeks after surgery, the markers of bone metabolism in the Sham group was not significantly different, and bone metabolism after SG tended toward bone destruction. This was also confirmed by assessment of BMD. At the 16 weeks after surgery, BMD in the SG group was significantly lower than in the Sham group, but there were no significant differences in the 2 groups at 2 weeks after surgery. In the SG group, BMD at 16 weeks after surgery was lower than at 2 weeks, but in sham group the difference was not significant.

As a neurotransmitter, 5-HT participates in bone resorption and bone remodeling [18,20]. Peripheral 5-HT is mainly distributed in gastrointestinal chromaffin cells. It can block the relationship between transcription factor forkhead box protein O1 (FOXO1) and cyclic adenosine phosphate effect element binding protein (CREB) to inhibit bone formation [37]. Peripheral 5-HT also can promote the expression of interleukin (IL)-6 and induces bone resorption [38]. In this study, we detected 5-HT in serum, and found that there was no significant difference in 5-HT in 2 weeks after surgery between the

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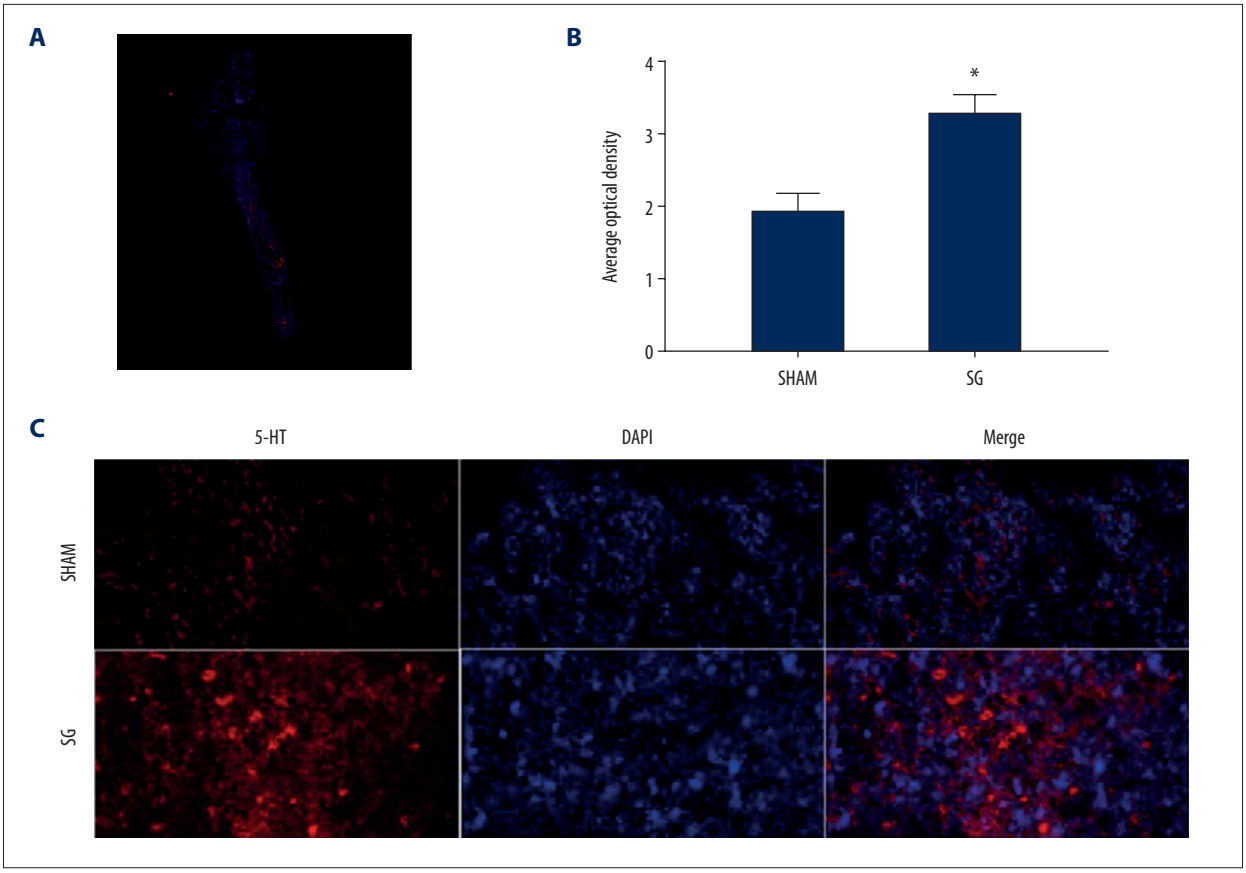

Figure 7. (**A**) Detection of 5-HT in a rat hind limb bones by immunofluorescence. The primary antibody was anti-5-HT, and the second antibody was cy3-goat anti-rabbit. 5-HT was red-stained and the nuclei were blue-stained by DAPI staining. (**B**) Average optical density of the SG group and Sham group. The positive expression of 5-HT in the SG group was higher than in the Sham group (* P<0.05). (**C**) Images were observed under a microscope at 40× magnification. The upper row of the picture is the immunofluorescence of the lower limb bone of rats in the Sham group, and the lower row is that in SG group. Red color indicates the expression of 5-HT.

SG group and Sham group, but at 16 weeks after surgery the 5-HT in the SG group was higher than in the Sham group. In addition, in the SG group, the 5-HT at 16 weeks after surgery was significantly higher than at 2 weeks. Our results show that 5-HT in serum increased after SG surgery.

Yadav [39] found that peripheral 5-HT produced a marked effect on bone metabolism by acting on bones. In the present study, we performed immunofluorescence detection in the hind limb bones of rats, showing that 5-HT was highly expressed in bone and the 5-HT level in the SG group was significantly higher than in the Sham group, indicating there was more 5-HT acting on bone after surgery. Our results suggest that SG affects the level of serum 5-HT, and 5-HT appears to be involved in the mechanism by which SG surgery affects bone metabolism.

The present study explored changes in serum 5-HT levels after SG and whether 5-HT participates in the process of bone metabolism after surgery. The specific mechanism involved requires further study and discussion. Other studies by our research group showed that after SG surgery, gastrointestinal tract structure and hormone levels were changed [40,41]. In addition, relevant studies have found that intestinal flora was associated with bone mass loss and osteoporosis, and researchers [42] have suggested that SCFAs, the major metabolite of intestinal flora, act directly on bone cells. SCFAs can increase bone mineral density and bone strength in rats. In some pathological conditions, such as inflammation, the decrease of intestinal probiotics resulted in a decrease of SCFAs produced by intestinal flora, thus promoting osteoporosis. It has been suggested that the production of 5-HT is affected by the intestinal flora and its metabolites, especially spore-producing (SP) bacteria and SCFAs [43–46]. Based on the above research, we discussed the potential mechanisms by which SG surgery regulates 5-HT levels by changing of the structure and hormone level of the gastrointestinal tract caused by changes in of intestinal probiotics and the change of SCFAs produced by intestinal flora, and then it affected the change of 5-HT in

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peripheral tissues. From the perspective of obese rats, there were some factors that could affect BMD and bone metabolism. For example, overweight could affect bones, and the lack of exercise could affect bone formation and absorption. Whether there are other mechanisms that alter bone metabolism and whether they interact with 5-HT require further study.

In summary, we explored the effect of SG surgery on bone metabolism and serum 5-HT by measuring the change of bone metabolic markers, BMD, and 5-HT after surgery. We detected 5-HT in the hind limb bones of rats and speculated that 5-HT was involved in the process of bone metabolism after SG. On the one hand, this can guide and intervene in comprehensive clinical monitoring of bone health in people who underwent weight-loss surgery to prevent bone loss and fracture. On the other hand, with increasing attention paid to peripheral 5-HT and its related receptors, although there have been many controversial conclusions, significant progress has been made in this area. With the deepening understanding of the pathogenesis of osteoporosis and the further study on the role of peripheral 5-HT, 5-HT and its related system had shown great potential as a new therapeutic target and an effective treatment for osteoporosis. 5-HT receptor blockers and 5-HT receptor antagonists were expected to become a new class of effective drugs to prevent and improve the osteoporosis caused by weight-loss surgery.

Conclusions

The findings of this study showed that BMD decreases and bone metabolism is damaged after SG. We found that SG surgery affected the level of 5-HT in serum and bone tissue and that the 5-HT may be involved in the process through which SG affects bone metabolism. These results may help improve comprehensive clinical monitoring of bone health in people who underwent weight-loss surgery to prevent bone loss and fracture. Research on the pathogenesis of osteoporosis and the role of peripheral 5-HT and its related system will help discover new therapeutic targets and improve prevention and treatment of osteoporosis caused by weight-loss surgery.

Conflict of interests

None.

References:

1. Stigler FL, Lustig RH, Ma JI: Mechanisms, pathophysiology, and management of obesity. N Engl J Med, 2017; 376(15): 1491
2. NCD Risk Factor Collaboration (NCD-RisC): Trends in adult body-mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet, 2016; 387(10026): 1377–96
3. Wolf AM, Colditz GA: Current estimates of the economic cost of obesity in the United States. Obes Res, 1998; 6(2): 97–106
4. Chang SH, Stoll CRT, Song J et al: The effectiveness and risks of bariatric surgery an updated systematic review and meta-analysis, 2003–2012. JAMA Surg, 2014; 149(3): 275–87
5. Cummings DE, Overduin J, Shannon MH, Foster-Schubert KE, 2004 ABS Consensus Conference: Hormonal mechanisms of weight loss and diabetes resolution after bariatric surgery. Surg Obes Relat Dis, 2005; 1(3): 358–68
6. Benaiges D, Mas-Lorenzo A, Goday A et al: Laparoscopic sleeve gastrectomy: More than a restrictive bariatric surgery procedure? World J Gastroenterol, 2015; 21(41): 11804–14
7. Ivaska KK, Huovinen V, Soinio M et al: Changes in bone metabolism after bariatric surgery by gastric bypass or sleeve gastrectomy. Bone, 2017; 95: 47–54
8. Adamczyk P, Buzga M, Holeczy P et al: Body size, bone mineral density, and body composition in obese women after laparoscopic sleeve gastrectomy: A 1-year longitudinal study. Horm Metab Res, 2015; 47(12): 873–79
9. Schollenberger AE, Heinze JM, Meile T et al: Markers of bone metabolism in obese individuals undergoing laparoscopic sleeve gastrectomy. Obes Surg, 2015; 25(8): 1439-45
10. Upala S, Sanguankeo A: Association between bariatric surgery and bone metabolism. Obes Surg, 2016; 26(1): 154-55
11. Liu C, Wu D, Zhang JF et al: Changes in bone metabolism in morbidly obese patients after bariatric surgery: A meta-analysis. Obes Surg, 2016; 26(1): 91–97
12. Obinwanne KM, Riess KP, Kallies KJ et al: Effects of laparoscopic Roux-en-Y gastric bypass on bone mineral density and markers of bone turnover. Surg Obes Relat Dis, 2014; 10(6): 1056–62
13. Raoof M, Naslund I, Rask E, Szabo E: Effect of gastric bypass on bone mineral density, parathyroid hormone and vitamin D: 5 years follow-up. Obes Surg, 2016; 26(5): 1141–45
14. Yu EW: Bone metabolism after bariatric surgery. J Bone Miner Res, 2014; 29(7): 1507–18
15. Han YJ, You XL, Xing WH et al: Paracrine and endocrine actions of bone-the functions of secretory proteins from osteoblasts, osteocytes, and osteoclasts. Bone Res, 2018; 6: 16
16. Kumm J, Tamm A, Lintrop M, Tamm A: Diagnostic and prognostic value of bone biomarkers in progressive knee osteoarthritis: A 6-year follow-up study in middle-aged subjects. Osteoarthritis Cartilage, 2013; 21(6): 815–22
17. Gershon MD, Tack J: The serotonin signaling system: From basic understanding to drug development-for functional GI disorders. Gastroenterology, 2007; 132(1): 397–414
18. Hasler WL: Serotonin and the GI tract. Curr Gastroenterol Rep, 2009; 11(5): 383–91
19. Yadav VK, Ryu JH, Suda N et al: Lrp5 controls bone formation by inhibiting serotonin synthesis in the duodenum. Cell, 2008; 135(5): 825–37
20. Takada I, Kouzmenko AP, Kato S: Molecular switching of osteoblastogenesis versus adipogenesis: implications for targeted therapies. Expert Opin Ther Targets, 2009; 13(5): 593–603
21. Yadav VK, Oury F, Suda N et al: A serotonin-dependent mechanism explains the leptin regulation of bone mass, appetite, and energy expenditure. Cell, 2009; 138(5): 976–89
22. Wu QZ, Zhang X, Zhong MW et al: Effects of bariatric surgery on serum bile acid composition and conjugation in a diabetic rat model. Obes Surg, 2016; 26(10): 2384–92
23. Rocha-Rodrigues S, Goncalves IO, Beleza J et al: Physical exercise mitigates high-fat diet-induced adiposopathy and related endocrine alterations in an animal model of obesity. J Physiol Biochem, 2018; 74(2): 235–46
24. Calle EE, Kaaks R: Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms. Nat Rev Cancer, 2004; 4(8): 579–91
25. Ohnishi H, Saitoh S, Akasaka H et al: Incidence of hypertension in individuals with abdominal obesity in a rural Japanese population: The Tanno and Sobetsu Study. Hypertens Res, 2008; 31(7): 1385–90

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26. Sun D, Liu SZ, Zhang GY et al: Sub-sleeve gastrectomy achieves good diabetes control without weight loss in a non-obese diabetic rat model. Surg Endosc, 2014; 28(3): 1010–18
27. Pereferrer FS, Gonzalez MH, Rovira AF et al: Influence of sleeve gastrectomy on several experimental models of obesity: Metabolic and hormonal implications. Obes Surg, 2008; 18(1): 97–108
28. Bruinsma BG, Uygun K, Yarmush ML, Saeidi N: Surgical models of Roux-en-Y gastric bypass surgery and sleeve gastrectomy in rats and mice. Nat Protoc, 2015; 10(3): 495–507
29. Kawasaki T, Ohta M, Kawano Y et al: Effects of sleeve gastrectomy and gastric banding on the hypothalamic feeding center in an obese rat model. Surg Today, 2015; 45(12): 1560–66
30. Mosialou I, Shikhel S, Liu JM et al: MC4R-dependent suppression of appetite by bone-derived lipocalin 2 (vol 543, pg 385, 2017). Nature, 2017; 546(7658): 440
31. Wang J, Chen L, Zhang Y et al: Association between serum vitamin B-6 concentration and risk of osteoporosis in the middle-aged and older people in China: A cross-sectional study. BMJ Open, 2019; 9(7): e028129
32. Friedman MA, Bailey AM, Rondon MJ et al: Calcium- and phosphorus-supplemented diet increases bone mass after short-term exercise and increases bone mass and structural strength after long-term exercise in adult mice. PLoS One, 2016; 11(3): e0151995
33. Narmada IB, Rubianto M, Putra ST: The role of low-intensity biostimulation laser therapy in transforming growth factor beta1, bone alkaline phosphatase and osteocalcin expression during orthodontic tooth movement in *Cavia porcellus*. Eur J Dent, 2019; 13(1): 102–7
34. Guanabens N, Gifre L, Peris P: The role of Wnt signaling and sclerostin in the pathogenesis of glucocorticoid-induced osteoporosis. Curr Osteoporos Rep, 2014; 12(1): 90–97
35. Hu K, Olsen BR: Osteoblast-derived VEGF regulates osteoblast differentiation and bone formation during bone repair. J Clin Invest, 2016; 126(2): 509–26
36. Granchi D, Ciapetti G, Gomez-Barrena E et al: Biomarkers of bone healing induced by a regenerative approach based on expanded bone marrow-derived mesenchymal stromal cells. Cytotherapy, 2019; 21(8): 870–85
37. Chabbi-Achengli Y, Coudert AE, Callebert J et al: Decreased osteoclastogenesis in serotonin-deficient mice. Proc Natl Acad Sci USA, 2012; 109(7): 2567–72
38. Alonso N, Soares DC, McCloskey EV et al: Atypical femoral fracture in osteoporosis pseudoglioma syndrome associated with two novel compound heterozygous mutations in LRP5. J Bone Miner Res, 2015; 30(4): 615–20
39. Frost M: Patients with high-bone-mass phenotype owing to Lrp5-T2531 mutation have low plasma levels of serotonin (vol 25, pg 673, 2010). J Bone Miner Res, 2010; 25(8): 1896
40. Liu Q, Wang S, Wei M et al: Improved FGF21 sensitivity and restored FGF21 signaling pathway in high-fat diet/streptozotocin-induced diabetic rats after duodenal-jejunal bypass and sleeve gastrectomy. Front Endocrinol (Lausanne), 2019; 10: 566
41. Wang TT, Hu SY, Gao HD et al: Ileal transposition controls diabetes as well as modified duodenal jejunal bypass with better lipid lowering in a non-obese rat model of type II diabetes by increasing GLP-1. Ann Surg, 2008; 247(6): 968–75
42. Charles JF, Ermann J, Aliprantis AO: The intestinal microbiome and skeletal fitness: Connecting bugs and bones. Clin Immunol, 2015; 159(2): 163–69
43. Maynard CL, Elson CO, Hatton RD, Weaver CT: Reciprocal interactions of the intestinal microbiota and immune system. Nature, 2012; 489(7415): 231–41
44. Lucas S, Omata Y, Hofmann J et al: Short-chain fatty acids regulate systemic bone mass and protect from pathological bone loss. Nat Commun, 2018; 9: 55
45. Ooi JH, Li YF, Rogers CJ, Cantorna MT: Vitamin D regulates the gut microbiome and protects mice from dextran sodium sulfate-induced colitis. J Nutr, 2013; 143(10): 1679–86
46. Yano JM, Yu K, Donaldson GP et al: Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis (vol 161, pg 264, 2015). Cell, 2015; 163(1): 258

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