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Levels of GLP-1 In Response to The Most Common Used Bariatric Procedures in Obese Patients with Type 2 Diabetes Mellitus

Amira M. Elsayed*[1], Walaa M. lbrahim[1], Ahmed M.F.Salama[2] , Maha H.Morsy[4] , Eman M. Araby[3] , Rasha O. Abdelmoniem[1].

[1] Department of Internal Medicine, [2] Department of General Surgery,
[3] Department of Public Health and Community, Faculty of Medicine, Benha University, Egypt.
[4] Department of Respiratory Care Technology, Faculty of Applied Health Sciences Technology, Misr Univeristy for Science and Technology, Egypt.
***Corresponding author:** Amira M. Elasyed, Mobile: 00201017994486, **E-mail:** amiramohamady@gmail.com, **ORCID ID**: 0000-0002-2863-3120.

ABSTRACT

Background: In the last two decades, extreme obesity and its comorbidities have often been treated with bariatric surgery.

Objective: Our goal was to compare the levels of GLP-1 in individuals who are severely obese three months after undergoing any of the three more frequent bariatric methods: sleeve gastrectomy (SG), Roux en Y gastric bypass (RYGB), or intragastric balloon (IGB).

Patients and Methods: This is prospective research being done at Benha University Hospital for people with obesity and type 2 diabetes who have been recruited 3 months prior to having any bariatric surgeries. Patients were subjected to measurement of WC, BMI and laboratory assay of HbA1c, fasting plasma glucose (FPG), fasting insulin, HOMA-IR, ALT, AST, glucagon-like peptide-1 (GLP-1) and lipid profile before and after 3 months of procedures.

Results: There was significant improvement of FPG, and HbA1c in RYGB operation in comparison with other bariatric procedures. Fasting insulin was substantially lower in the RYGB surgery than the in SG and IGB ($p < 0.05$) with substantial improvements of HOMA-IR for RYGB surgery ($p < 0.05$). In RYGB surgery, there was highly substantial increase in GLP-1 levels compared to SG and IGB procedures ($p <0.001$). The change in BMI were significant ($p <0.001$) in RYGB but waist circumference did not change significantly after 3 months of any of three procedures.

Conclusion: Our results demonstrated that GLP-1 values were increased after RYGB compared to SG and IGB after three months of the procedures.

Keywords: Diabetes Mellitus, GLP-1, Bariatric procedures.

INTRODUCTION

In the last two decades, extreme obesity and its comorbidities have often been treated with bariatric surgery [1]. Bariatric operations often involve restrictive or a mix of restrictive and malabsorptive approaches [2]. Sleeve gastrectomy (SG) is a type of restrictive operation keeping the whole length of the gastrointestinal tract [3].

While, the restrictive and malabsorptive surgery is accomplished by gastric bypass that was known as a Roux-en-Y gastric bypass (RYGB) [4]. Intragastric balloon (IGB) placement is a transitory, less invasive procedures for weight reduction by causing satiety through application of a balloon with a 400 ml volume [5]. Numerous gastrointestinal (GI) hormones, such as ghrelin, peptide YY (PYY), and glucagon-like peptide-1 (GLP-1), communicate with peripheral tissues and the central nervous system to control glucose regulation and energy balance. Distal intestine L-cells release PYY and GLP-1 to reduce hunger, boost satiety, and delay gastrointestinal motility [6].

Additionally, GLP-1 functions as an incretin to boost glucose-stimulated insulin release, while PYY enhances insulin sensitivity [7]. Ghrelin is an orexigenic hormone that is released by the proximal small intestine and gastric fundus to promote hunger, boost gut motility, and reduce insulin excretion [8]. The levels of postprandial GI hormones after bariatric operation, precisely GLP-1, seems to be the most crucial hormone for glucose regulation and weight reduction [9].

Remission of diabetes varied from 45 to 97% of patients based on the type of operation (restrictive, poorly absorbing, or both) and the design of the study [10]. Even though several trials showed comparable elevations in postprandial active GLP-1, some publications claim that RYGB boosts postprandial GLP-1 more than VSG [11].

Our aim was to perform a comparative analysis of the levels of GLP-1 in morbidly obese patients after 3 months of any of the three most popular bariatric procedures; SG, RYGB or IGB. Additionally, to determine whether treatments may lead to greater improvements in the metabolic syndrome's constituents as possible indicators of future comorbidities.

SUBJECTS AND METHOD

The study was conducted at Benha University Hospital. A total of 49 type 2 diabetic patients with morbid obesity (BMI ≥ 35), were planned to undergo either RYGB, IGB or SG. The following clinical data were recruited; age, sex, type of bariatric surgeries, waist circumference (WC), body mass index (BMI) and blood pressure. The patients were divided into 3 groups; IGB-operated group (15 patients), RYGB-operated group (17 patients) and SG-operated group (17 patients).

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Exclusion criteria: Age less than 18 years old**,** psychiatric illness, substance abuse, previous gastrointestinal surgery, and treatment with weight loss medications (thiazolidinediones, dipeptidyl peptidase 4 (DPP-4) inhibitors or GLP-1 agonists).

Study Design:
This was a prospective research of participants with obesity and type 2 diabetes who were included before and three months after their bariatric surgeries. HbA1c values of ≥ 6.5% (48 mmol/ml), fasting glucose values of ≥ 126 mg/dL, and 120 min postprandial glucose values of 200 mg/dL were used to identify diabetes mellitus [12]. WC and change of BMI were assessed before and after 3 months of the procedures. HbA1c, fasting plasma glucose (FPG), fasting insulin, HOMA-IR, ALT, AST, GLP-1 and lipid profile were measured before and after 3 months of procedures.

Measurement of GLP-1:
ELISA was performed to determine the total GLP-1 level using a Multiskan TM Microplate photometer (Thermo Fisher Scientific Oy, Ratastie, Finland). Radioimmunoassay was employed to assess plasma insulin levels. Benha University Hospital's labs carried out all hormone testing.

Bariatric procedures:
RYGB
The gastric cardia was separated from the remaining stomach to create a tiny gastric pouch with a capacity of ~30 cm^3. After that, the small intestine was separated by 30 to 50 cm distal to the Treitz ligament. The distal end of the divided small intestine was dragged up in an antecolic fashion (on top of the colon) and anastomosed to the newly formed gastric pouch as part of the Roux limb technique. The Roux limb ranged from 75 to 150 centimeters in length [4].
SG: About 80% of the stomach's tissue was removed vertically to create the SG, leaving behind a long, tubular gastric pouch [13].

IGB: We performed diagnostic esophagogastroduodenoscopy before IGB to exclude any contraindications. MedSil (Novomytishchinski, Mytischi, Moscow region, Russia) balloon was implanted under sedation with the patient in lateral decubitus position. Then, the balloon was inflated with 600–700-ml saline and 10-ml methylene blue solution under endoscopic vision. After the procedure, the patient stayed for 2 hours under observation [14].

Diet after procedures:
However, the postoperative diet was advised to consist of clear liquids during the first week, a pureed diet during weeks three to five, and solid meals beginning in week four [15].

Ethical consideration:
The Ethics Committee of Benha University in Egypt gave its approval for all operations involving human subjects in this research that adhere to the standards outlined in the World Medical Association's Declaration of Helsinki. Each patient provided written permission prior to enrollment.

Statistical methods
Using IBM-SPSS Statistics for Windows, version 23.0 (Copyright IBM Corp., Armonk, N.Y., USA.), data were checked, coded by the researcher, and analyzed. Non-parametric test (Kruskall-Wallis) was used to compare between mean ranks of the three groups regarding laboratory outcome, hormonal changes & changes in WC and BMI before & 3 months after the three bariatric procedures. Percentages were calculated for categorical data. When the p-value is equal to or lower than 0.05, it was deemed substantial.

RESULTS
The mean age of the study population was 42.92 ± 3.34 years with non-substantial variation among the three groups (p=0.928). 71.4 % of all patients were females (35 patients) while 28.6 % of them were males (14 patients) **(Table 1).** Overall, 49 patients underwent interventions (IGB= 15, 17= RYGB, SG=17) for morbid obesity. **Table (2)** provided a summary of the patients' primary features. There was significant improvement of fasting plasma glucose, and HbA1c, in RYGB operation in comparison with other bariatric procedures, while the lipid profile did not change significantly among the three bariatric procedures **(Table 3)**.

In terms of hormonal changes after the procedures; fasting insulin was significantly lower in the RYGB surgery than in the SG and IGB with significant improvements of HOMA-IR of the RYGB surgery ($p < 0.05$). In RYGB surgery, there was highly significant increase in GLP-1 levels compared to SG and IGB procedures ($p<0.001$) **(Table 4 & figure 1)**.

For weight loss parameters, the change in waist circumference was non-significant after 3 months of the procedures ($p >0.05$) while there was significant decrease of BMI after 3 months of RYGB surgery ($p<0.001$) **(Table 5 & figure 1)**.

Table (1): Sex distribution of studied group

Sex	IGB (n=15)	RYGB (n=17)	SG (n=17)	Total
Male	4 (28.6%)	5 (35.7%)	5 (35.7%)	14
Female	11 (31.4%	12 (34.3%)	12 (34.3%	35

Table (2): Baseline characteristics of the obese patients with type 2 diabetes before each type of intervention

Operation / Mean rank	IGB No.=15	RYGB No.=17	SG No.=17	Kruskal- Wallis test	P-value
Age (years)	26.2	24.7	24.3	0.15	>0.05
BMI (Kg\m^2)	23.0	22.1	29.7	2.85	>0.05
WC (cm)	23.7	23.2	27.9	1.13	>0.05
SBP (mmHg)	22.8	23.4	28.5	1.63	>0.05
DBP (mmHg)	27.4	20.5	27.4	2.64	>0.05
FPG (mg/dl)	22.0	22.6	30.0	3.29	>0.05
HbA1c (%)	29.6	22.9	22.9	2.33	>0.05
FI (µIu/ml)	22.1	23.0	29.5	2.73	>0.05
HOMA-IR	23.7	21.7	29.5	2.81	>0.05
GLP-1 (P mol/L)	28.3	28.6	18.5	5.61	>0.05
TC (mg/dl)	26.4	25.9	22.9	0.59	>0.05
HDL (mg/dl)	21.9	21.1	31.6	5.64	>0.05
LDL (mg/dl)	26.1	26.0	23.0	0.51	>0.05
TG (mg/dl)	26.7	23.4	25.1	0.43	>0.05
ALT (IU/L)	28.4	18.9	28.1	4.76	>0.05
AST (IU/L)	25.3	28.7	21.0	2.50	>0.05

Table (3): Laboratory outcome after three months of the three bariatric procedures

Operation / Mean rank	IGB No.=15	RYGB No.=17	SG No.=17	Kruskal-Wallis test	P-value
FPG (mg/dl)	34.9	15.7	25.7	14.7	<0.001**
HbA1c (%)	41.3	13.6	22.0	31.6	<0.001**
TC (mg/dl)	24.9	24.8	25.4	0.02	>0.05
HDL (mg/dl)	18.1	26.0	30.0	5.69	>0.05
LDL (mg/dl)	28.3	22.3	24.8	1.45	>0.05
TG (mg/dl)	29.7	20.9	24.9	3.06	>0.05
ALT (IU/L)	28.1	24.6	22.7	1.16	>0.05
AST (IU/L)	27.8	28.4	19.2	4.41	>0.05

***Highly significant*

Table (4): Hormonal changes after each procedure

Operation / Mean rank	IGB No.=15	RYGB No.=17	SG No.=17	Kruskal-Wallis test	P-value
FI (Iu/ml)	34.0	16.4	25.6	12.3	<0.05*
HOMA-IR	33.1	16.0	26.8	11.9	<0.05*
GLP-1 (P mol/L)	8.0	40.7	24.3	42.3	<0.001**

**significant **highly significant*

Table (5): Waist circumference & BMI after 3 months of each procedure

Operation / Mean rank	IGB No.=15	RYGB No.=17	SG No.=17	Kruskal-Wallis test	P-value
WC (cm)	26.7	20.2	28.3	3.08	>0.05
BMI (Kg\m^2)	28.9	13.9	32.6	16.4	<0.001**

***Highly significant*

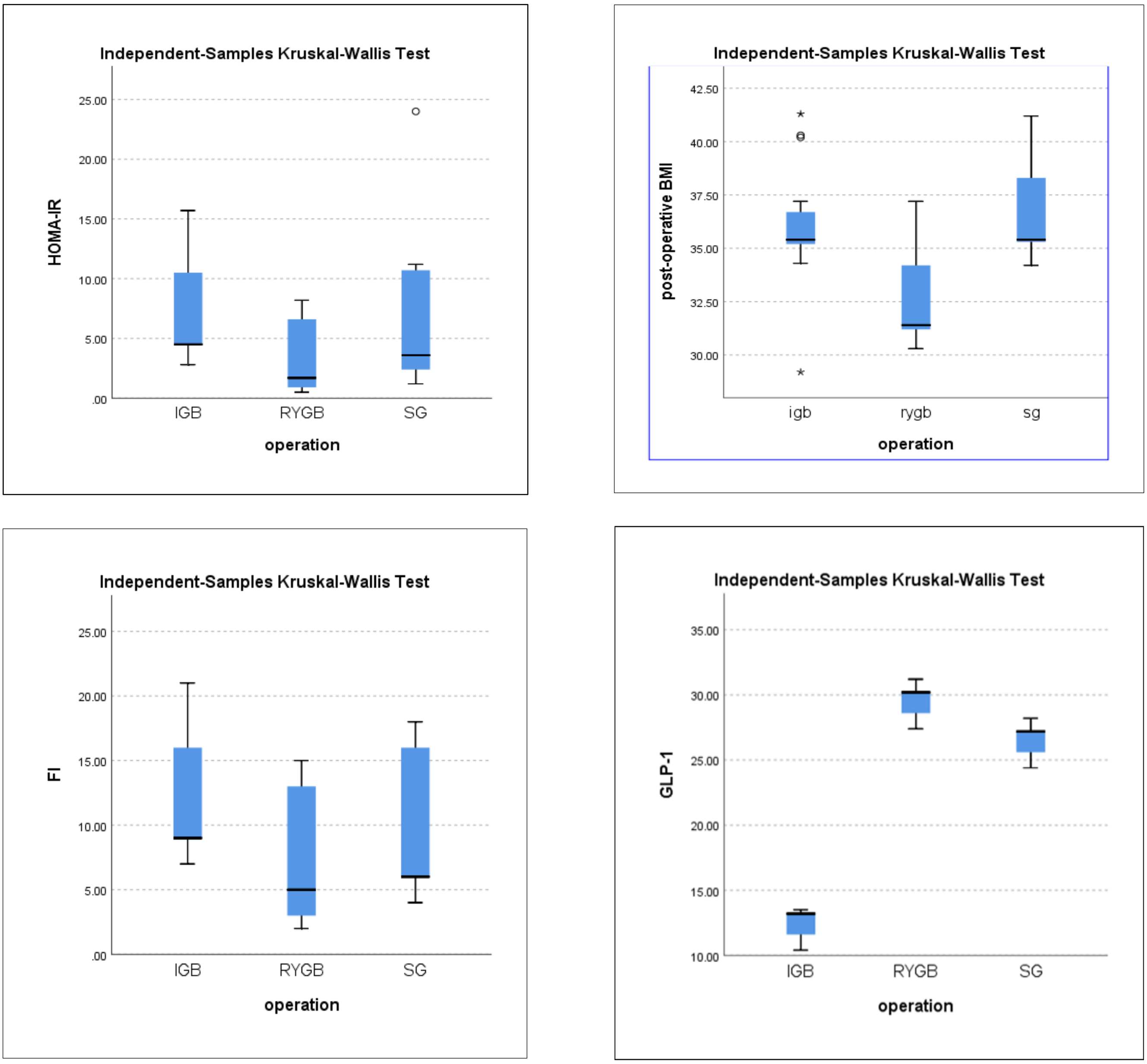

Figure (1): post-operative changes in BMI, HOMA-IR, FI & GLP-1

DISCUSSION

Adults with BMI more than 40 kg/m^2 may successfully manage their morbid obesity with bariatric operation [10]. In order to understand its function in the underlying mechanism of weight reduction in obese individuals with type 2 DM, we looked at changes in the levels of GLP-1 in the blood following various kinds of bariatric surgeries. Researchers have looked how GLP-1 functions as a modulator of post-operative advantages that lead to weight reduction and T2D remission [16]. Our results showed that WC, BMI, SBP, DBP, FPG, FI, HOMA-IR, GLP-1, HbA1c, lipid profile, ALT and AST were almost similar before any of the three procedures. Likewise, one study demonstrated non-significant difference with respect to BMI, insulin levels, hypertension, hyperlipidemia and liver enzymes before RYGP, SG, sleeve gastrectomy with jejunal bypass [10]. Another study revealed similar baseline BMI, HbA1c, and diabetes-duration before either SG or RYGB [15].

Our results showed improvement of glycemic control in RYGB among the three types of procedures. In the same context, RYGB has been shown to achieve better remission of type 2 DM than SG [17]. Additionally, in a large retrospective multicenter study, RYGB produced 10% higher remission rate of diabetes than SG [18]. Two studies showed better remission rate for type 2 DM in RYGB in comparison with banding [15].

But **Mullally *et al*.** [16] demonstrated similar improvement of beta-cell function after SG and RYGB in obese patients with type 2 DM. A remission of diabetes was detected in 20%, 29%, 62.5%, and 52% of patients after gastric banding, calibrated gastrectomy type Mason (CGMa), SG, and RYGB respectively. Diabetes remission was obviously better after SG than gastric banding (P = 0.0026). Contrary, the superiority of RYGB on gastric banding was statistically insignificant (*P* = 0.051). It has been proposed that variations in ghrelin, GLP-1, and peptide YY secretion that take place after SG or RYGB may be crucial for diabetes remission, increasing insulin sensitivity, and resuming the original insulin secretion phase [15]. Previously, an intravenous glucose tolerance test (IVGTT) three days after SG, revealed significant increases in peripheral insulin sensitivity and insulin production in diabetes patients with a duration of less than 10.5 years, as well as a decline in ghrelin, an increase in GLP-1, and an increase in glucose-stimulated PYY. According to the authors, removing a portion of the gastric tissue from SG enhances insulin production by removing any extra-pancreatic and/or extra-intestinal components that may accumulate in the stomach and restrict insulin release [15]. In RYGB, excluding the proximal small intestine may lead to a higher improvement in insulin secretion because nutrients are excluded from the proximal small intestine and unabsorbed nutrients are quickly sent to the distal small intestine, which is hypothesized to boost release of GLP-1 and PYY [19].

Meanwhile, accelerated stomach emptying after SG has been demonstrated in scintigraphy experiments, and this may also improve postprandial GLP-1 and PYY release after SG [16].

Concerning insulin resistance parameters in our study, fasting glucose, FI, and HOMA-IR were improved significantly in the group underwent RYGB with improvement of diabetes control. One study showed improvement of HOMA-IR in patients underwent RYGB in comparison with laparoscopic adjustable gastric banding (LAGB) after one year of surgery. Insulin sensitivity improved similarly in the two surgical groups after 10 and 20 % of weight loss [15]. After three months of the operations, our data revealed no statistically substantial change in total cholesterol, HDL-C, LDL-C, and triglyceride levels. Previous studies reported that RYGB's had greater capacity to lower blood triglyceride levels [20]. However, **pham *et al.*** [15] found no difference in triglyceride levels between four types of bariatric surgery. Inconsistency of the results concerning lipid profile may be related to different study designs and periods of follow up postoperatively.

Our results demonstrated significant decrease in BMI in RYGB, while waist circumference did not change significantly among the bariatric procedures. It was previously mentioned that weight did not change significantly in rats subjected to SG, gastric bypass or ileal transposition [21]. Comparing the balloon's long-term weight reduction to those of drugs and bariatric surgery, the balloon's results were less favorable [22]. After two years of treatments, the proportions of excess weight reduction following gastric bypass, gastric sleeve, and gastric band operations were 70, 60, and 50%, respectively [15].

Our study revealed that GLP-1 increased significantly 3 months postoperative in patients underwent RYGP. Similar study found greater release of GLP-1 in RYGB, compared to LAGB, at any level of weight loss [15]. Another research showed that only in the RYGB group did GLP-1 and PYY significantly rise and remain elevated until year 4 [23]. At 26 weeks, GLP-1 area under curve (AUC) post SG was considerably greater than baseline, however it was not sustained at 52 weeks. While, GLP-1 AUC substantially elevated following RYGB from the starting point at 26 weeks and sustained at 52 weeks [24]. However, one study on rates proved an elevation in the basal and glucose-stimulated GLP-1 values in the case of SG compared to gastric bypass and ileal transposition [21]. Specialized enteroendocrine K- and I-cells released the hormones cholecystokinin (CCK) and glucose-dependent insulinotropic peptide (GIP), whereas enteroendocrine L-cells create the hormones GLP-1, GLP-2, PYY, and oxyntomodulin [25].

While, proximal “L-cells” produce significant amounts of GLP-1 [10]. But these cells also co-express CCK, GIP, neurotensin, or secretin [26]. Some gut hormones were not an essential mechanism of improvement in weight and glucose management following bariatric surgery, according to data on variations in post-surgical hormonal gut peptides. Numerous studies have shown that following VSG compared to RYGB, fasting ghrelin levels were considerably lower [10]. However, mice with ghrelin genetic defects lose weight normally, indicating that this drop in ghrelin is not required for metabolic benefits following VSG [27]. The peptide CCK works as a satiety peptide and promotes gallbladder contraction. Although postprandial CCK levels were observed to be elevated in individuals who received RYGB surgery two weeks after the procedure and one and two years after the procedure, the postprandial increase is less in RYGB than in VSG [28]. Another peptide called glucose-dependent insulinotropic peptide (GIP) is released by enteroendocrine cells (K-cells) in the proximal gut and is crucial for controlling gastric secretion and motility as well as insulin secretion. Postprandial GIP levels have reportedly remained stable throughout the course of two weeks after RYGB compared to baseline. However, postprandial GIP levels were discovered to be lower a year following RYGB and VSG surgery [29 & 30]. Preproglucagon, the gene that makes GLP-1, is responsible for the tissue-specific coding of number of peptides. Both oxyntomodulin and GLP-1 are thought to control satiety and glucose homeostasis. However, GLP-2 plays a more important part in controlling the shape of the intestine [31]. DPP 4 is an enzyme that quickly breaks down GLP-1. Because of this, only 10–15% of secreted GLP-1 reaches peripheral tissue in its complete form [10]. Despite this, it has been shown that RYGB and VSG both consistently raise GLP-1 levels. Notably, individuals who lost the same amount of weight by calorie restriction did not experience the benefits of RYGB and VSG on postprandial GLP-1 levels, underscoring the significance of surgery [31]. After surgery, GLP-1 levels both overall and actively rise. Following RYGB and VSG, the concentration of GLP-1 is about ten times greater [28]. Certain findings have shown that RYGB raises postprandial GLP-1 to a larger extent than VSG, even though some clinical investigations demonstrated comparable postprandial raises in active GLP-1[32, 10 & 29].

The significant postprandial release of GLP-1 after bariatric surgery is believed to be the consequence of quick nutrient delivery down into the GI tract, where the bulk of L-cells are situated, as it was shown after RYGB via alterations in GI tract structure [32]. Additionally, VSG accelerates gastric emptying rate due to increased gastric pressure, increasing nutrient delivery to the distal intestine [31]. These findings support the hypothesis that enteroendocrine cell numbers or nutritional sensitivity of the existing enteroendocrine cell population are growing in the intestinal physiology in response to fast nutrient entry. For instance, long-term consumption of high-fat meals alters the structure and functionality of the gut's nutrition sensing pathways [33]. Such as adjustments to cell number in people who continue to consume high fat diets [34] and on either chow or high fat diets [10] in VSG surgery causing intestinal hypertrophy upon dietary exposure. Conversely, RYGB surgery increases the release of GLP-1 through increase of L-cell hypertrophy and numbers, irrespective of diet exposure [34]. The substantial rise in plasma bile acid levels and types observed with both RYGB and VSG provides another method by which nutrient-sensing is connected to the rise in postoperative GLP-1. However, there is disagreement over whether bile acids contributed to the rise in GLP-1 after surgery [10].

CONCLUSION

Our results demonstrated that GLP-1 levels were increased after RYGB compared to SG and IGB after three months of the procedure with improvements of insulin sensitivity and DM. BMI but not waist circumference were significantly lower in RYGB procedure. Hence, bariatric procedure choice remains open choice according to the situation of the patient.

Limitations of the study:

The discovery of several elements that contribute to the metabolic advantages of SG, IGB, and RYGB and the distinctions between these treatments was hindered by the small population and brief research durations.

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