Impact of Laparoscopic Sleeve Gastrectomy on Obese Type 2 Diabetic Patients and Role of Gut Hormones Peptide Tyrosine Tyrosine and Glucagon Like Peptide 1on Remission of Diabetes

Heba H. Zayed[1*], Karim Sabry[3], Yasser M Abdelraouf [1],
Wessam M. Salah[2], Ingy Abdel Wahab[1] and Mabrouk R EL-Sheikh[1]

[1]Department of Internal Medicine, Faculty of Medicine, Tanta University, Egypt.
[2]Department of Clinical Pathology, Faculty of Medicine, Tanta University, Egypt.
[3]Department of General Surgery, Faculty of Medicine, Ain Shams University, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. Authors HHZ and YMA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MRES and IAW managed the analyses of the study. Author WMS managed the laboratory searches. Author KS did the surgical part. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Our Study Aimed: To investigate the effect of laparoscopic sleeve gastrectomy (LSG) on obese T2DM patients, its effect in remission of diabetes and role of gastrointestinal Glucagon like peptide 1(GLP1) and Peptide tyrosine tyrosine (PYY) hormones. Metabolic surgery should be recommended as an option in type 2 diabetic patients (T2DM) with body mass index (BMI) ≥40 Kg/m^2, in patients who have BMI ≥35 Kg/m^2 and in selected patients with BMI < 35 Kg/m^2, if not achieving diabetes control with maximum tolerated anti-hyperglycemic treatment.
Methods: 30 T2DM patients with BMI ≥ 40 kg/m^2 underwent laparoscopic sleeve gastrectomy after full clinical evaluation, routine blood tests, glucagon like peptide 1, Peptide tyrosine tyrosine

_____

Corresponding author: E-mail: dr_hebazayed@yahoo.com;

(fasting, 0.5-hour post-mixed meal test (MMT) serum levels) and upper GIT endoscopy. Follow-up visits were at 3, 6 and 9 months postoperatively to evaluate body weight, BMI and glycated hemoglobin (HbA1C) and at 18th month for confirmation of diabetes remission. Gut hormones were measured at 15 days and 9 months postoperatively.

Results: (53.3%) of patients had partial remission of T2DM according to HbA1C remission criteria. There was significant increase in fasting and post-MMT levels of peptide tyrosine tyrosine, glucagon like peptide 1 postoperatively. The only independent predictors for remission of T2DM were the baseline serum low density lipoprotein cholesterol (LDL-Ch), duration of diabetes, preoperative post MMT Peptide tyrosine tyrosine plasma level, serum thyroid stimulating hormone (TSH) and age.

Conclusions: laparoscopic sleeve gastrectomy can induce partial remission of diabetes in younger patients who had shorter duration of diabetes, higher level of preoperative post-MMT peptide tyrosine tyrosine, lower levels of preoperative serum LDL-Ch and thyroid stimulating hormone.

1. INTRODUCTION

Diabetes mellitus is a worldwide rapidly growing problem affecting more about 425 million individuals with expected 50% increase in the number by the year 2045 [1]. IDF ATLAS 8th edition) Most of patients have type 2 DM (T2DM), which is a result of insulin resistance and/or insulin deficiency [2]. The rapid increase in the epidemic of T2DM is due to the global increased epidemic of obesity as it is estimated that the number of overweight or obese individuals is 1.9 billion, out of them, 600 million are obese according to WHO estimates in 2016 [3].

Lifestyle modification, including diet and exercise, is the initial treatment of both, T2DM and obesity, with initiation of metformin therapy in T2DM. The treatment of individuals with T2DM, not achieving HbA1C target while on lifestyle and maximally tolerated dose of metformin, is upgraded with add one of other oral or injectable drugs based on patients specific criteria [4].

Cardiometabolic surgery has to be considered in T2DM individuals with BMI≥40 kg/m^2, also, in patients with BMI≥35 Kg/m^2 and some selected patients with BMI<35 Kg/m^2 who are not well controlled T2DM on maximally tolerated treatment [5].

Previous reports have different remission rates of T2DM after bariatric surgery, according to our knowledge none of them was conducted in the MENA region which is heavily populated with T2DM patients and great number of obese individuals. This study was conducted to evaluate the effect of laparoscopic sleeve gastrectomy on remission of T2DM and possible role of plasma levels of gut hormones, glucagon like peptide 1(GLP1) and peptide tyrosine tyrosine(PYY), in diabetes remission.

2. MATERIALS AND METHODS

2.1 Study Design

This is a prospective intervention cohort study conducted at Tanta University Hospitals, The Endocrinology Unit and Surgical Department, Egypt.

The study was conducted in a period between April 2016 and October 2017.

2.2 Subjects

The study included 30 obese T2DM patients. They were recruited from The Endocrinology Unit Outpatient Clinic, Tanta University Hospital, Egypt, according to inclusion and exclusion criteria.

Inclusion criteria: T2DM patients with BMI ≥ 35 kg/m2. Diabetes was not well controlled on maximally tolerated medical treatment. Patients who were on oral drugs refused to have insulin injection due to financial, social and psychic aspects towards insulin injection in rural areas and were motivated to have operation for loss of weight.

Exclusion criteria: Secondary causes of diabetes mellitus and obesity, advanced liver and kidney diseases, pregnancy, patients with active

malignancy on clinical bases, advanced cardiac and pulmonary disease and patients with psychotic or eating disorders.

2.3 Methods

Full history taking, clinical examination, routine laboratory tests and upper gastrointestinal endoscopy to ruleoutintra gastric pathology and to evaluate the presence of gastroesophageal reflux disease (GERD), were done for all patients. Endocrine evaluation was done to rule outpossible endocrine causes of diabetes or obesity.

The plasma level of PYY and GLP 1 were measured in the fasting state (after 10 hours over night fasting) and half an hour after mixed meal challenge test [semiliquid meal (70 gm dried milk in 100 ml water) consisting of 26% protein, 26.7% fat, and 38.2% carbohydrate; 347 kcal in total), at base-line and at the 15th day, 9 months postoperatively. For PPY measurement, Human PYY ELISA Kit (MY-BioSource, USA) was used, and for measurement of GLP1, Human GLP1 (7-36) ELISA Kit (Abcam, USA) was used.

Ten-year ASCVD risk score was determined, according to the 2013 American College of Cardiology/American Heart Association risk calculator.

American Diabetes Association (ADA) criteria of diabetes remission was adopted to define remission in this work, depending on HBA1C [6]. Partial remission was defined as: at least 1 year of HbA1c level 5.7–6.4% and complete remission was defined as: at least 1 year of normoglycemia (HbA1c level <5.7%), both in the absence of drug therapy.

A decision to offer surgery followed a comprehensive interdisciplinary assessment. The core team included endocrinologist, anesthetist, surgeon, psychiatrist, dietitian and a nurse, all are experienced in bariatric surgery.

Operative Intervention: Laparoscopic sleeve gastrectomy was performed for all candidates with 4 cm division point from the pyloric ring, over 36 French calibrating tube with staple line enforcement to obtain 80 to 100 ml gastric tubule.

Postoperatively: Follow-up visits were scheduled at 3, 6, 9, 12 and 18 months postoperatively. During each visit, evaluation of weight, BMI and presence of late complications or not, change in metabolic parameters and blood pressure, nutritional deficiencies such as iron, vitamin B12, vitamin D and calcium, improvement of Hb_{A1C} by standardized techniques(Data of HbA1Cwere collected at 12 and 18 months to confirm for remission of diabetes). We measured plasma levels of GLP1, PYY hormones as previously mentioned.

2.4 Statistical Analysis of the Data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. We used Chi-square test for categorical variables, to compare between different groups, Monte Carlo correction test used for chi-square when more than 20% of the cells have expected count less than 5. We used Student t-test for normally distributed quantitative variables, to compare between two studied groups, ANOVA with repeated measures for normally distributed quantitative variables, to compare between more than two periods or stages. Mann Whitney test for abnormally distributed quantitative variables, to compare between two studied groups periods, Friedman test for abnormally distributed quantitative variables, to compare between more than two periods. Multivariate regression analysis to detect the most independent affecting factor for remitter.

3. RESULTS

3.1 Baseline Characteristics of Patients

According to ADA remission criteria, diabetes partial remission was seen in 16 of our 30 patients (53.3%) at 1year post-surgery. There was significant difference between remitters and non-remitters in all baseline characteristics except gender, serum levels of HDL, total cholesterol, TG and waist circumference which is shown in (Table 1). Regarding to preoperative plasma levels of fasting and 0.5 hr post MMT GLP1 and PYY, they were significantly higher in remitter group than in non-remitter group as shown in (Table 2).

Table 1. Comparison between remitters and Non remitters according to baseline characteristics [32, 33]

Baseline characteristics		Remitter (n= 16)		Non remitter (n= 14)		Test of Sig.	P
		No.	%	No.	%		
Gender	Male	8	50.0	3	21.4	^{2}=2.625	0.105
	Female	8	50.0	11	78.6		
Age (years)	Mean ± SD.	36.75 ± 3.75		54.64 ± 3.32		t=13.746*	<0.001*
D.M duration	Mean ± SD.	4.63 ± 1.59		15.07 ± 4.57		U=1.0*	<0.001*
Anti D.M Drugs	Oral hypoglycemic	16	100.0	2	14.3	^{2}=22.857*	<0.001*
	Insulin	0	0.0	12	85.7		
Anti HTN drugs	No	15	93.8	2	14.3	^{2}=19.591*	^{MC}p
	Diuretic	1	6.3	7	50.0		<0.001*
	B.blockers	0	0.0	5	35.7		
SBP (mmHg)	Mean ± SD.	120.0 ± 8.94		155.0 ± 15.7		t= 7.673*	<0.001*
DBP (mmHg)	Mean ± SD.	80.62 ± 2.50		92.14 ± 6.99		t= 5.845*	<0.001*
LDL-Ch (mg/dl)	Mean ± SD.	97.50 ± 10.27		106.86 ± 10.67		t=2.445*	0.021*
HDL-Ch(mg/dl)	Mean ± SD.	36.81 ± 6.51		37.36 ± 6.82		t=0.223	0.825
Cholesterol (mg/dl)	Mean ± SD.	232.19 ± 23.90		237.07 ± 25.36		t= 0.543	0.592
TG (mg/dl)	Mean ± SD.	178.19 ± 47.93		180.64 ± 33.21		U=84.50	0.257
TSH (U/Ml)	Mean ± SD.	1.63 ± 0.61		3.69 ± 0.51		U=4.0*	<0.001*
Weight(Kg)	Mean ± SD.	127.75 ± 7.71		137.50 ± 9.60		t= 3.085*	0.005*
WC (Cm)	Mean ± SD.	128.69 ± 4.05		127.50 ± 12.03		t=0.352	0.729
BMI (kg/m^2)	Mean ± SD.	44.64 ± 3.05		48.59 ± 3.21		t=3.454*	0.002*
HB A1 C (%)	Mean ± SD.	8.08 ± 0.37		8.59 ± 0.29		t=4.166*	<0.001*
FPG (mg/dl)	Mean ± SD.	189.62 ± 14.84		218.0 ± 14.32		t=5.311*	<0.001*
2 hrpppg (mg/dl)	Mean ± SD.	263.12 ± 28.69		309.57 ± 22.10		t=4.912*	<0.001*
Antiplatelet drugs	No	16	100.0	3	21.4	^{2}=19.850*	<0.001*
	Yes	0	0.0	11	78.6		
Serum creatinine	Mean ± SD	0.80 ± 0.07		0.83 ± 0.13		t=0.743	0.466
ASCVD score	Mean ± SD.	3.63±1.26		15.94±9.12		U=12.0*	<0.001*
AST (U/L)	Mean ± SD	64.87±7.73		70.07 ± 3.50		t= 2.421*	0.024*
ALT (U/L)	Mean ± SD.	70.69 ± 11.25		75.86 ± 4.93		t= 1.589	0.123

*t: Student t-test , U: Mann Whitney test , p: p value for comparing between remitter and Non remitter , *: Statistically significant at p ≤ 0.05.*

Anti HTN drugs (antihypertensive drugs), SBP (systolic blood pressure), DBP (diastolic blood pressure), LDL-Ch (low density lipoprotein), HDL-Ch (High density lipoprotein), TG (triglycerides), WC (Waist circumference), BMI (body mass index), HB A1 C (hemoglobin A1 c), FPG (fasting plasma glucose), 2hr pppg (2hr postprandial plasma glucose), ASCVD risk score (atherosclerotic cardiovascular disease score), AST (aspartate aminotransferase), ALT (alanine aminotransferase)

3.2 Effect of LSG on Anthropometric Measures, Cardiometabolic Parameters and Liver Enzymes

All patients, regardless diabetes remission, had improvement in anthropometric measures, cardiometabolic parameters and liver enzymes. This improvement was statistically significant at all periods of follow up except for ASCVD score and DBP, at 3 months, but these parameters showed significant improvement later as shown in (Table 3).

However, when compared between remitters and non-remitters in improvement of baseline characteristics, the remitters had better reduction in body weight and BMI, 10 years calculated ASCVD score and liver enzymes while there was non-significant reduction in other parameters between two groups (Table 4).

Effect of LSG on plasma levels of GLP1 and PYY: At 15 days and 9 months postoperatively, fasting and 0.5 hr post MMT levels of GLP1, PYY increased in comparison with preoperative levels and were significantly higher in remitters than non-remitters (Tables 5, 6).

Multivariate regression analysis: Multivariate regression analysis was done using the only significant different variants at baseline. We found that age (younger patients (36.7 ± 3.7), less duration of diabetes (4.63± 1.59), lower baseline serum TSH (1.63± 0.61), lower baseline levels of serum LDL-Ch (97.50 ± 10.27), and higher post MMT challenge PYY plasma level

were the only independent predictors for T2DM remission after LSG. Although, none of remitters was on insulin therapy, type of therapy wasn't an independent predictor of diabetes remission.Type of therapy is good indicator of β cell reserve, so patients on insulin therapy with less functioning β cells had less probability to regain function and have remission of T2DM. But in our study, small number of patients prevents type of therapy to be statistically independent predictor among baseline characteristics.

4. DISCUSSION

Our study aimed to investigate diabetes remission ofT2DM morbid obese who had sleeve gastrectomy and effect of GLP1 and PYY on this remission by testing these gut hormones response to MMT preoperative and comparing it with postoperative levels. We found that 53.3% of studied patients went into partial remission of diabetes according to ADA criteria of partial remission published in 2009, None of the studied patients had complete remission for T2DM. Insulinunits requirements per day were reduced. None of our patients had postoperative complications. There was increase in postoperative serum levels of fasting and 0.5 hr post MMT GLP1 and PYY at both periods 15 days and 9 months compared with preoperative levels. This increment was more in remitters than non-remitters.In our study, we found that age (younger patients (36.7 + 3.7)), less duration of diabetes (4.63+1.59), lower baseline serum TSH (1.63+ 0.61) and higher post MMT challenge PYY serum level were the only independent predictors for T2DM remission after LSG.

By studying baseline characteristics, we found that partial remission of T2DM patients occurred in patients with younger age, less T2DM duration, lower BMI, lower body weight, lower TSH, HbA1C, fasting and postprandial glucose. Our study included also serum TSH, its level, within normal reference range, could beinvolved in the metabolic syndrome, either in general or could be associated with independent component of the syndrome [7]. This parameter in our opinion might beanother explanation, even partially, to the remission of diabetes in our patients and the improved cardiometabolic profile.

There were different remission rates of diabetes in different studies as PR Schauer, et al. [8], at 5-year time point was 25%,Ejarque, et al. 151 found that rate of complete diabetes remission at 1 year was 53.8%, Marco Milone, et al.,157

proved that at 3 months post-LSG, diabetes remission was 53.3%, 66.7% at 12 months postoperative. Others reported, in their systematic review, that partial and complete remission at post-LSG follow up period of 13 months, was 66% and 27% respectively. But, at two years postoperative in a metabolic sub-study of the STAMPEDE trial, Kashyap et al. [9], reported only negligible improvement after SG with similar weight loss with patients who had RYGB. The difference of remission rates between our study and other research works can be explained on bases of difference in number of treated patients, duration of diabetes, duration of follow up, baseline BMI and body weight and preoperative antidiabetic drugs, preoperative levels of GLP1 and PYY hormones and their levels postoperatively. Also, differences in the postoperative compliance, adherence of patients to proper nutrition, care, social, environmental, educational and cultural aspects play a role.

Similar to our results, Guo-Feng Wang, et al., carried-out a met-analysis of 15 studies involving 1,753 bariatric surgeries, two studies used LSG (Levi et al.,2013, in Spain [6] and Biro et al., 2013, in USA) [10]. They proved that there was an insignificant association between gender and T2DM remission [11] and also, Golomb I, Matan Ben David, et al. [12] but the last study found on contrary with our study, there was no correlation with age and this difference may be due to higher mean age in their study (42.9 years) compared to our mean age for remitters which was 36.5 years. In agreement with our results, other studies proved that expected duration of T2DM >8 years [13] insulin use, and poorer glycemic control are consistently associated with lower rates of remission of T2DM and/or an increased risk of relapse [14,15]. Also, Capoccia, et al. Revealed same results.In contrary with our results, Guo-Wang, et al., proved that in Asian patients, higher baseline BMI showed more remission rate. But BMI, in their study, had different range (26.5-51 Kg/M^2) from our present study [11]. Against both of us, Danila Capoccia, Federica Coccia, et al., showed that the baseline BMI did not correlate with long-term remission or relapse of T2DM [16]. In database concluded from the Swedish Obese Subjects (SOS) study and two randomized controlled studies, in total Seven hundred twenty-seven patients (415 surgical and 312 medical patients). They found that age and preoperative BMI did not influence the rate of remission, but mean duration of diabetes and previous insulin treatment was greater in the non-remission group [17].

Table 2. Comparison between remitters and Non remitters according to preoperative levels of GLP1 and PYY (fasting and 0.5hr post MMT)

GLP1	Fasting		0.5 hr post MMT	
pmol/L	Remitter (n= 16)	Non remitter (n= 14)	Remitter (n= 16)	Non remitter (n= 14)
Mean ± SD.	39.49 ± 12.75	19.86 ± 6.40	44.55 ± 14.84	22.69 ± 6.80
U(p)	2.0[*](<0.001[*])		0.0[*](<0.001[*])	
PYY pg/ml				
Mean ± SD.	63.41 ± 8.72	45.04 ± 4.79	66.57 ± 8.45	49.10 ± 4.77
t(p)	7.004[*](<0.001[*])		6.834[*](<0.001[*])	

U: Mann Whitney test, p: p value for comparing between remitter and Non remitter, *: Statistically significant at $p \le 0.05$. GLP1: glucagon like peptide 1, PYY: Peptide tyrosine tyrosine, MMT: mixed meal test

Table 3. Comparison between the different studied periods in all patients regarding changes in baseline characteristics

	Pre-operative	3 months	6 months	9 months	Ch (pre - 9)	Test of sig.	p_0
AST							
Mean ± SD.	67.30± 6.58	62.90± 9.09	56.27±10.37	49.70±12.26	17.60±9.57	**F=91.709**[*]	<0.001[*]
pPre		0.004[*]	<0.001[*]	<0.001[*]			
ALT							
Mean ± SD.	73.10± 9.12	66.70± 9.38	59.07± 9.85	52.57±10.80	20.53± 7.86	**F=173.182**[*]	<0.001[*]
pPre		<0.001[*]	<0.001[*]	<0.001[*]			
Systolic B.P							
Mean ± SD.	136.33± 21.6	129.2±19.05	125.6±18.27	119.5±18.85	16.80± 6.29	**F=134.656**[*]	<0.001[*]
pPre		<0.001[*]	<0.001[*]	<0.001[*]			
Diastolic B.P							
Mean ± SD.	86.0± 7.70	82.93± 8.67	78.20± 6.97	74.80± 7.59	11.20± 5.62	**F= 61.951**[*]	<0.001[*]
pPre		0.053	<0.001[*]	<0.001[*]			
Cholesterol							
Mean ± SD.	234.47± 24.3	222.1± 20.83	207.0± 18.26	191.17± 20.0	43.30± 23.13	**F= 87.074**[*]	<0.001[*]
pPre		<0.001[*]	<0.001[*]	<0.001[*]			
TG							
Mean ± SD.	179.3± 41.04	167.0± 33.96	154.4± 28.76	142.8± 17.84	36.50±27.98	**F= 47.811**[*]	<0.001[*]
pPre		<0.001[*]	<0.001[*]	<0.001[*]			
LDL							
Mean ± SD.	101.87± 11.3	91.20± 10.55	82.03± 9.47	75.0± 8.75	26.87± 10.89	**F=134.452**[*]	<0.001[*]
pPre		<0.001[*]	<0.001[*]	<0.001[*]			
HDL							
Mean ± SD.	37.07± 6.55	41.93±5.72	46.40± 5.28	51.83± 4.52	-14.77± 4.83	**F=185.581**[*]	<0.001[*]

	Pre-operative	3 months	6 months	9 months	Ch (pre - 9)	Test of sig.	p_0
pPre		<0.001[*]	<0.001[*]	<0.001[*]			
Weight							
Mean ± SD.	132.30± 9.82	123.0± 11.26	114.87± 12.1	106.73± 13.2	25.57± 6.62	**F=301.965**[*]	<0.001[*]
pPre		<0.001[*]	<0.001[*]	<0.001[*]			
BMI							
Mean ± SD.	46.48± 3.67	43.22± 4.08	40.36± 4.35	37.52± 4.83	8.96± 2.24	**F=322.232**[*]	<0.001[*]
pPre		<0.001[*]	<0.001[*]	<0.001[*]			
WC ratio							
Mean ± SD.	128.13±8.59	119.37±9.31	110.1±10.24	98.93±9.74	29.20± 5.12	**F=480.001**[*]	<0.001[*]
pPre		<0.001[*]	<0.001[*]	<0.001[*]			
ASCVD score							
Mean ± SD.	9.37 ±8.78	6.16 ± 5.80	4.68 ± 4.74	4.67 ±5.45	4.70 ± 8.48	Fr=47.970[*]	<0.001[*]
pPre		**0.516**	**<0.001**[*]	**<0.001**[*]			

F: F test (ANOVA) with repeated measures, Sig. bet. periods were done using Post Hoc Test (Bonferroni)
Fr: Friedman test, Sig. bet. Periods were done using Post Hoc Test (Dunn's)
*p_0: p value for comparing between the different periods, pPre: p value for comparing between preoperative and each other periods *: Statistically significant at p ≤ 0.05*

Table 4. Comparison between Remitters and Non-remitters according to Δ changesin baseline characteristics (baseline- 9 months):

Ch (baseline - 9)		Remitter (n= 16)	Non remitter (n= 14)	U	P
AST (U/L)	Mean ± SD.	25.25 ± 5.51	8.86 ± 3.86	4.0[*]	**<0.001[*]**
ALT (U/L)	Mean ± SD.	26.25 ± 5.92	14.0 ± 3.35	4.0[*]	**<0.001[*]**
S.B.P (mmHg)	Mean ± SD.	14.87 ± 6.53	19.0 ± 5.42	71.50	0.093
D.B.P(mmHg)	Mean ± SD.	11.0 ± 3.10	11.43 ± 7.70	107.50	0.854
Cholesterol (mg/dl)	Mean ± SD.	50.19 ± 26.75	35.43 ± 15.57	68.0	0.070
TG (mg/dl)	Mean ± SD.	40.19 ± 35.34	32.29 ± 16.41	105.50	0.790
LDL (mg/dl)	Mean ± SD.	27.38 ± 10.51	26.29 ± 11.69	105.0	0.790
HDL(mg/dl)	Mean ± SD.	-14.94 ± 4.74	-14.57 ± 5.09	111.0	0.984
Weight (kg)	Mean ± SD.	30.12 ± 5.68	20.36 ± 2.41	20.0[*]	**<0.001[*]**
BMI (kg/m^2)	Mean ± SD.	10.49 ± 1.89	7.22 ± 0.98	16.0[*]	**<0.001[*]**
WC (Cm)	Mean ± SD.	31.06 ± 4.95	27.07 ± 4.60	65.0	0.052
ASCVD score	Mean ± SD.	2.43 ± 1.36	7.29 ± 12.03	54.0[*]	**0.015[*]**

*U: Mann Whitney test; p: p value for comparing between remitter and Non remitter *: Statistically significant at p ≤ 0.05*

As regard gut hormones, Korner et al. [18] reported a tenfold increase in postprandial PYY concentrations following RYGB. In a study by Peterli R et al. [19], post-surgery, patients had markedly increased postprandial plasma GLP-1 and PYY levels. In a randomized trial, Karamanakos et al. [20], found that VSG and RYGB resulted in comparable increases in PYY levels for the first 6 months postoperative. But significant reduction in PYY secretion occured at 12 months postoperative in the LSG group.

Table 5. Comparison between remitters and Non remitters according to postoperative levels of GLP1 (fasting and 0.5hr post MMT)

GLP1 pmol/L	Fasting		0.5 hr post MMT	
	Remitter (n= 16)	Non remitter (n= 14)	Remitter (n= 16)	Non remitter (n= 14)
After 15 d				
Mean ± SD.	82.72 ± 4.94	47.95 ± 17.91	101.70 ± 8.46	66.89 ± 17.65
U(p)	21.0[*](<0.001[*])		8.50[*](<0.001[*])	
Delta change	43.23 ± 11.66	28.09 ± 20.91	57.15 ± 14.10	44.20 ± 20.44
U(p)	40.0[*](0.002[*])		58.0[*](0.025[*])	
After 9 months				
Mean ± SD.	80.81 ± 13.01	54.79 ± 34.96	101.06 ± 12.20	61.99 ± 33.43
U(p)	32.0[*](0.001[*])		31.0[*](<0.001[*])	
Delta change	41.32 ± 14.39	34.92 ± 38.31	56.51 ± 15.45	39.29 ± 36.90
U(p)	54.0[*](0.015[*])		50.0[*](0.009[*])	

*U: Mann Whitney test p: p value for comparing between remitter and Non remitter *: Statistically significant at p ≤ 0.05. GLP1: glucagon like peptide 1, MMT: mixed meal test*

Table 6. Comparison betweenremitters and Non-remitters according to postoperative levels of PYY (fasting and post 0.5hr post MMT)

PYY pg/ml	Fasting		0.5 hr post MMT	
	Remitter (n= 16)	Non remitter (n= 14)	Remitter (n= 16)	Non remitter (n= 14)
After 15 d				
Mean ± SD.	101.20 ± 14.65	69.24 ± 6.66	137.04 ± 18.65	94.55 ± 17.75
t(p)	7.499[*](<0.001[*])		6.366[*](<0.001[*])	
Delta change	37.79 ± 18.80	24.20 – 6.17	70.47 ± 22.79	45.45 ± 14.84
U(p)	49.50[*](0.008[*])		28.0[*](<0.001[*])	
After 9 months				
Mean ± SD.	114.53 ± 13.24	78.83 ± 10.82	152.95 ± 33.50	93.77 ± 12.60
t(p)	8.010[*](<0.001[*])		6.225[*](<0.001[*])	
Delta change	51.11 ± 14.61	33.79 ± 7.95	86.38 ± 36.15	44.67 ± 11.05
U(p)	28.50[*](<0.001[*])		10.0(<0.001[*])	

*t: Student t-test, U: Mann Whitney test,p: p value for comparing between remitter and Non remitter *: Statistically significant at p ≤ 0.05 PYY: Peptide tyrosine tyrosine, MMT: mixed meal test*

According Yousseif A et al., nutrient-stimulated PYY and active GLP-1concentrations increased post-LSG and RYGB. However, LRYGBP induced greater, more sustained hormones increments compared to LSG [21]. Nannipieri, et al., showed that serum GLP-1hormone level in response to the meal increased, at 1 year, and PYY hormone level. In remitters, fasting GLP-1 was higher, but its meal response was flat compared with that of non-remitters postoperative, however, the GLP-1 response was higher [22]. Ejarque, et al. showed that 1 year after surgery, the increase in the area under curve (AUC) for GLP-1 was significantly higher in the RYGB group than in SG. Less clear is the extent to which GLP-1 changes are responsible for T2DM remission [23].

The reasons for this increase in GLP-1 post-surgery are unclear but have been attributed to the greater delivery of intact nutrients to the ileum through anatomical changes or increased intestinal transit (hindgut hypothesis) [24] in RYGB surgery there is an alternative hypothesis, the foregut hypothesis, suggests that exclusion of the upper small intestine is responsible for the beneficial aspects of bariatric surgery, possibly through decreased secretion of an' anti-incretin' factor [25].

Regarding to predictors of diabetes remission in other studies, Nannipeire et al., found that the only predictors of diabetes remission in a logistic regression were presurgery β-cell glucose sensitivity and mealstimulated GLP-1 response [22] while, Jimenez et al., found that GLP-1 response to a MMT in patients 2 years after LSG was similar regardless of postoperative T2DM remission or no remission or relapse [26]. According to Milone et al., total of 15 subjects underwent SG (48.4%), high hemoglobin A1c was determined to be a negative predictor of diabetes remission at 12 months [27].

In another multivariate regression model including age and BMI, β-cell glucose sensitivity was negatively associated with HbA_{1c} values, diabetes duration and the GLP-1 response. Torquati et al. [28], found that preoperative treatment with oral antidiabetic agents (as opposed to insulin) and smaller preoperative waist circumference predicted diabetes remission, after adjusting for BMI, sex and preoperative A1C level.

Two studies reported that patients with duration of T2DM > 10 years, preoperative insulin use, and poor preoperative glycemic control were less likely to achieve diabetes remission [29, 30]. However, these studies did not control for important confounding factors that may also influence diabetes remission, including age, sex, preoperative BMI, and preoperative A1C level.

Schauer et al., reported that Reduction in BMI and Duration of T2DM < 8years were the independent predictors for remission of T2DM after LSG [13]. Simona Panunzi, et al., reported in their study that shorter diabetes duration, lower fasting glycemia before surgery, and gastric diversion versus gastric only procedures independently predict higher rates of remission, whereas baseline HbA1c and waist circumference predict improved glycemic control [17].

In another study, although type of surgery was an important factor, especially RYGB, the absence of insulin treatment at baseline along with greater ΔGLP-1AUC$_{b-1m\ (basal-1\ month)}$were the strongest clinical factors associated with a better probability of diabetes remission [31].

The difference in independent predictors of diabetes remission between our study and other studies [32,33] could be explained on bases of difference in the health care systems, either considering early initiation of insulin or not, missed evaluation of beta cell function in our work, the type of bariatric surgery, the technique of surgery and the degree of gastric size reduction.

5. LIMITATIONS OF THIS STUDY

The study had some potential limitations such as; The limited numbers of patients, the lack of preoperative and postoperative evaluation of beta cell function, the under power of evaluation of remission of hypertension and dyslipidemia. The short follow-up period is another limitation of the work beside being two center study.

In this study, remitters had better improvement of BMI, body weight and levels of GLP1 and PYY hormones as compared to non-remitters. But, there was no significant improvement in relation to waist circumference (WC). The fact that, insulin resistance is more related to WC rather than BMI and body weight, raises the possibility that increase of GLP1 and PYY hormones, in remitters more than non-remitters, could be the contributing factor for T2DM remission in remitters.

6. CONCLUSION

Delay in considering bariatric surgery, as a treatment option in uncontrolled T2DM, is as wrong as delay in upgrading pharmacologic treatment. However, it is recommended to select patients, who are going for bariatric surgery, to get the maximal benefit of diabetes remission. Patients with lower age, duration of T2DM, serum TSH level, LDL leveland higher post MMT plasma PYY level, are the patients expected to have the higher rate of remission of diabetes.

CONSENT AND ETHICAL APPROVAL

The protocol was approved by the local ethics committee, and all patients signed a consent form before the study. We select only volunteers patients who met inclusion criteria.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, Malanda B. IDF Diabetes atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045.DIABETES Res Clin Pract. 2018;138:271-281.
DOI: 10.1016/j.diabres.2018.02.023

2. Zaccardi F, Webb DR, Yates T, Davies MJ. Pathophysiology of type 1 and type 2 diabetes mellitus: a 90-year perspective. Postgrad Med J. 2016;92(1084):63-69.
DOI: 10.1136/postgradmedj-2015-133281

3. World Health Organization obesity and overweight fact sheet; 2016.
Available:https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight Accessed at 5/5/2019 at 6 p.m

4. Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: A comprehensive review. Circulation. 2016;133(2):187-225.
DOI: 10.1161/CIRCULATIONAHA.115.018585

5. (English WJ, Williams DB. Metabolic and bariatric surgery: A viable treatment option for obesity. Prog Cardiovasc Dis 2018;61(2):253-269.
DOI: 10.1016/j.pcad.2018.06.003

6. Ramos-Levi A, Sanchez-Pernaute A, Matia P, Cabrerizo L, Barabash A, Hernandez C, Calle-Pascual A, Torres A, Rubio M. Diagnosis of diabetes remission after bariatic surgery may be jeopardized by remission criteria and previous hypoglycemic treatment. Obes Surg. 2013; 23(10):1520-1526.
DOI: 10.1007/s11695-013-0995-y

7. Abd El Raouf Y, Alghazaly G, Elsharawy T. The relationship between serum thyroid stimulating hormone (TSH) level within normal reference range and metabolic syndrome.Life Sci J 2015;12(10):105-112.

8. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy for diabetes-5-year outcomes. N Engl J Med. 2017;376(7):641-651.
DOI: 10.1056/NEJMoa1600869

9. Kashyap SR, Bhatt DL, Wolski K, et al. Metabolic effects of bariatric surgery in patients with moderate obesity and type 2 diabetes: analysis of a randomized control trial comparing surgery with intensive medical treatment. Diabetes care. 2013; 36(8):2175-2182.
DOI: 10.2337/dc12-1596

10. Biro SM, Olson DL, Garren MJ, Gould JC. Diabetes remission and glycemic response to pre-bariatric surgery diet. J SURG RES 2013;185(1):1-5.
Available:https://doi: 10.1016/j.jss

11. Wang GF, Yan YX, Xu N, et al. Predictive factors of type 2 diabetes mellitus remission following bariatric surgery: a meta-analysis. Obes surg. 2015;25(2):199-208.
Available:https://10.1007/s11695-014-1391-y

12. Golomb I, David MB, Glass A, Kolitz T, Keidar A. Long-term metabolic effects of laparoscopic sleeve gastrectomy. JAMA surg. 2015;150(11):1051-1057.
Available:https://doi: 10.1001/jamasurg

13. Schauer PR, Bhatt DL, Kirwan JP et al. Bariatric surgery versus intensive medical therapy for diabetes-3-year outcomes. N Engl J Med. 2014;370(21): 2002-2013.
Available:https://DOI:10.1056/NEJMoa1401329

14. Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G, Bucher HC, Nordmann AJ. Bariatric surgery versus non-surgical treatment for obesity: A systematic review and meta-analysis of

randomised controlled trials. Bmj. 2013;347:f5934.
Available:https://DOI:10.1136/bmj

15. Martinez-Ortiz CA, Saldívar-Frías JB, Rodriguez-Gonzalez AA, Cuevas-Marban CY. Evolution of type 2 diabetes mellitus in patients undergoing vertical sleeve gastrectomy or Roux-en-Y gastric bypass. Appl Food Sci J. 2017;2(1):25-33.
Available:http://creativecommons.org/licenses/by-nc/4.0/

16. Capoccia D, Coccia F, Guarisco G, Testa M, Rendina R, Abbatini F, Silecchia G, Leonetti F. Long-term metabolic effects of laparoscopic sleeve gastrectomy. Obes Surg. 2018;28(8):2289-2296.
Available:http://doi:10.1007/s11695-018-3153-8.

17. Panunzi S, Carlsson L, De Gaetano A, Peltonen M, Rice T, Sjöström L, Mingrone G, Dixon JB. Determinants of diabetes remission and glycemic control after bariatric surgery. Diabetes Care. 2016; 39(1):166-172.
Available:http:// doi: 10.2337/dc15-0575.

18. Korner J, Inabnet W, Conwell IM, Taveras C, Daud A, Olivero-Rivera L, Restuccia NL, Bessler M. Differential effects of gastric bypass and banding on circulating gut hormone and leptin levels. Obesity 2006;14(9):1553-1561.
Available:http:// doi: 10.1038/oby.2006.179

19. Peterli R, Steinert R, Wölnerhanssen B, et al. Metabolic and hormonal changes after laparoscopic roux-en-Y gastric bypass and sleeve gastrectomy: A randomized, prospective trial. Obes Surg. 2012;22(5): 740-748.
Available:http:// doi: 10.1007/s11695-012-0622-3

20. Karamanakos SN, Vagenas K, Kalfarentzos F, Alexandrides TK. Weight loss, appetite suppression, and changes in fasting and postprandial ghrelin and peptide-YY levels after Roux-en-Y gastric bypass and sleeve gastrectomy: A prospective, double blind study. Ann Surg 2008;247(3):401-407.
Available:http://doi:10.1097/SLA.0b013e318156f012

21. Yousseif A, Emmanuel J, Karra E, et al. Differential effects of laparoscopic sleeve gastrectomy and laparoscopic gastric bypass on appetite, circulating acyl-ghrelin, peptide YY3-36 and active GLP-1 levels in non-diabetic humans. Obes surg 2014; 24(2):241-52.

Available:http://doi:10.1007/s11695-013-1066-0.

22. Nannipieri M, Baldi S, Mari A, et al. Roux-en-Y gastric bypass and sleeve gastrectomy: Mechanisms of diabetes remission and role of gut hormones. J Clin Endocrinol Metab. 2013;98(11):4391-4399.
Available:http://doi:10.1210/jc.2013-2538

23. Ejarque M, Guerrero-Pérez F. de la Morena, N et al. Role of adipose tissue GLP-1R expression in metabolic improvement after bariatric surgery in patients with type 2 diabetes. Sci Rep. 2019;9:6274.
Available:http://DOI:10.1038/s41598-019-42770-1

24. Nausheen S, Shah IH, Pezeshki A, Sigalet DL, Chelikani PK. Effects of sleeve gastrectomy and ileal transposition, alone and in combination, on food intake, body weight, gut hormones, and glucose metabolism in rats. Am J Physiol Endocrinol Metab. 2013;305(4):E507-E18.
Available:http://DOI:10.1152/ajpendo.00130.2013

25. Korner J, Bessler M, Inabnet W, Taveras C, Holst JJ. Exaggerated glucagon-like peptide-1 and blunted glucose-dependent insulinotropic peptide secretion are associated with Roux-en-Y gastric bypass but not adjustable gastric banding. SurgObesRelat Dis. 2007;3(6):597-601.
Available:http://DOI:10.1016/j.soard.2007.08.004

26. Jiménez A, Mari A, Casamitjana R, Lacy A, Ferrannini E, Vidal J. GLP-1 and glucose tolerance after sleeve gastrectomy in morbidly obese subjects with type 2 diabetes. Diabetes. 2014;63(10):3372-3377.
Available:http://DOI: 10.2337/db14-0357

27. Milone M, Di Minno MND, Leongito M et al (2013) Bariatric surgery and diabetes remission: sleeve gastrectomy or mini-gastric bypass? World J Gastroentero 19(39):6590–6597.
DOI: 10.3748/wjg.v19.i39.6590.

28. Torquati A, Lutfi R, Abumrad N, Richards WO. Is Roux-en-Y gastric bypass surgery the most effective treatment for type 2 diabetes mellitus in morbidly obese patients? J Gastrointest Surg. 2005;9(8): 1112-1118.
Available:http://DOI:10.1016/j.gassur.2005.07.016

29. Schauer PR, Burguera B, Ikramuddin S, et al. Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. Annsurg. 2003;238(4): 467-472.
Available:http://DOI:10.1097/01.sla.0000089851.41115.1b

30. Sugerman HJ, Wolfe LG, Sica DA, Clore JN. Diabetes and hypertension in severe obesity and effects of gastric bypass-induced weight loss. Ann Surg. 2003; 237(6):751-759.
Available:http://DOI:10.1097/01.SLA.0000071560.76194.11

31. Casajoana A, Pujol J, Garcia A, Elvira J, Virgili N, de Oca FJ, et al. Predictive value of gut peptides in T2D remission: Randomized controlled trial comparing metabolic gastric bypass, sleeve gastrectomy and greater curvature plication. Obes Surg. 2017;27(9):2235-2245.
Available:http://DOI:10.1007/s11695-017-2669-7.

32. Pham MH, Ballegaard C, de Knegt MC, Sigvardsen PE, Sørgaard MH, Fuchs A, Kofoed KF. Normal values of aortic dimensions assessed by multidetector computed tomography in the copenhagen general population study. European Heart Journal-Cardiovascular Imaging. 2019; 20(8):939-948.

33. Noronha Neto CC, Maia SS, Katz L, Coutinho IC, Souza AR, Amorim MM. Clonidine versus captopril for severe postpartum hypertension: A randomized controlled trial. PloS one. 2017;12(1): e0168124.