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Predictive Factors for Remission of Type 2 Diabetes Mellitus after Laparoscopic Gastric Sleeve

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Abstract: Background: Globally, obesity and its accompanying type 2 diabetes mellitus (T2DM) are enduring health-care difficulties. There are a close relationship between obesity and T2DM and still facing difficulties in control and management of them by the current available therapies, including drug therapy, food, and modification of behavior. There is robust indication that bariatric surgery could cure type II diabetes mellitusin patients with obesity. **Aim of the Work:** To determine different predictive factors affecting the outcome of type T2 DM after laparoscopic gastric sleeve. **Patients and Methods:** Prospective study included 40 obese diabetic patients with T2 DM who underwent laparoscopic sleeve gastrectomy. Diagnosis of T2 DM was depending on criteria of ADA: HbA1c ≥ 6.5%, random blood glucose ≥200 mg/dl, FPG > 126 mg/dl, or use of oral diabetes medication or insulin. Glycemic marker in the form of HbA1c and fasting blood sugar were measured just prior to surgery and at 3 months and 6 months postoperatively. **Results:** 42.5% of patients developed remission of type II DM, these patients are younger patients, with shorter diabetic age, age of diabetes was determined from the date of diagnose to the date of operation, with mean of 4 years (from 3 years to 6 years) with range of 1-20 years, moreover patients not using insulin with optimum pre-operative glycemic control with normal fasting blood sugar and HbA1c were the best candidates to achieve remission. **Conclusion:** Remission of T2DM is one of the major achievable goals of SG, identification of potential predictors of diabetes remission help to achieve this goal.
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1. Introduction

Numerous studies was established matching nonsurgical to surgical treatment of harmful obesity, it was found that bariatric surgery was liked with high loss of body weight and greater reduction rates of T2 DM. This is part of the widely used term "metabolic surgery". So, suggestions for carrying bariatric surgery are not restricted to management of loss of weight but also extended to metabolic control [(1)].

On the other hand, to obtain best results from the bariatric surgery for remission of T2DM the selection of participating patients must be suitable for the operation and those who will probably have a bad result are omitted from participation as not every patient achieves remission after surgery. So, it is of important to identify of patients who expecting to give a bad results from carrying bariatric surgery. Many former investigators have recognized a number of preoperative predictors liked with surgical results, such as gender, age, baseline body mass index (BMI), duration of diabetes, fasting blood glucose, glycemic control (HbA1c), and therapies used to control the level of glucose in the blood [(2)].

Although the gold standard in bariatric surgery is the Roux-en-Y gastric bypass, given sustained and substantial loss of weight and leading to resolve or enhancement of obesity-related diseases, laparoscopic sleeve gastrectomy has been increased greatly during the last few years, where it achieved a good results than other restraining methods and is similar in some features to the Roux-en-Y gastric bypass. These benefits have been associated with different pathophysiologic mechanisms like accelerating intestinal passage, and amplified gastric evacuation and stimulation of hormonal actions like elevated in glucagon-like peptide-1 (GLP-1) hormone and reduced ghrelin. By These mechanisms sleeve gastrectomy resulting in loss of body weight and the enhancement or firmness of T2DM [(4)].

Aim of the work

The target from the current work is to estimate different predictive factors affecting the outcome of T2 DM after Laparoscopic Gastric Sleeve.

2. Patients and Methods

After approval of the ethical committee in Ain Shams University, Eldemerdash Hospital, the current study was done in a period time between December

2017 and August 2018. Informed consent forms from all patients were obtained. It was a prospective study including 40 morbidly obese patients with T2 DM who underwent Laparoscopic Gastric Sleeve from El-Demerdash and Nasser Institute hospital. Glycemic markers in the form of fasting blood sugar and HbA1c are recorded preoperative and postoperative at 3 and 6 months.

The current study included Patient age between 18 to 65 year-old, with type II diabetes mellitus and with BMI <40 kg/m2. The excluded patients are unable to tolerate anesthesia, Patients who refused to participate in the study, reversible endocrine or other disorder that may cause obesity.

All patients had been informed that they were participating in a research. Operative steps, expected results, side effects and operative complications have been explained to all participants.

Preoperative evaluation including; Laboratory investigations including Fasting blood glucose and HBA1C, ECG, Chest X-ray, pulmonary function test for obstructive sleep apnea, Pelvi-abdominal ultrasound to exclude gall bladder stones, upper GI endoscopy to exclude hiatal hernia, gastritis or gastric erosions.

All the procedures performed laparoscopic with general anesthesia. Patient lied in supine position with both arms away from the body. During operation the patient was positioned in a modified reverse Trendelenburg position, footboard secured to bed. Surgeon situated in amid the patient's leg, and on the left side the assistant. Pnemo-peritonium of the abdomen done by a 12-mm optical trocar just left to the midline. Ports insertion under vision: two12-mm port in the left and right midclavicular line, assistant 5-mm port in the left midaxillary line. Sub-xiphoid 5mm port for the liver retractor. Initial decompression of the stomach was done with nasogastric tube. After exploration of the abdomen and the anterior wall of the stomach, the fifth port was introduced for liver retractor. As soon as trocars were inserted in the right position, the subject sated in slight reverse Trendelenburg. The liver retractor was immovableby using a mechanical arm to the bed. The greater omentum was then dissected 5 cm proximal to the pylorus from the greater curvature of the gut creating a window. Short gastric blood vessels and gastrophrenic connections were detached by using ligasure or a harmonic scalpel. Proximal dissection was complete at the onset of seeing the left crus. The hiatus must be inspected for the presence of hiatal hernia. Non-tapered round tip bougie A 36Fr, is advanced and located alongside the lesser curve of the gut. Use a surgical stapler 2-3 cm proximal to the pylorus on the greater curve of the gutstarting with 60-mm green cartridge the 4.8 mm staple height loads and transition to the 3.5 mm blue cartridge 60mm. Sometimes, staple line reinforcement is done. Precaution must be taken to prevent constricting the gastric pouch at the incisura. The Sleeve Gastrectomy continues, using the bougie as a guide. Intraoperative testing with diluted methylene blue with concurrent compression of prepyloric area is a complementary step The resected stomach is retrieved with endocatchsack and detached throughout the 15-mm trocar location. The bougie is removed and replaced with an orogastric tube then drain is inserted. Remove all trocars under direct vision.

Early Patients ambulating was recommended. A Gastrografin swallow was ordered if suspect a complication. A liquid diet was allowed on the first postoperative day, LMW heparin according to the patient weight to prevent DVT, tube drain was removed 24 hours after the surgery then patients were discharged home if they are able to tolerate liquids without complications.

One week post operation is the suitable time for the first follow up visit; Consequent follow-up visits are planned after 1, 3 and 6 months.

Surgical and nutritional was evaluated at each visit, follow up with BMI, Fasting blood sugar, HbA1c has been done and even if patients experience diabetes remission, glycemic control is continued for the potential for relapse.

Statistical analysis of the data:

During follow-up time, anthropometric (BMI), the demographic (sex and age), and an analytical (HbA1c and FPG) variables were collected.

The SPASS program was used in this study. Qualitative variables in the descriptive analysis, in each item are expressed as percentage and absolute frequencies. Quantitative variables are expressed as mean ± standard deviation (SD). The linked among qualitative variables was estimated by using the chi-square analysis. Independent t-test was applied to parallel the means of a normally distributed interval dependent variable for two independent groups. ANOVA was applied to parallel the means among non-dichotomous variables. Mann-Whitney test a non-parametric test used for variables that you do not assume a normally distributed interval variable. P-value is considered non-significant, significant and highly significant at *P*->0.05, <0.05 and < 0.01, respectively.

3. Results

Forty obese diabetic individuals submit to performed laparoscopic gastric sleeve in the period from December 2017 to August 2018, the number of females were 28, whereas, males were reached 12. Their ages averaged 42.5 years and BMI was averaged 46.84kg/m^2. Before operation, twelve

subjects were administering insulin and 28 were giving an oral doses of Hypoglycemic agents (OHA). Post operatively, 17 out of 40 (42.5%) of patients were stopping all therapies for Diabetes. Eleven patients were remaining taken OHAs doses and wholly the 12subjectson insulin remain require it in order to control blood sugar. On the other hand all patients observed an improvement in levels of accompanied with diminishing in the dosage of therapies.

Remission of diabetes mellitus type 2 was determined basing on American Diabetes Association (ADA) parameters; HbA1c level of6.0- 6.4 % and no use of antidiabetic drugs was considered partial remission. HbA1c concentration of less than 6.0 % and no use of antidiabetic drugs is considered a complete remission. When the concentration of HbA1c was ≥6.5 % without any medication for diabetes regulation is considered as no remission. The findings of the present work are shown in table 1.

Table (1): Results of the study (Remission, partial remission and non remission).

Complete Remission		**Partial Remission**		**No remission**	
3 months	6 months	3 months	6 months	3 months	6 months
10(25%)	13(32.5%)	4(10%)	4(10%)	26(65%)	23(57.5%)

Patients in partial and complete remission were combined in this study for analysis at 6 months. Multiple analysis to evaluate predictors for remission, pre-operative glycemic control (HbA1c and FBG), age, duration of diabetes and presurgical insulin requirement were the accurate preoperative forecasters of HbA1c >6.5 % at 6 months as shown in table 2. Seventeen out of 40 (42.5%) subjects had remission of diabetes mellitus type 2.

Table (2): Remission and non remission results of the study.

Remission (HbA1c < 6.5%, with no need for diabetes medication).		**No remission** (HbA1c ≥ 6.5% or active hypoglycaemic treatment)	
No.	%	No.	%
17	(42.5%)	23	(57.5%)

Multiple predictive factors for remission are studied;

Age:

Mean age for remission was 34.76 ± 78 and for non-remission was 48.17 ± 9.40. P-value was highly significant (P-value = 0.000) as shown in table 3.

Table (3): Age and diabetes remission.

Variable		**Remission**	**Non remission**	**Test value**	**P-value**	**Sig.**
		No. = 17	**No. = 23**			
Age	Mean±SD	34.76 ± 78	48.17 ± 9.40	-4.787•	0.000	HS
	Range	22 – 51	29 – 62			

•: Independent t- test. HS: Highly significant.

Gender:

In this study, 76.5% of patients who underwent remission were females and 23.5% were males whereas 65.2% of patients who had no remission were females and 34.8% of them were males. P-value was non-significant (p-value= 0.443) as shown in table 4.

Table (4): Gender and diabetes remission.

Variable		**Remission**	**Non remission**	**Test value**	**P-value**	**Sig.**
		No. = 17	**No. = 23**			
Gender	Female	13 (76.5%)	15 (65.2%)	0.589*	0.443	NS
	Male	4 (23.5%)	8 (34.8%)			

*: Chi-square test. NS: non significant.

Duration of diabetes:

Median diabetic age was 3 (2 - 4) years for patients who developed remission and 5 (4 - 10) years for patients who had no remission. P-value was highly significant (P-value = 0.000) as shown in table 5.

Table (5): Duration of diabetes and its remission.

Variable		Remission	Non remission	Test value	P-value	Sig.
		No. = 17	No. = 23			
Duration of Diabetes	Median (IQR)	3 (2 - 4) Y.	5 (4 - 10) Y.	-3.884‡	0.000	HS
	Range	1 – 5 Y.	2 – 20 Y.			

‡: Mann Whitney test. HS: Highly significant.

Pre-operative antidiabetic medications:

All patients who developed remission were using one type of antidiabetic drugs. Patients who had no remission were on insulin pre-operative. P-value was highly significant (P-value = 0.000) as shown in table 6.

Table (6): Preoperative antidiabetic medications and diabetes remission.

Variable		Remission	Non remission	Test value	P-value	Sig.
		No. = 17	No. = 23			
Preoperative Antidiabetic Medications	insulin	0 (0.0%)	12 (52.2%)	32.677*	0.000	HS
	one type oral	17 (100.0%)	2 (8.7%)			
	more than one type oral	0 (0.0%)	9 (39.1%)			

*: Chi-square test. HS: Highly significant.

Pre-operative HbA1c:

Mean Preoperative HbA1C was6.36 ± 1.02 for patients who developed remission and 8.18 ± 1.44for patients who had no remission. P-value was highly significant (P-value = 0.000) as shown in table 7.

Table (7): Preoperative HbA1c and diabetes remission.

Variable		Remission	Non remission	Test value	P-value	Sig.
		No. = 17	No. = 23			
Preoperative HbA1C	Mean±SD	6.36 ± 1.02	8.18 ± 1.44	-4.454•	0.000	HS
	Range	4.9 – 8.6	5.9 – 11			

•: Independent t- test. HS: Highly significant.

Pre-operative fasting biood sugar:

Mean Preoperative Fasting blood sugar was 130.00 ± 37.38for patients who developed remission and 173.65 ± 38.28for patients who had no remission. P-value was highly significant (P-value = 0.000) as shown in table 8.

Table (8): Preoperative fasting blood glucose and diabetes remission.

Variable		Remission	Non remission	Test value	P-value	Sig.
		No. = 17	No. = 23			
Preoperative Fasting blood sugar	Mean±SD	130.00 ± 37.38	173.65 ± 38.28	-3.600•	0.001	HS
	Range	90 – 234	117 – 280			

•: Independent t- test. HS: Highly significant.

Preoperative BMI:

Mean Preoperative BMI was45.61 ± 6.40 for patients who developed remission and 47.74 ± 8.01for patients who had no remission. P-value was non-significant (P-value = 0.371) as shown in table 9.

Table (9): Preoperative BMI and diabetes remission.

Variable		Remission	Non remission	Test value	P-value	Sig.
		No. = 17	No. = 23			
Preoperative BMI	Mean±SD	45.61 ± 6.40	47.74 ± 8.01	-0.906•	0.371	NS
	Range	37.6 – 58	37.7 – 63.6			

•: Independent t- test. NS: non significant.

Postoperative BMI at 6 Months:

Mean Postoperative BMI at 6 months was34 ± 4.80 for patients who developed remission and 37.3 ± 6.62 for patients who had no remission. P-value was non-significant (P-value = 0.089) as shown in table 10.

Table (10): Postoperative BMI at 6 months and diabetes remission.

Variable		Remission No. = 17	Non remission No. = 23	Test value	P-value	Sig.
BMI at 6 Months postoperative	Mean±SD	34 ± 4.80	37.3 ± 6.62	-1.743•	0.089	NS

4. Discussion

One of the main objectives of SG is the remission of T2DM. Identification of the best candidates to achieve this goal is so important. In this study, identification of potential predictors of diabetes remission after SG was the main goal.

At the end of this study, 42.5% of patient developed remission of type 2 diabetes. Data from 10 researches (n = 754 patients) on the development of diseases post SG were statistically analyzed. Remission from T2DM was averaged 14 to 100 % of patients. Some investigators, Cottam et al., 2006 showed that 81 % of T2DM patients submitted to SG was recovered from T2DM. Whereas, Han et al. found that T2DM remission was reached 100 % after 6 months follow–up. In addition, Vidal et al., 2007 in their study found that gastric bypass (GBP) and SG had a nearly the same effect on diabetes (62 % and 51.4, respectively, P =.332) after 4 months follow-up period and an equal remission rate (84.6 %, P =.618) post twelve months of observation [(5)].

It is unreliable if there are a great differences concerning remission rates among the results of the studies of SG are relevant to patient criteria (ethnicity), or to the deficiency of a indistinct description of resolution of T2DM. Alternative clarification could be due that these studies used various definitions of "improvement," "resolution," "remission," or "cure" of diabetes.

In this study, there was no association between gender and T2DM remission after SG (insignificant p value=0.443)

These results are similar to a meta-analysis by **Wang et al. [(2)],** with a total number of patients (in 13 studies) reached 1,113 patients suffering from T2DM, the data showing an insignificant association between gender and T2DM remission [(2)].

Another issue confirmed by this study is that Older age is also associated with lower remission rates (p. value >0.001). Hence, older age is considered in this study as negative prognostic factor for remission of T2DM. Nedelcu et al., confirmed this results. Another study in Germany also found that postoperative metabolic failure associated with increasing age was an independent significant predictor**.** A metaanalysis of 13 studies (n=1149) demonstrated a significant negative correlation among T2DM remission rate and preoperative age (OR: -2.46, p< 0.01) [(2)].

In T2DM patients, duration of diabetes is recognized to redirect the residual β cell mass, equally in non-morbidly and morbidly obese individuals. Therefore, the impact of the SG on remission of T2DM appears to be linked to β-cell spare of patients. In this study long time diabetes duration is associated with lower remission (p. value 0.001). A shorter in the duration of T2DM were associated with T2DM remission without drug therapies, and better glycemic control as reported by Vidal et al.,. Also, Nedelcu et al., confirmed that there is solid confirmation that a shorter signs of T2DM may profit more than those with a long duration of diabetic one. **Kheniser and Kashyap** [(6)] had similar results [(6)]. Lee et al., concluded in an Asian study that duration of diabetes is the morecriticalas prognosticator for remission rate of diabetes post-operation.

Casella et al. [(5)], 75% sensitivity and 96% specificity for diabetes remission after SG was reported in diabetic patients suffering from the disease for 10- years. The study demonstrated that DM remission happened in 100 % of subjects suffering from T2DM for a period of <10 years and averaged 31 % of T2DM patients for a duration of >10 years [(5)]. While, **Robert et al. [(7)],** showed that a 79% sensitivity and 80% specificity (p=0.0001) to predict resolution at one year among T2DM patients suffering for a duration of <4 years.

The results of this study also confirmed that HbA1c and fasting blood glucose is significantly predictor for remission (p. value<0.001 and 0.001 respectively). Hence inadequate pre-operative glycemic control is negatively associated with the T2DM remission.

In addition, some researcher recorded that HbA1c <7.1% and fasting glucose <114mg/dL were forecasters for resolution of T2DM patients at one year, irrespective of the kind of bariatric operations [(7)]. Nedelcu et al., demonstrated that high preoperative

HbA1C levels can predict failure of resolution of T2DM. In a study by **Kheniser and Kashyap [6],** rate of HbA1c at 7.5% is defined as poorly controlled diabetes, may be prognostic of bad glucose control and lower rates of diabetes remission **[6].** In the same time, **Jurowich et al.,** 17/ 82 of patients didn't respond and not improved the status of diabetes by the surgical approach in addition to elevated preoperative HbA1c level (p=0.033)

Furthermore, in this study BMI baseline, non-significantly (p value =0.371) influence the rate of diabetes remission. This finding is coordinated with the results of some authors **[8],** they recorded nearly the same T2DM remission rate in two studied groups (BMI <35 and a BMI >35 kg/m^2) **[8].**

Lee et al. [9], demonstrated that the rate of diabetes remission was averaged remission 45 (72.5%) in patients post surgical incision in GIT, surgery with SG one of them revealing the BMI was a significant factor for remission during the postoperative follow-up **[9].**

Sex and BMI could not show any role in prediction of successful treatment of T2DM. P value of sex was.

This study further confirmed that diabetes remission rate was significantly lower in patients depending on insulin as a therapy for diabetes mellitus Type II in comparison with those patients taking oral oral hypoglycemic drugs (p-value >0.001). No remission occurred in patients using insulin pre-operatively. Insulin treatment may indicate the severity of diabetes. Some investigators, suggested that patients depending on insulin treatment for T2DM may have poorer β cell function. Also**,** some authors showed that non-insulin based treatments was an independent predictor for remission of DM post-surgical operation by one year (p=0.0001, specificity 60%) and sensitivity 96%) **[7].**

On the contrary, some investigators found that patients not given insulin pre-operatively respond well to the treatment and the remission rate was higher for (53.8% vs 13.5%, p<0.001) **[10].**

Another work shows that preoperative T2DM patients who take insulin have substantially lower overall remission rates, regardless of their HbA1C levels **[11].**

There are limitations in this study. The period of follow-up post-operation was short-term changes. Also, the variations in the centers and experiences of surgeons play an important role in the results obtained. The permanence and long-term safety outline of our data still indecisive. Though, it is recommended to continue follow-up of participating patients in the prospective part of the investigation with data harvesting will be continued. Such attempt should permute supplementary estimation of safety results and long-term efficiency in addition to recognition of other critical predictors such as excess weight loss (%EWL) and C-peptide. In the current study, the outcomes not compared between various kinds of bariatric procedures. The definitive target from the current work was to assist selection of patients preoperatively for the purposes of achieving a high remission rate in a short-term diabetes following SG, accepted as the more popular and technically simple metabolic and bariatric surgery procedure.

Conclusion

In conclusion, Gastric Sleeve surgery by using Laparoscopic can enhance significantly the remission rate among T2DM patients and in severely obese individuals. Remission of T2DM was achieved in 42.5% of patients underwent SG. This study also showed that younger patients, with shorter diabetic age, not using insulin and optimum pre-operative glycemic control (normal fasting blood sugar and HbA1c) were the best candidates to achieve remission (HbA1c <6.5% and no need for antidiabetics) after SG. Yet this work was carried out on small scale of peoples in a short period of follow-up. Additional studies must be performed in a large scale of population and longer period of follow in order to verify these data.

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