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BARIATRIC SURGERY AND ITS EFFECT ON THE METABOLIC ASPECT IN DIET INDUCED OBES RAT MODEL

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ABSTRACT

Bariatric surgery is the only treatment for obesity after failure of medication that may confers the definitive weight loss at long-term duration. Furthermore to weight loss there is a strong evidence to cure various co-morbid conditions originated with obesity like obstructive sleep apnea, hypertension, Type II diabetes mellitus, asthma, gastro-esophageal reflux disease and osteoarthritis. While systematic study on the bariatric surgical mechanisms is still unknown. The main objective is to measure the effects of sleeve gastrectomy on the treatment of obesity and insulin resistance in high fat diet-induced obese (DIO) rats. Sleeve gastrectomy was performed in DIO rats. Food intake, body weight and fasting blood glucose were measured after SG. Blood plasmic parameter such as GLP-1, Gut harmone (Adipokines). Blood glucose, fasting ghrelin level and insulin during meal test from 1 to 3 and 5 month were measured periodically. The insulinogenic index and (HOMA) Homeostatic model assessment were measured between sleeve and sham operated rats. Sleeve gastrectomy (SG) play a potential role in producing weight loss and resolving in type 2 diabetes also show higher successive rates and lower mortality and represent reliable restrictive procedure to treat obesity and their associated co-morbidities.

KEY WORDS: Diabetes, Sleeve gastrectomy, obesity, metabolic indices.

INTRODUCTION

Obesity is a major health problem worldwide because it develope and promotes different diseases such as type 2 diabetes mellitus (T2DM) and cardiovascular disease, which causes greater rate of mortality [1] Insulin resistance by obesity is a major metabolic problem that causes the development of type 2 diabetes mellitus. Body weight reduction can maintain metabolic status and minimize the risk of type 2 diabetes mellitus [2-3] but control of weight in obesity is difficult for most patients. Current therapies, including exercise, medication, diet, and lifestyle modification are insufficient to treat the obesity. There is strong evidence which suggest that bariatric surgery can cure not only obesity but also treat its co morbidities [4-8]. Sleeve gastrectomy (SG) was used initially as the first steps to treat obesity after the medication failure. Sleeve gastrectomy is usually used in obese patients with or T2DM and are the most effective approach to achieve long-term weight loss [9-11]

In sleeve gastrectomy, the stomach volume is restricted with the removal of fundus from the stomach. Recently, SG showed the lower levels of the appetite stimulant gastric hormone such as, ghrelin, and produce effective weight loss [12]. However, the mechanism of weight loss and their co-morbidities which associated from obesity, such as type 2 diabetes after sleeve gastrectomy, have not yet been identified.

The beneficial effects of bariatric surgery include reduced in insulin resistance, loss of weight, , and minimize the risk factors for cardiovascular disease 2 [13].

Now Bariatric surgery has been carried out on a huge variety of animal models, including the Rats, pig and dog. The result of these experiments support that weight loss is mainly related to reduce gastric volume and changes in the regulation of gut hormones. However, the mechanisms of bariatric surgery on glucose metabolism, and on hormone secretion and action remain to be elucidated. Recent findings from bariatric experiment show changes in meal patterns, glucose metabolism, energy expenditure and food choice [14-16]. These studies showed that the improvement in glucose tolerance is due to increased insulin sensitivity. The developments of bariatric surgery in rats were accomplished in high fat diet-induced obese (DIO) animals. These studies shows a higher surgical success rate of survival and fewer surgical complications were observed in rats with sleeve gastrectomy and mRYGB procedures [17].

MATERIALS AND METHODS

Animals

Twenty adult Wistar rats of either sex of 10 weeks old were used in this study. The rats were obtained from Animal Facilitation centre, R.V.Northland Institute Dadri, Greater Noida. The study were conducted after obtaining ethical committee clearance from the Institutional Animal Ethics Committee. The rats were kept at a room temperature of 25 ± 2 °C with relative humidity of 50–60% and on 12hrs light/12 hrs dark cycles in the Animal House. Animals were provided with standard rodent pellet diet (Amrut, India) and the food was withdrawn 18-24 h before the experiment though water was allowed *ad libitum*. The composition of diet is 10% protein, 4% arachis oil, 1% fibers, 1% calcium, 1000 IU/gm vitamin A and 500 IU/gm vitamin D for 14 weaks. All surgery was performed under sevoflurane anesthesia, and all efforts were made to minimize suffering. All experiments were performed in the morning accordance with the current guidelines for the care of laboratory animals and the ethical guidelines for investigations of experimental animals approved by Institutional Animals Ethical Committee.

Bariatric Surgical preparations

Animals were fasted prior to the surgical preparations for 14 to 18 hours. Isoflurane as surgical anesthesias were used to induced and maintained anesthetic condition throughout the surgery (2-3% with O2). Followed by aseptic preparation midline incisions were performed to expose the gastrointestinal tract. At the last of study of the bariatric surgery, the midline incisions were closed and the rats were recovered on a water-circulated heating pad.

Obesity Parameter

Body mass index (BMI) = body weight (g)/length^2 (cm^2).

Specific rate of body mass gain (g/kg) = dM/Mdt, where dM represents the gain of body weight during dt = t_2-t_1 and M is the rat body weight at t_1

Based on food and caloric intake, the following nutritional parameters were calculated:

Energy intake (kJ/day) = mean food consumption × dietary metabolizable energy

Feed efficiency (FE; %) = (mean body weight gain×100) / energy intake

Sleeve Gastrectomy

Rats were randomly divided into two groups. Group I as SG (n = 10) and Group II served as sham operation (SO) group (n = 10). After 16 h of food deprivation, penicillin as antibiotics (20,000 units/kg) were administered intramuscularly 30 min before operation and Sleeve gastrectomy were then performed in anesthetized rats with Isoflurane. The procedure involves the excision of approximately 70 percent of the stomach. A gastric tube were made along with the lesser curvature with the incision line starting at the body, 1 cm distal to the gastro esophageal junction and extending to around 1 cm proximal to the pylorus along the lower great curvature. The stomach tube (1 cm in diameter) was closed using 9-0 Ethilon sutures. In this way, gastric continuity is started and the greater curvatures of gastric part were removed. But in the sham surgery the stomach, duodenum and jejunum were mobilized and the stomachs were clamped without incision.

Postoperative care

At the last of every SG, 10 mL of 0.9% saline were administered subcutaneously to avoid dehydration in rats. Rats were placed for fasting 48 h after surgery and received only 10 mL normal 0.9% saline and 20,000 units/kg penicillin subcutaneously once per day to maintain body homeostasis in rats. The rats were fed with Ensure liquid (1 kcal/mL; Abbott Japan Co, LTD, Osaka, Japan) from day 3 and normal feed from day 8 after surgery. Rats were observed for 1to 5 month after surgery.

Outcome and Laboratory assays

Blood were taken from tail vein to measure fasting serum glucose levels using a hand-held glucometer (Sanwa Kagaku Kenkyusho Co, LTD, Tokyo, Japan) after overnight fasting, including serum Adipokines, insulin, Leptin, glucagon-like peptide-1 (active), ghrelin (active), homeostatic model (**HOMA)** assessment were measured by using this formula: fasting glucose (mmol/L) × insulin (U/mL)/22.5 [18]. ELISA test were used to measure the serum ghrelin and adiponectin levels (#EK- 031-31 and #EK-ADI-02;).

Meal test

The rats were allowed for fasting overnight. Meal tests were performed in conscious rats by administrating of 4 mL/kg Ensure liquid (1 kcal/mL; Abbott Japan Co, LTD) by oral gavages [19], at the rate of 1 mL/min [20]. Blood glucose levels were measured from the tail vein at 0, 10, 30, 60, 120, and 180 min after Ensure liquid administered. After that blood sample (180mL) were collected into the tubes containing a protinin through a catheter from the femoral vein and then centrifuged and stored at -80^{0}C till hormone assays were performed.

Hormone assays

ELISA kit were used to assayed the fasting plasma ghrelin levels. Mitsubishi Kagaku Iatron Inc (Tokyo, Japan). The fasting plasma Insulin and GLP-1 level during meal test were assayed by a kit respectively.

Insulinogenic index and insulin sensitivity

Insulinogenic index were measured by dividing blood plasma insulin increasement relative to the fasting level by the corresponding net increase of blood glucose [O insulin (μU/mL)/O glucose (mg/dL)] during the meal test at 10 min. The Homeostatic model assessments (HOMA-IR) were determined from fasting blood plasma glucose and fasting insulin by using this formula -- HOMA-IR = fasting insulin (μU/mL) × fasting blood glucose (mg/dL)/405 [21].

Statistical Methods

The data obtained was compiled in excel and were analyzed using the Instate 5 The significance differences between the means was evaluated by the analysis of variance followed by Dunnet's Multiple comparison test. Data were presented as mean ± standard deviation. The P values below 0.05 were considered to be statistically significant.

RESULTS

Surgery

The Group I of 10 rats were performed sleeve gastrectomy and group II (n= 10) served as sham surgery. In the sleeve group (n= 10), 7 were survived to the last of the study. 2 were killed prematurely because of distress secondary to abscess, 1 rat were unable to recover from anesthesia. In the sham group (n= 10), 8 rats were survived at the last of the study and 2 rats were die due to internal distress. At the last of the experiment, 2 rats in sleeve group were noted to have a >2-cm abscess. These rats were excluded from analysis because of the potential effect of inflammation on the study results.

Body weight and food intake

Food intake and Body weights were reduced in sleeve-treated compared with Sham Operated-treated rats during the 5 month of the study (Fig. 1 &2). After surgery weight of rats suddenly decreases in first month, after that it again gain with time as compared to sham operated. Food intake during first month decreases but during 2nd of month rats were increases there caloric intake with respect to the sham operated.

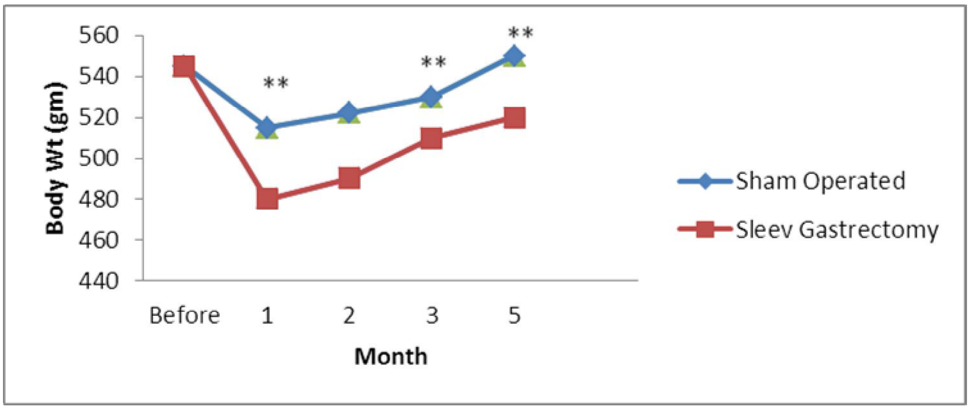


Fig. 1 : Changes of body weight and food intake after surgery in (A,B) DIO rats. Data are presented as mean ± standard deviation. **P < 0.01, *P < 0.05 between SG and SO rats.

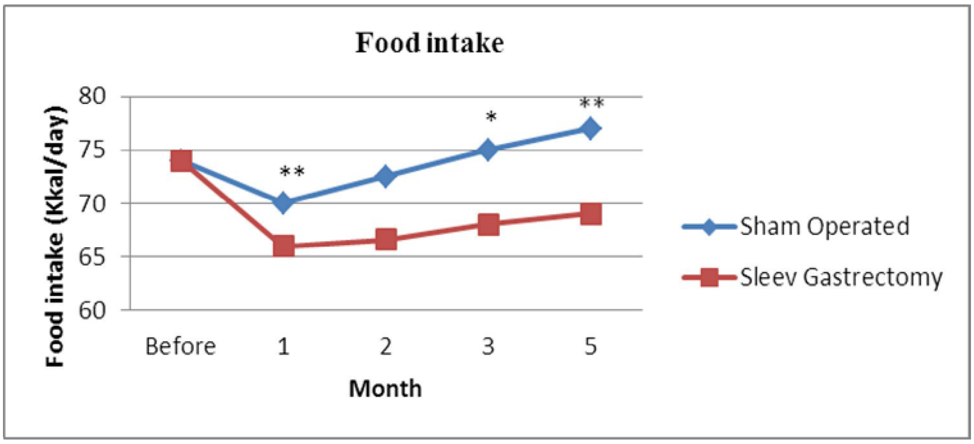


Fig. 2 : Food intake after surgery in DIO rats. Data are presented as mean ± standard deviation. **P < 0.01, *P < 0.05 between SG and SO rats.

Fasting blood glucose

Fasting glucose levels of sleeve-treated were significantly decreases as compared to the SO-treated rats during 5 mo after surgery in DIO rats (Fig. 3).

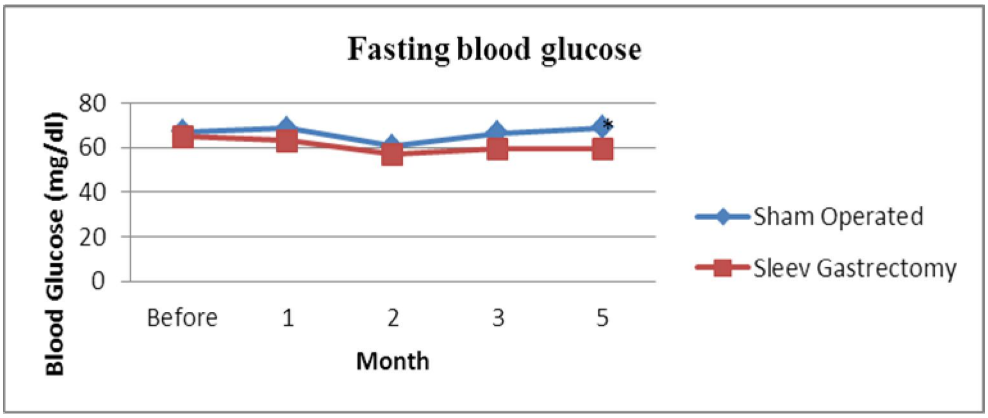


Fig. 3 : Changes of fasting blood glucose levels after surgery. Data are presented as mean ± standard deviation. *P < 0.05 between SG and SO rats

Blood glucose, insulin, and GLP-1 levels during meal test in DIO rats

Blood glucose levels at 60, 120 and 180 min during meal were improved in sleeve -treated rats at 1 month after surgery (Fig. 4a). The improvement appeared clearly at 3 mo after surgery (Fig. 4 b) and associated with significantly increase in early insulin secretion and sensitivity (Fig. 4c). GLP-1 secretions were significantly increased during meal test after 3 month in SG-treated rats (Fig. 4d).

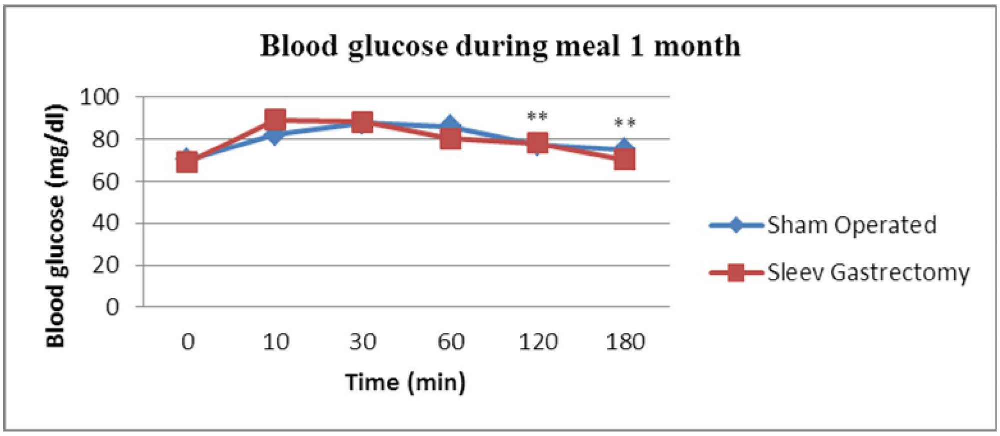


Fig. 4. A

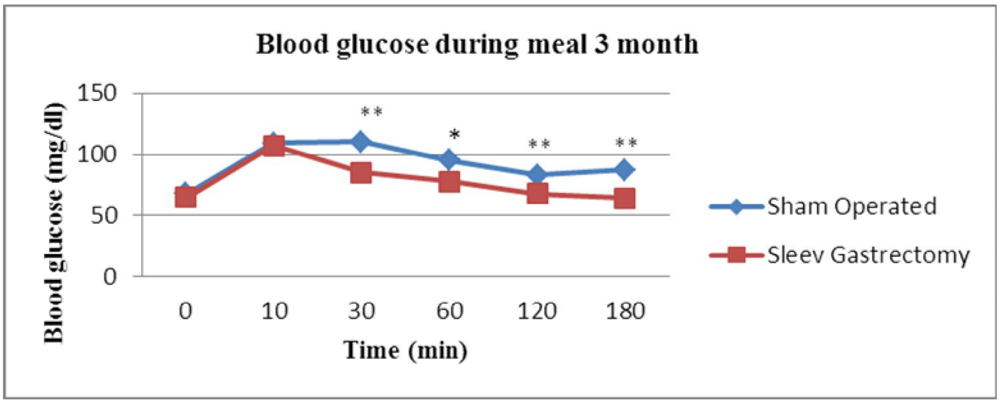


Fig. 4.b

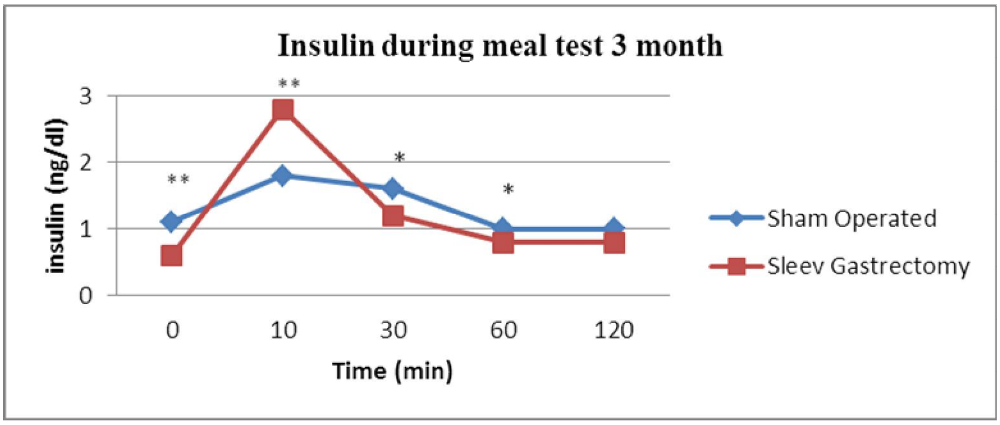


Fig. 4.c

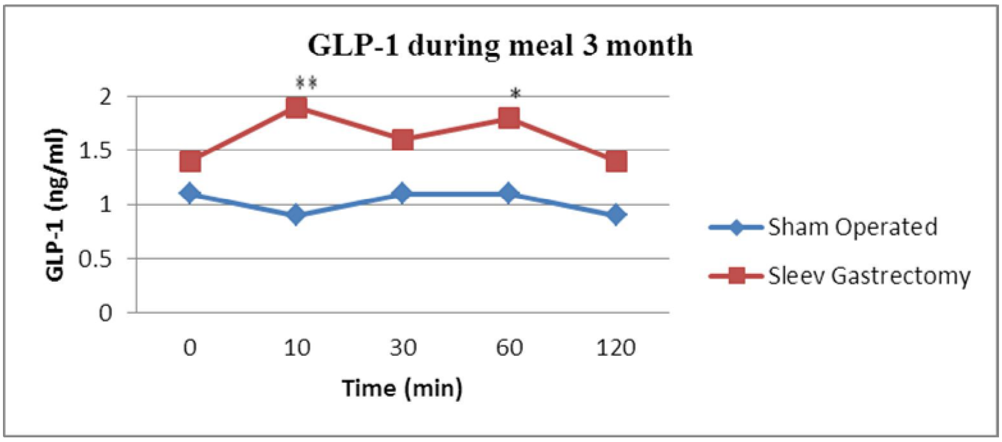
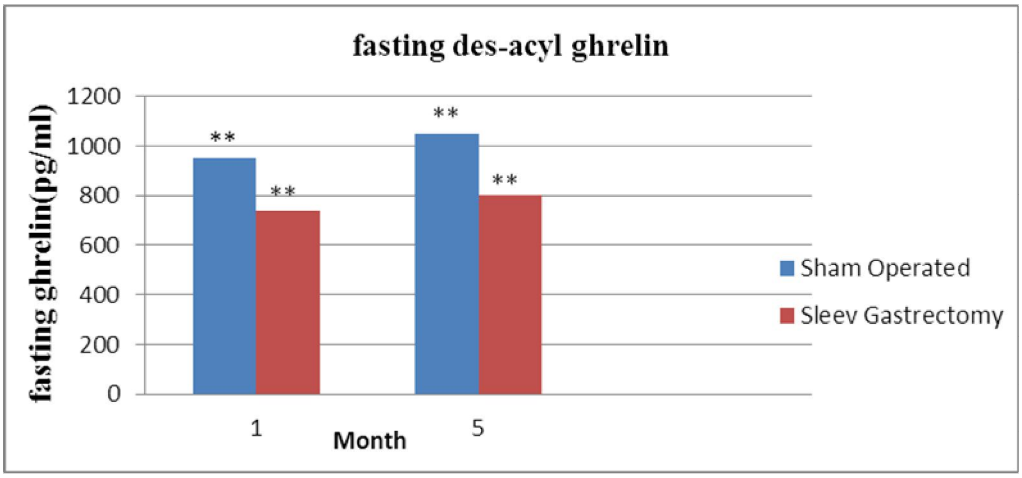


Fig. 4.d

Blood glucose (fig. 4.a) during meal test at 1 month after surgery. (fig.4.b) Blood glucose during meal test at 3 month, (fig. 4.C) insulin, and (fig. 4.D) GLP-1 levels during meal test at 3 mo after surgery in DIO rats. Data are shown as mean ± standard deviation. **P<0.01, *P<0.05, P < 0.05 between SG and SO rats.

Des-acyl ghrelin

In both DIO and GK rats, fasting des-acyl ghrelin levels were significantly lower in SG-treated rats compared with those in SO-treated rats at 1 and 5 mo after surgery (Fig. 5).



Fasting des-acyl ghrelin levels in DIO rats at 1 and 5 mo after surgery. Data are shown as mean ± standard deviation. **P < 0.01, between SG and SO rats.

Adipokines

The adiponectin levels in the sleeve treated were greater as compared to the sham treated rats. (0.42 ± 0.18 versus 0.17 ±.14 ng/mL; *P* < 0.004). The Leptin levels were significantly lower in the sleeve group than in the sham group (1.2 ± 1.3 versus 3.4 ± 2.4 ng/mL; *P* <.01. In contrast,

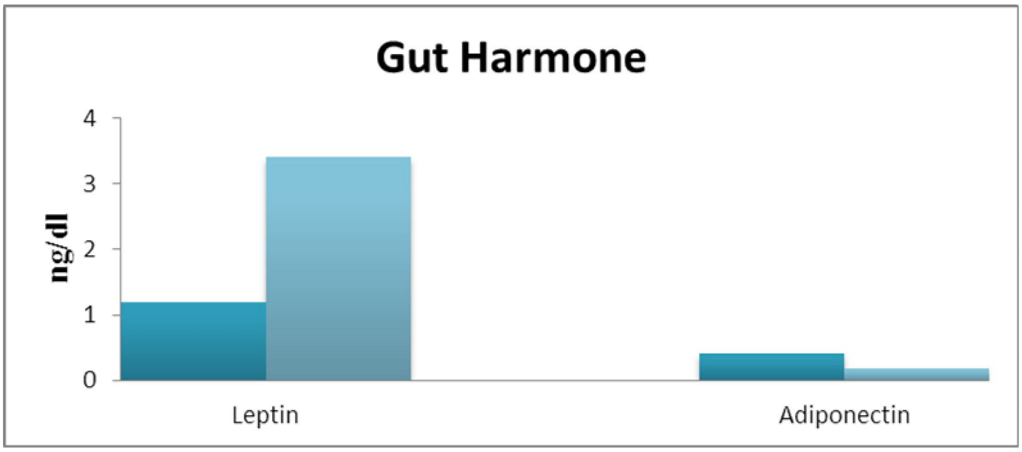


Fig. 5

HOMA-IR and insulinogenic index during meal test at 5 month after surgery in DIO rats.

DIO rats			**P value**
	SG	SO	
HOMA-IR	2.3 ± 0.8	3.6 ± 0.7	0.005
Insulinogenic index	1.6 ± 0.8	0.5 ± 0.3	0.004

Data are presented as mean ± standard deviation.

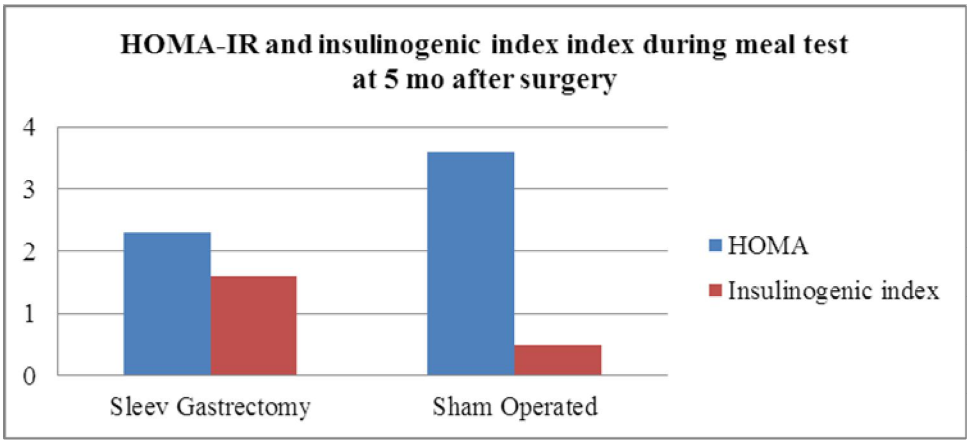


Fig. 6 : No significant difference in HOMA-IR between the SO and SG groups.

DISCUSSION

The present study showed that sleeve gastrectomy maintain the glucose tolerance, with increased Glucagon Like Peptide-1 secretion and insulin secretion and action during meal test after the surgery and reduced the level of fasting ghrelin, not only in non obese insulinopenic diabetic rats but also in obese insulin-resistant rats. After the sleeve gastrectomy rats were regain weight faster and more prominently and also shown the improvement in glucose tolerance were seen earlier in DIO rats. The glucose tolerance improvement mechanism after

SG in DIO rats is based on early insulin response during meal test were enhanced and insulin resistance were decreased after sleeve gastrectomy as compared to the SO.

The decreases in food intake and weight loss in the present study after the SG rats were smaller than we had expected. In contrast, greater food intake decreasement and weight loss are usually observed after SG in humans. One main thing is that this sleeve gastrectomy procedure may not reduce the sufficient gastric volume in order to decrease food intake in rats. However, the appropriate exclusion in gastric volume during SG procedure in rats is technically critical.

Nutritional control is the another possible explanation to control weight loss, since nutritional care is one of the important factors to obtain expected weight reduction after SG in humans [22]. Carelessness in nutritional care may also leads to the smaller weight loss or early regain weight after SG in humans. So, lack of dietary care could partly explain small weight loss and early weight regain after SG in this study. The similar decrease in food intake and smaller weight loss after SG were also observed in previous studies [23-27]. According to this study, rat model may not completely fit to the sleeve gastrectomy model in humans. However, our study found a difference in improvement in glucose tolerance. Therefore, this study can provide the evidence about the impact of SG on insulin-deficient non obese diabetes rats.
This study showed that des-acyl ghrelin levels were decreased in DIO rats after SG. So we decided to measure des-acyl ghrelin level at place of acyl ghrelin because previous study [28] showed a significant reduction in des-acyl ghrelin but no significant change in acyl ghrelin after SG, and implied that des-acyl ghrelin could play a major role in the mechanisms of weight loss after SG.

This bariatric surgery demonstrated a significant improvement in Adipokines and weight loss (decreased Leptin and increased adiponectin). These outcome are consistent with other rodent and human studies based on sleeve gastrectomy [29-30]. Improvements in the Adipokines level causes decreasement in inflammation.

Our studies also conclude that there are no differences in ghrelin levels between the sleeve and sham operated group rats. Ghrelin is an orexigenic hormone mainly produced by A cells of the gastric mucosa in the fundus and gastric body. Therefore, ghrelin levels should theoretically decrease after sleeve gastrectomy. After sleeve gastrectomy decrease in a ghrelin levels has been announced in humans [31]. However, in rodent models an opposite effect has been documented after sleeve gastrectomy.

[32-33]. The Anatomical differences between the human stomach and rat might account for some of these differences, because a large area of the rats stomach is composed of an aglandular fore stomach. Therefore, SG in rodents model might result in the removal of less ghrelin producing glandular stomach than in humans. In addition, extra gastric production of ghrelin in rodents has been proposed [34].

As ghrelin level decreases, resulting decrease in appetite and subsequent weight loss. and may also have contributed to improved glucose homeostasis, as ghrelin exerts several diabetogenic effects. However sleeve gastrectomy in DIO rats resulted in decreased ghrelin levels after surgery compared with sham-operated rats [35-36], but had no significant effects in other studies.

Several guidelines suggest that bariatric procedure should be considered for morbidly obese person. There is huge evidence which suggest that bariatric surgery could resolve type 2 diabetes mellitus in patients with low-body mass index and defined as “metabolic surgery”. This study results provide the evidence about the effects of sleeve gastrectomy in diabetic subjects with normal body weight and insulin deficiency.

CONCLUSION

In conclusion, this study show that in DIO rats SG could improve glucose tolerance with increased insulin action or secretion. The improvement in glucose tolerance was shown earlier in DIO rats and weight regain after SG occurred faster and more prominently in sham operated as compared to the SG rats. However the present study results provide the evidence about the effects of SG in diabetic subjects can induce weight loss and improve the Leptin and adiponectin level by way of mechanisms also independent to the ghrelin level with normal body weight and insulin deficiency.

Disclosures

The authors declared that there is no any conflict of interest in relation to this article.

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