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## Effect of Laparoscopic Roux-En-Y Gastric Bypass on Metabolic Syndrome and GLP-1 Hormone

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### ABSTRACT

**Background:** An enlarged incretin response after Roux-en-Y gastric bypass (RYGBP) has been proposed to promote weight loss and obesity-related comorbid conditions amelioration especially type 2 diabetes mellitus (T2DM). The dramatic amelioration of T2DM following RYGBP could be accounted for by changes in glucagon-like peptide-1 (GLP-1) secretion. The objective of the study is to evaluate the effect of RYGBP as a metabolic surgery on metabolic syndrome parameters and on fasting serum GLP-1 after one year in 30 patients with BMI of 35-39 Kg/m<sup>2</sup>. This aimed to prove that a metabolic surgery should be able to resolve one or more of the metabolic syndrome parameters without causing any undue weight loss.

**Methods:** The selected group of patients had different degrees of glucose tolerance: normal glucose tolerance (NGT, n=9), impaired glucose tolerance (IGT, n=9), and type 2 diabetes (n=12). This study was done to determine the changes of GLP-1, BMI, insulin resistance before and 1 year after RYGBP.

**Results:** A high significant increase in serum GLP-1 was recorded in the three included groups. Moreover, high significant decrease in fasting glucose from 145.3 to 99.2 mg/dl, associated with significant decrease in fasting insulin from 16.1 to 11.3  $\mu$ U/liter, in all these three groups, postoperatively, along with a high significant decrease in Homeostasis Model of Assessment - Insulin Resistance (HOMA-IR). All other metabolic syndrome components improved significantly postoperatively, including dyslipidemia, hypertension, and obesity.

**Conclusion:** Our study supports that RYGBP is associated with alterations in glucose kinetics leading to improvement of type II DM. We consider RYGBP as a proposed treatment for type 2 diabetes.

## INTRODUCTION

The prevalence of obesity has increased markedly worldwide in the past years[30]. Excess adiposity increases the risk of a variety of comorbid conditions[22]. Recent studies have shown that bariatric surgery is not only highly efficient in promoting weight loss, but it also leads to an improvement, or resolution of most of the obesity-related co-morbidities[18]. In particular, patients with diabetes mellitus show a marked improvement in glucose homeostasis after undergoing surgery for weight loss[8]. RYGB improves glycemic control through mechanisms beyond weight loss and reduced caloric intake[12]. GLP-1 is an incretin hormone that has a wide range of effects on glucose metabolism and cardiovascular function[33]. GLP-1 is released in response to nutrient ingestion from endocrine L cells, most densely located in the distal ileum. Under physiological conditions, GLP-1 acts primarily to augment insulin secretion after an oral glucose load. GLP-1 has been shown to decrease glucagon secretion[10], stimulate the growth and differentiation of pancreatic beta cells and exert cytoprotective and antiapoptotic effects on beta-cells[16]. It also plays a role in the ileal brake mechanism, in which the presence of nutrients in the ileal lumen leads to a decrease in gastric motility and emptying[22]. In obese patients, the mechanism whereby obesity lowers GLP-1 secretion may be related to insulin resistance that accompanies weight gain[10]. RYGB results in accelerated delivery of nutrients to the hindgut, which results in decreased gastric

emptying and GI transit, dubbed the “ileal brake.” GLP-1 has been suggested as one of the mediators of the “ileal brake.” GLP-1 release is augmented after RYGB[4]. Hunger was decreased and satiety increased 6 weeks after RYGB with concomitant increases in plasma GLP-1[20]. Thus, increased postprandial plasma GLP-1 after RYGB may decrease food intake and lower plasma glucose[21]. The inhibition of gastric emptying plays an important role as this greatly reduces postprandial glucose excursions and increases satiety. Also weight loss leads to alleviation of insulin resistance that occurs in type 2 diabetes[18]. In the brain, GLP-1 receptors are found in the paraventricular nucleus and other hypothalamic regions involved in the regulation of appetite and body weight[9]. GLP-1 appears to cross the blood-brain barrier[13] and postprandial increases in circulating GLP-1 are temporally associated with neural activation in areas of the hypothalamus and prefrontal cortex that are involved in the regulation of feeding behavior[23]. The aim of this work was to evaluate the effect of laparoscopic Roux-en-Y gastric bypass as a metabolic surgery on metabolic syndrome parameters and on fasting serum GLP-1 after one year in patients with BMI of 35-39 Kg/m<sup>2</sup>. This aimed to prove that a true metabolic surgery should be able to resolve one or more of the metabolic syndrome parameters independently of the body weight and without causing any undue weight loss.

## MATERIALS AND METHODS

This prospective study was carried on 30 metabolic syndrome obese patients. They included 22 females and 8 males. Their ages ranged from 21-62 years with mean of age  $39.4 \pm 11.9$ . Body mass index (BMI) ranged from 35.3-39.95 with a mean of  $39.02 \pm 1.5$ .

All patients were subjected to Lonroth's laparoscopic Roux-en-Y Gastric Bypass. The study was carried in the Department of General Surgery at Ain Shams University Hospitals and Ahmed Maher Teaching Hospital from June 2011 till June 2012. Twenty apparently healthy volunteers were taken as controls.

The selected patients satisfied the criteria of the metabolic syndrome with BMI between 35-39 and one or more of the following criteria: D.M type II ,dyslipidemia and hypertension.

Control subjects were normal ranged BMI with normal glucose tolerance and with  $< 6.2\%$  of HbA1c. They were age and sex matched to the patients group. HbA1c was measured by chromatographic technique using kits obtained from Stanbiolaboratories, Texas, USA.

Preoperatively, the patients were subjected to general examination with particular attention to measuring weight, height, accurate calculation of body mass index (BMI). An informed consent was obtained from all participants and the study was approved by the Ain Shams Medical Ethics Committee.

Blood samples were collected by venipuncture after overnight fast. Serum was centrifuged (1500 g for 15 min) and measurement was done for

biochemical markers including triglyceride, LDL cholesterol, HDL cholesterol, insulin, and plasma glucose. They were measured in the clinical laboratory of Ain shams University Hospital.

Fasting serum GLP-1 concentration (ng/ml) was evaluated using the GLP-1 enzyme immunoassay (ELISA) kit (DRG International Inc., USA), according to the instructions of the manufacturer. The minimum detectable concentration was 10 pg/ml. The intra- and inter-assay coefficients of variation were both  $< 13\%$ . Fasting serum insulin concentration ( $\mu\text{IU/ml}$ ) was evaluated using the insulin enzyme immunoassay (ELISA) kit (Monobid Inc., lake forest ,USA), according to the instructions of the manufacturer. The minimum detectable concentration was 0  $\mu\text{IU/ml}$ . The intra-assay and inter-assay coefficients of variation were 6.4% and 9.5% respectively.

HOMA-IR was used as a measure of insulin resistance and was calculated as  $\text{fasting serum insulin } (\mu\text{U/mL}) \times \text{glucose (mg/dL)} / 405$  [17].

Effect of the operation on the Metabolic Syndrome parameters was recorded after one year by calculating the postoperative BMI, re-measurement of the blood pressure, fasting blood sugar, total lipid profile, fasting serum insulin, fasting serum level of GLP-1 hormone and re-calculation of HOMA-IR.

### *Statistical analysis*

Statistical analysis was done using a personal computer soft ware package for Social Science (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Data were expressed as Mean  $\pm$  SD for quantitative parametric measures and both number

and percentage for categorized data. Student's *t* - test was used for comparison between two independent groups for parametric data. Paired *t*-test was used for comparison between two dependent groups for parametric data. Spearman correlation coefficient was calculated to evaluate the correlations between circulating levels of fasting GLP-1 and selected variables.  $P > 0.05$  was considered non significant,  $p < 0.05$  was considered significant and  $p < 0.01$  was considered highly significant.

## RESULTS

The anthropometric and metabolic variables at baseline and 1 year after surgery are presented in Table 1. There was a lower statistically significant mean postoperatively when compared to preoperative results regarding BMI, fasting blood glucose, systolic blood pressure, diastolic blood pressure and serum LDL, cholesterol and triglycerides with  $p$  value  $< 0.01$ . Regarding HDL, there was highly statistically significant mean postoperatively when compared to preoperative results with  $P$  value  $< 0.01$ .

**Table (1):** Anthropometric and metabolic variables preoperatively and 1 year postoperatively.

	Preoperative		Postoperative		t	p
	Mean	±SD	Mean	±SD		
BMI (kg/m <sup>2</sup> )	39.02	1.50	29.053	3.73	17.293	.001
Fasting blood glucose (mg/dL)	145.30	66.77	99.20	13.92	4.141	.0001
Systolic blood pressure (mmHg)	151.00	12.892	122.33	4.302	13.723	.001
Diastolic blood pressure (mmHg)	95.87	8.270	80.33	1.826	13.723	.001
Serum HDL (mg/gL)	41.20	5.73	47.23	3.56	-10.292	.0001
Serum LDL (mg/gL)	104.90	25.70	95.73	15.50	3.012	.005
Cholesterol (mg/gL)	162.20	29.83	151.40	24.81	4.826	.0001
Triglycerides (mg/gL)	114.43	44.51	99.50	31.00	3.886	.001
Fasting serum insulin (μIU/ml)	16.13	5.52	11.33	4.44	7.171	.0001
HOMA-IR	5.45	2.35	2.78	1.077	7.727	.0001
Fasting serum GLP-1 (ng/ml)	63.76	30.98	123.0	32.71	7.01	.001

Both fasting glucose and insulin decreased so that there was a high significant reduction in HOMA-IR from  $5.45 \pm 2.35$  to  $2.78 \pm 1.077$  in all subjects with  $p$  value  $< 0.01$ .

GLP-1 significantly increased ( $123.0 \pm 32.71$ ), at follow up, compared with presurgical hormonal levels ( $63.76 \pm 30.98$ ) with  $p$  value  $< 0.01$ .

There was inverse correlation between postoperative GLP1 and fasting blood glucose HOMA-IR and insulin (table 2).

**Table (2):** Correlation between post operative fasting GLP-1 and BMI, fasting blood glucose, insulin and HOMA-IR.

	Postoperative serum GLP-1		
	r	p	Sig.
Post BMI (kg/m <sup>2</sup> )	-0.397	>0.05	NS
Post fasting blood glucose (mg/dl)	-0.455	<0.05	S
Post insulin (μIU/ml)	-0.401	<0.05	S
Post HOMA-IR	-0.488	<0.05	S

There was no statistically significant difference between fasting serum GLP1 in preoperative cases when compared to controls with p value >0 .05

GLP-1 was significantly higher in patients with previous history of bariatric surgery (141.50±26.03) when compared to cases without history of any bariatric surgery (113.75±.32.27) with p value < 0.05.

GLP1was significantly higher postoperatively in subjects with normal glucose tolerance (< 100 mg/dl), subjects with impaired glucose tolerance (100-126 mg/dl) and subjects with type II DM (> 126 mg/dl), with P value in all these three groups < 0.01 (table 3). There were 9 cases having

impaired glucose tolerance, all of them returned to normal fasting blood glucose level postoperatively. There were 12 patients having type II diabetes mellitus, 8 patients of them were on oral hypoglycemics that were stopped completely post operatively and returned to normal fasting blood glucose level and the other 4 diabetic patients that were on insulin, shifted to oral hypoglycemic(table 4)

**Table (3):** Comparison between pre and post operative fasting serum GLP-1 in:

	Pre fasting serum GLP-1		Post fasting serum GLP-1		t	p	Sig.
	Mean	±SD	Mean	±SD			
A (n = 9)	53.33	25.86	111.67	30.62	-20.207	<0.01	HS
B (n= 9)	56.67	35.00	114.44	38.36	-34.195	<0.01	HS
C (n= 12)	76.67	29.02	137.92	25.71	-31.267	<0.01	HS

A → subjects with normal glucose tolerance (< 100 mg/dl)

B → Subjects with impaired glucose tolerance (100-126 mg/dl)

C → Subjects with type II DM (> 126 mg/dl)

**Table (4):** Description of improvement of diabetes among patients with impaired glucose tolerance and patients with type II diabetes mellitus

Preoperative state	Postoperative state	Number	%
Impaired glucose tolerance	Complete cure	9	42.85%
Patients on oral hypoglycemics	Stopped and complete cure	8	38.10%
Patients on insulin	Shifted to oral hypoglycemics	4	19.05%

## DICUSSION

In our study we found a highly significant reduction of HOMA-IR after RYGBP . One proposed explanation for the improvement in insulin resistance following RYGBP is that exclusion of the duodenum and proximal jejunum from nutrient stimulation enhances insulin sensitivity. In fact, Rubino (2008)[26] suggested that the underlying primary pathology of insulin resistance could be due to perturbed small bowel signaling and is corrected with duodenal bypass. The development of obesity invariably leads to a reduction of insulin sensitivity. Although weight loss by dieting improves insulin resistance, sustained weight loss is difficult to achieve.

(RYGBP) is among the most successful therapies for sustained weight loss and results in the rapid improvement of type II diabetes[29]. After RYGBP-mediated weight loss, there is an increased expression of muscle insulin receptors and decreased hepatic and skeletal muscle lipid content, this is at least partially due to reduced body weight[7].

RYGBP combines gastric restriction and significant bypass of the stomach and proximal intestine[17]. Gastric volume restriction is an important determinant of increased satiety after laparoscopic adjustable gastric banding[8], Nonetheless, because malabsorption does not appear to play a major role after short-limb

RYGBP[5], it has been hypothesized that a disruption in other factors in the network of signals involved in energy balance[32] accounts for plain gastric restrictive operations being less effective than gastric bypass surgery[29]. Gut-derived hormones have important sensing and signaling roles in the regulation of energy homeostasis[2]. Thus, it has been hypothesized that a critical factor to the efficacy of RYGBP is change in the gut-derived hormones known to influence appetite[15]. The increased Peptide YY(PYY) and GLP-1 concentrations and enhanced ghrelin suppression are compatible with reduced food intake after RYGBP[25]. We found that many studies demonstrated that that serum postprandial GLP-1 concentration is elevated, following RYGBP, for this reason we evaluated serum fasting GLP-1 concentration in our study. In our prospective study, it was observed that RYGBP is associated with a high statistically significant increase in fasting serum GLP-1 level, one year after the surgical procedure, and our results are in disagreement with Isbell et al.(2010)[11] who demonstrated that GLP-1 response was not altered. Additionally, Clements et al. (2004)[6] failed to demonstrate a significant change as they observed that fasting GLP-1 was increased postoperatively but not significantly. It is unclear why these conflicting results, but the cause may be related to differences in the assays used, differences in sample size, or the particular characteristics of the subjects.

Additionally, this study demonstrated a significant negative correlation between fasting GLP-1 and

insulin and this indicates that the increase in fasting GLP-1 level could be due to the presence of negative feedback loop between insulin and GLP-1 levels and this might confirm the exclusion of the duodenum and proximal jejunum from the transit of nutrients may prevent secretion of a putative signal that promotes insulin resistance and type 2 diabetes (“hypothesis of the proximal intestine”)[26]. The bulk of published information suggests that RYGBP causes increased postoperative secretion of GLP-1[25]. The increase in the post-operative secretion of GLP-1 may be due to accelerated gastrointestinal transit time in RYGBP-operated subjects and this hormonal change potentially contributes to reduced appetite after surgery[20].

The mechanism whereby obesity lowers GLP-1 secretion is not known, but may be related to the insulin resistance that accompanies weight gain[11] or may be related to an increase in plasma non-esterified fatty acids[24]. On the other hand, we found in our study that the lean controls had higher levels of fasting serum GLP-1 (but not significantly) than the preoperative obese cases. This could be explained by that the preoperative group did not include morbidly obese patients but only included obese patients with limited BMI between 35-39.9 Kg/m<sup>2</sup>. This is in contrast to different studies that found that GLP-1 is higher in lean than the obese patients[1].

In our study we observed preoperative higher levels of fasting serum GLP-1 in obese patients with previous history of bariatric surgery (gastric banding and VBG) than those obese patients

without. This could be explained by that weight loss after gastric banding surgery improves insulin resistance and this leads to a relative increase in GLP-1 level by a negative feedback loop.

In our study, there was a significant inverse correlation between fasting serum GLP-1 and HOMA-IR postoperatively which are consistent with Yamaoka-Tojo et al, (2010)[33]. This could be explained by acceleration of GLP-1 to lipolysis in adipocytes, which may result in improved insulin sensitivity[10]. Also, in the present study we found a significant inverse correlation between fasting serum GLP-1 and fasting serum glucose postoperatively as consistent with other different studies[18]. This could be explained by that GLP-1 stimulates insulin secretion by binding to GLP-1 receptors on the beta cell[34]. In our study, we observed that RYGBP causes a high significant increase in GLP-1 secretion in patients with normal glucose tolerance, patients with impaired glucose tolerance and also in patients with type II DM. In our study, there were 9 cases having impaired glucose tolerance, all of them returned to normal fasting blood glucose level postoperatively. There were 12 patients having type II diabetes mellitus, 8 patients of them were on oral hypoglycemics that were stopped completely post operatively and returned to normal fasting blood glucose level and the other 4 diabetic patients that were on insulin, shifted to oral hypoglycemic, this means that there is an improvement of glucose tolerance in all these three groups. Furthermore, large clinical series have shown that the relatively few patients whose

diabetes does not completely resolve after RYGBP have typically suffered from the disease for a long time (usually 8–10 years) and required more insulin to maintain glycemic control before surgery[27]. These findings suggest that end-stage beta cell failure, characteristic of long standing type II diabetes, may render these patients' condition irreversible. Accordingly, a surgical approach should be offered early rather than late in the natural course of the disease[26].

In our study ,there was no correlation between fasting serum GLP-1 and BMI postoperatively. On the other hand ,there was a statically statistically significant correlation between fasting serum GLP-1 and HOMA-IR . This might indicate th the improvement of HOMA-IR that occurs postoperatively was independent of weight loss. Similarly, a study done by Le Roux et al. (2006)[14] demonstrated that obese subjects treated with GB had equivalent weight loss and improvements in insulin resistance as measured by HOMA to bypass patients, but did not have the insulin or gut hormone responses indicating that the endocrine changes are a consequence of the particular type of surgery rather than weight loss. Additionally, it was shown that return to euglycemia and normal insulin levels are observed within days after surgery, suggesting that weight loss alone cannot entirely explain why surgery improves diabetes[26].

We observed in our study that that all metabolic syndrome components show statistically significant improvement at follow-up when measured one year postoperatively after RYGBP.



This is consistent with Batsis et al, (2008)[3] who found the same results in a studied group of morbid obese patients .However, no significant correlation between fasting serum GLP-1 and some components of metabolic syndrome including dyslipidemia and hypertension. These results are consistent with Yamaoka-Tojo et al. (2010)[33] who found the same results .

RYGBP is not only highly efficient in promoting weight loss, but it also leads to an improvement of most of the obesity-related co-morbidities[31] .

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