Abstract

Background Duodenal-jejunal bypass brings an acceptable glycemic control when added to sleeve gastrectomy in Duodenal-jejunal bypass with sleeve gastrectomy. This approach combines the principles and advantages of sleeve gastrectomy and a duodenal switch. There is not enough reported evidence following DJB-SG in diabetic patients with BMI less than 30.

Objective The aim of this study was to evaluate the effect of DJB-SG on type 2 diabetes remission in patients with BMI less than 30.

Methods In this study we did DJB-SG for 20 patients who suffered from type 2 diabetes with BMI less than 30. All patients had a normal fasting c-peptide with acceptable post prandial c-peptide rising (>20% rise) in our private hospital from October 2016 to October 2018. Complication rates, weight loss, and remission of diabetes and co-morbidities were evaluated and analyzed at 1,3,6 and 12 month after surgery.

Results Twenty diabetic patients were entered the study, 12 males and 8 females, while 11 of them were insulin dependent. Mean age was 48.7 ± 10.3 years, and the duration of diabetes was 10.5 ± 9.3 months. Evaluation of the results preoperative and 12 months after surgery: BMI 28.4 ± 1.8 vs 23.8 ± 1.7 kg/m^2, fasting plasma glucose (FPG) 156.9 ± 31.2 vs. 95.7 ± 6 mg/dL, HbA1c 8.26 ± 1.8 vs 6.1 ± 0.7%, were all statistically significant (p value < 0.05).

Conclusion This study showed, combining duodenal switch with sleeve gastrectomy is highly effective in control of diabetes and metabolic syndrome in non-obese patients (BMI < 30). Further evaluation on more cases with longer follow-ups is essential.

Keywords Sleeve gastrectomy · Duodenal-jejunal bypass · Type 2 diabetes · C-peptide · Metabolic syndrome

Introduction

Diabetes mellitus is a chronic disease which has involved more than 422 million people all around the world[1]. Bariatric/ metabolic surgery is an accepted treatment option for type 2 diabetes mellitus (T2DM) based on American Diabetes Association(ADA) [2].
Traditionally, T2D has been treated with lifestyle changes and anti diabetic medications, though there are lots of patients who fail to achieve adequate glycemic control despite maximum dosage of medications.
One of the most compelling arguments for weight loss-independent effects of upper gastrointestinal(UGI) tract bypass surgery is the observation that remission of type 2 diabetes without weight loss has occurred in patients who have had duodenal-jejunal bypass (DJB) surgery [3].
Although bariatric/ metabolic surgery is recommended for T2DM Asian patients with BMI 27.5- 32.4 kg/m2 [2], reported evidences are not much, specially in patients with BMI less than 30kg/m2. Therefor we designed this prospective study to evaluate the effect of DJB-SG in diabetic patients with BMI<30 in our private hospital.

Material and Methods

We designed a prospective study on 20 patients suffered from T2DM with BMI less than 30 kg/m2. All of them underwent DJB-SG in our hospital after signing informed consent. All surgeries have done by one bariatric surgen from October 2016 to October 2018.
We explained DJB-SG and its effects on diabetes and metabolic syndrome in detail based on literature, and discuss its pros and cons before surgery.
Inclusion criteria were T2DM, BMI less than 30, a normal fasting C-peptide, rising of C-peptide more than 20% two hours post prandial and age within 18 to 65 years. Non of the patients included in the study had previous bariatric or a major abdominal surgery.
Exclusion criteria were moderate or severe gastro esophageal reflux disease, BMI more than 30, fasting C-peptide lower than normal, inadequate post prandial C-peptide rising (less than 20%) and age under 18 or above 65 years. Preoperative parameters that analyzed were as such:age, BMI, duration of T2DM, insulin use and its duration, anti diabetic medications, FPG, glycosylated hemoglobin(HbA1c), fasting C-peptide, 2 hours post prandial C-peptide, Triglyceride, cholesterol and postoperatively we assessed FPG, HbA1c and weight loss after surgery. All patients were followed-up by a multi disciplinary team and data were collected and analyzed 1,3,6 and 12 month after surgery .

Surgical procedure:
Patients were placed in a reverse trendlenburge position with the legs elevation of 30 degree. The main surgeon stood between 2 legs of the patient, and 5 laparoscopic ports were inserted (Fig. 1). A 10-mm port was inserted 18 cm below the xyphoid , after the creation of pneumoperitoenum by a Verress needle (port 1). Then, a 12-mm Trocar was placed 12 cm lateral to the first port on the left side and another 12-mm trocar ,at mid clavicular line on right side, both at the same level of the first trocar (ports 2and 3).
A 5-mm Trocar was placed at the left anterior axillary line ,2cm below the ribs margin and another 5-mm trocar was placed below the xiphoid (ports 4 and 5).
DJB-SG: After abdominal exploration, the omentum was separated beginning at 2 cm away from pylorus, along the greater curvature and until the His angle. The gastrosplenic ligament was cut. A 60-Fr Bougie was inserted to the distal pylorus, and Endo-GIA linear staplers (green and blue) were employed for sleeve gastrectomy towards the His angle. The pylorus was preserved, and a tube-like stomach sac was formed. The

Bougie was withdrawn. The duodenum was separated about 2-3 cm at the duodenal bulb and then cut with **a purple tri-stapler** . The intestine was chosen 120 cm distal to Treitz ligament. Then, the proximal end of the duodenum was mannually anastomosed to the jejunum forming a 3-cm side to side anastomosis (Figure 2).
Data are presented as mean ± SD. A Student *t* test was to compare differences between mean. All tests were considered statistically significant with $p < 0.05$.

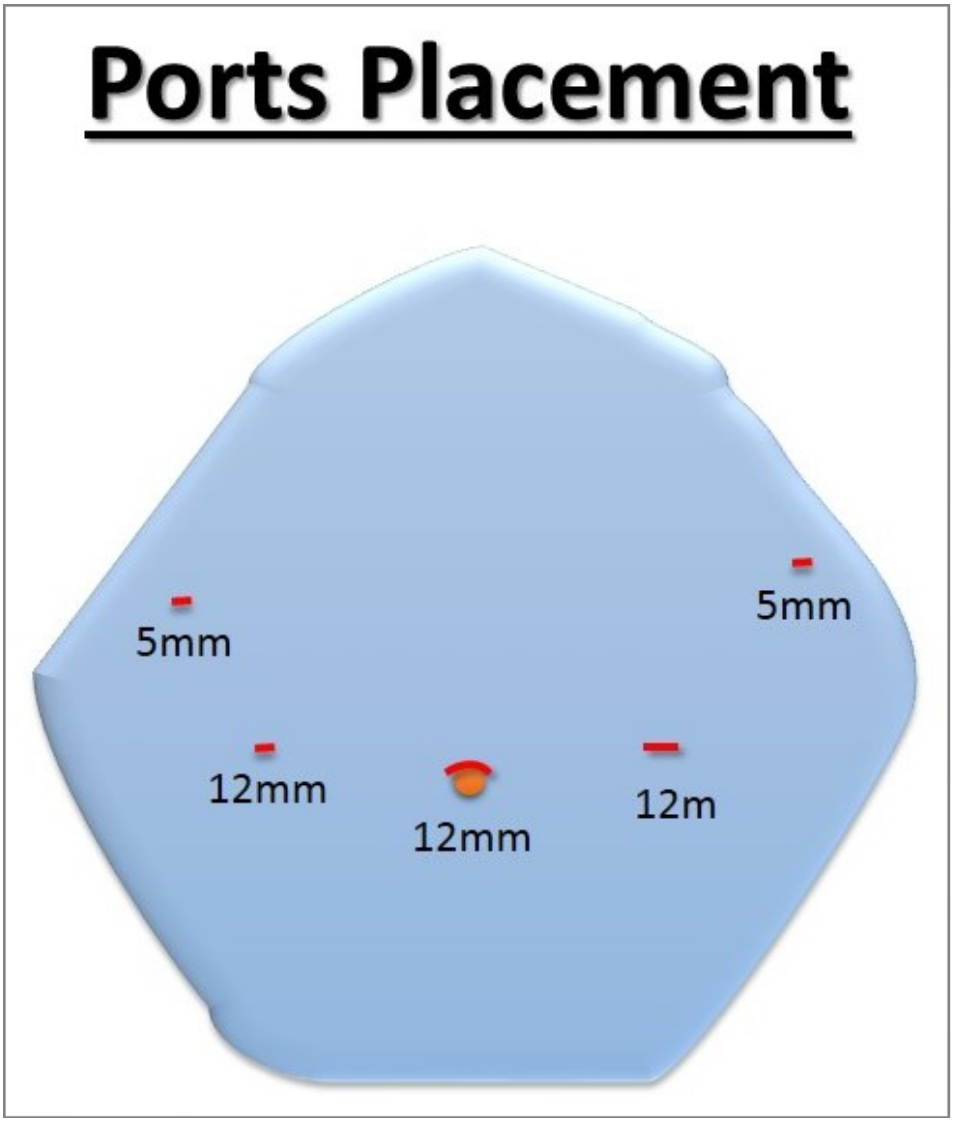

Figure 1 : ports placement

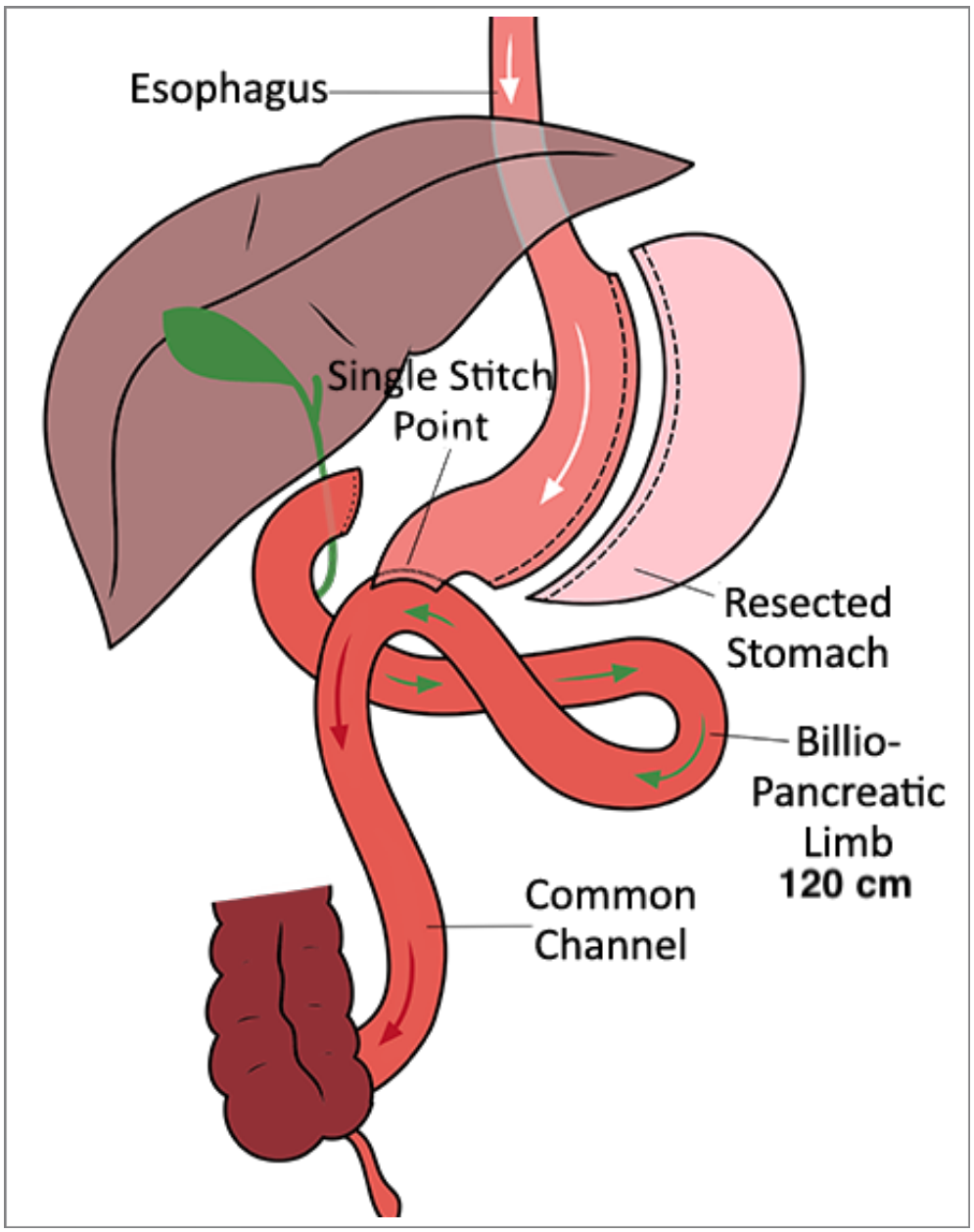

Figure 2: Single Anastomosis Duodenal Jejunal Bypass with Sleeve Gastrectomy

Results

Twenty patients (12 males and 8 females) with T2DM and BMI less than 30 kg/m2 underwent DJB-SG between October 2016 and October 2018 in our hospital By one bariatric surgeon while eleven of them were insulin dependent. Mean age was 48.7 ± 10.3 years (range:39-65) and mean BMI was 28.4±1.8 kg/m2 (range:25.2-30.2). Duration of diabetes was 10.5-9.3 years (range:1-20) and duration of insulin use was 6.9±3 years (range:1-20) in insulin dependents. Preoperative lab evaluations were : Fasting Plasma Glucose (FPG) 156.9±31.2 mg/dl (range:77-221), HbA1c 8.26±1.8% (range:5.9-11.9), fasting C-peptide 2.2±1 ng/ml (range:1.1-3.45) and 2 hour post prandial C-peptide 4.9±2.2 ng/ml (2.5-8.2) (Table 1).

Table 1: Preoperative Data

	Patients (n=20)	Range
Gender (M/F)	12 males / 8 females	-
Age	48.7±10.3	39-65
IDDM / NIDDM	11 / 9	-
Body Mass Index (kg/m2)	28.4 ±1.8	25.2-30.2
Weight (kg)	82±10.3	64-108
Height (m)	1.69±0.1	1.55-1.87
FPG (mg/dL)	156.9±31.2	77-221
HbA1c %	8.26±1.8	5.9-11.9
Fasting C -peptide (ng/mL)	2.2±1	1.1-3.45
C peptide 2hours post prandial (ng/mL)	4.9±2.2	2.5-8.2
Duration of Diabetes (year)	10.5±9.3	1 - 20
Duration of insulin use (year)	6.9 ±3	1 - 20

All surgeries were performed in our hospital by one bariatric surgeon . We didn't have any severe short term or long term complications. Mean operative time was 80±10 minutes. All patients were discharged the day after surgery after toleration of clear liquid diet . One patient had severe vomiting 2 days after surgery that readmitted and was controlled by anti emetics. Non of them had vomiting or any significant complaint at first postoperative visit ,one week after surgery. We followed our patients at month 1,3,6 and 12. Weight loss, FPG, HbA1c and anti diabetic medications were recorded and analyzed.

The mean weight before surgery was 82±10.3 kg and decreased significantly to 73.6±10.4, 69±9.3, 67.2±9.3 and 66.7±9.1 kg at 1,3,6 and 12 month follow up, respectively (table 2). The preoperative mean BMI was 28.4±1.8 % that significantly declined to 26.1±1.5, 24.4±1.6, 23.8±1.8 and 23.8±1.8 % at postoperative 1,3,6 and 12 month, respectively (p value< 0.05) (table 2and figure 3). To evaluate the diabetic outcome we followed FPG and HbA1c and both of them decreased significantly. Preoperative FPG was 156.9±31.2 mg/dl that decreased to normal range (105±12.4mg/dl), six month after surgery and also 95.7±6mg/dl at 12 month follow up(p value<0.05). HbA1c was 8.26±1.8 ng/ml before surgery and decreased to 6.1±0.7 ng/ml at month 12(p value<0.05)(table 2 and figure 4), less than 6 ng/ml in seven patients (35%), between 6 and 6.5 ng/ml in eleven patients (55%) and between 6.6 to 7 ng/ml in 2 patients (10%). All insulin dependents (11 patients) stopped insulin injection after surgery and five of them (45%) didn't need even to oral hypoglycemic medications. The use of oral hypoglycemics stopped in all non insulin dependents.

Table 2: Postoperative Data

		Baseline n=20	1 month n=20	3 month n=20	6 month n=20	12 month n=20
WEIGHT (kg)	Range Values	64-108 82±10.3	55-87 73.6±10.4	55-84 69±9.8	54-83 67.2±9.3	54-80 66.7±9.1
Body Mass Index (kg/m2)	Range Values	25.2-30.2 28.4±1.8	20.1-28.2 26.1±1.5	20-27.4 24.4±1.6	20-26.2 23.8±1.8	20.1-26.3 23.8±1.8
Fasting Plasma Glucose (mg/dL)	Range Values	77-221 156.9±31.2	90-150 119.4±21	88-158 115.6±23.2	85-144 105±12.4	82-139 95.7±6
HbA1c (ng/mL)	Range Values	5.9-11.9 8.26±1.8	4.9-9.1 7.3±1.6	4.7-8 6.3±1.2	5.1-7 6.1±0.8	5.1-7 6.1±0.7

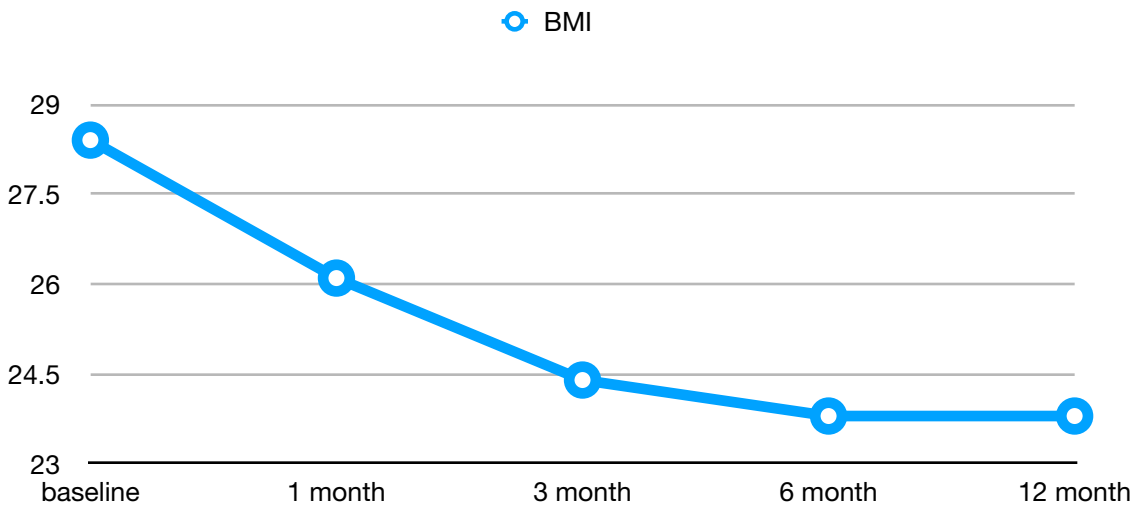

Figure 3 changing BMI from baseline to 12 month follow-up period

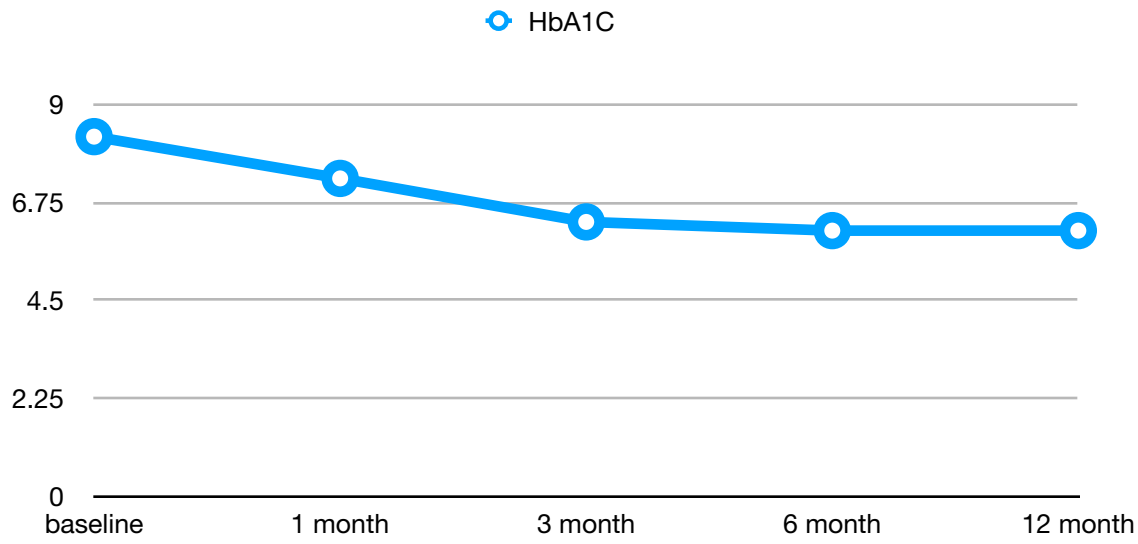

Figure 4. Changing HbA1c from baseline to 12 month follow-up period

Discussion

Type 2 diabetes mellitus have emerged as a major health problem worldwide. Obesity surgery is an excellent way to improve or resolve T2DM in obese patients [5.6.7.8], and a lot of important institutions like ASMBS, IFSO, IDF, and SECO believe that bariatric and metabolic surgeries are effective on glycemic control not only in morbid obesity but also in patients with mild obesity[9.10.11.12]. These institutions agree that bariatric and metabolic surgeries are also effective in poorly controlled T2DM[9.10.11.12]. DJB-SG is proven to be safe and effective in control of T2DM in patients with mild obesity and evidences show good results[13.24.26].

This study suggested that, this particular type of surgery(DJB-SG) is highly effective on diabetes control in non or mildly obese patients (BMI<30kg/m2) at least up to one year postoperatively in patients with a normal C-peptide. Our study realized that at 6 month after surgery all of 20 patients reached to HbA1c < 7 with a normal FPG, less than 6ng/ml in seven (35%), between 6 to 6.4 ng/ml in eleven(55%) and between 6.5 to 7ng/ml in 2 patients(10%). Mean duration of diabetes was 10.5±9.3 year, from the minimum range of 12 month to maximum of 20 years. Those who were insulin dependent (11patients), stopped using insulin postoperatively with an acceptable glycemic control and five of them (45%) didn't need even to oral hypoglycemic medications. The use of oral hypoglycemics stopped in all non insulin dependents. Regardless of normal or near normal BMI of our patients, 12 month postoperative weight loss was acceptable (BMI: 20-26.3 kg/m2). All surgeries were performed in our hospital by one bariatric surgeon . We didn't have any severe short term or long term complications. Mean operative time was 80±10 minutes. All patients were discharged the day after surgery after toleration of clear liquid diet. All patients left the operating room with a drainage tube that removed before discharge .

Duodenal-jejunal bypass(DJB) is significantly effective on T2DM improvement independent of weight loss. Though the mechanism of action is not fully understood, there are lots of evidences that realize DJB can activate brain insulin signals and brain glucose utilization [14-15]. This procedure has also its intestinal effect on glucose absorption and decrease insulin resistance by its hormonal effect(GLP1)[16.17.18]. Recent studies found that duodenum exclusion plays an important role on T2DM treatment and metabolic surgery with duodenum exclusion is more effective than other procedure for the

treatment of T2DM [15.32-34]. On the other hand sleeve gastrectomy(SG) itself has a significant effect on T2DM Improvement [19.20.21]. Though the mechanism of action is not fully understood, there are evidences that show sleeve gastrectomy acts by grelin reduction due to removal of fondus of stomach and limitation of contact between ingested food and gastric mucosa[22.23]. DJB-SG has the effects of DJB and SG on glucose control together.

A normal range fasting C-peptide with 20% rise 2 hours postprandial, strongly determined the effect of medical treatment or metabolic surgery on T2DM [24.26]. Fasting and postprandial C-peptide were important criteria for our patients to enter this study. Many studies reported that fasting C-peptide is an important predictor of T2DM remission because C-peptide may represent the residual β-cell function of T2DM patients [24.25.26]. Lee found that elevated C-peptide is very important in predicting the success of T2DM remission after LSG in low BMI patients for the first time [24.26].C-peptide test is a blood test which help to find out how much insulin your body is producing. It is useful for determining whether you have insulin resistance. C-peptide is a useful marker of insulin production because c-peptide remains in the blood longer than insulin.The normal range for a fasting c-peptide test is: 0.51 to 2.72 nanograms per millilitre (ng/mL) which taken 8 to 10 hours fast [27.28.29].c-peptide levels following oral glucose ingestion are a consistently sensitive measure of beta cell function, which may be associated with diabetes type and future use of insulin[30.31].

We have certain limitations in our study and the most important one was the small sample size. We entered only 20 patients in our study who had BMI less than 30 with a normal fasting and postprandial C-peptide. Short term follow up was the second limitation in this study. Our study was not a clinical trial to compare results with the control group. Further studies with long term follow up and a larger sample size are needed to understand the effects of DJB-SG on T2DM improvement better.

Conclusion

Results of this study show the benefits of DJB-SG on mild or non obese diabetics while its a safe procedure with low complication rate. Its highly effective on improvement or even remission of T2DM in selected patients. Selection criteria played a main role in high success rate in our short term study. A better study design with longer follow up duration and larger sample size is mandatory for better evaluation.

Compliance with Ethical Standards

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its latter amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

References

1.Diabetes Mellitus – epidemiology. 2. Diabetes Mellitus – prevention and control. 3. Diabetes, Gestational. 4. Chronic Disease. 5. Public Health. I. World Health Organization. ISBN 978 92 4 156525 7 (NLM classification: WK 810).

2.American Diabetes Association. 7. Obesity management for the treatment of type 2 diabetes: standards of medical care in diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S65–72.

3. Cohen RV, Rubino F, Schiavon C, Cummings DE. Diabetes remission without weight loss after duodenal bypass surgery. Surg Obes Relat Dis. 2012 Sep-Oct; 8(5):e66-8.

4.Widjaja, J., Pan, H., Dolo, P.R. *et al.* Short-Term Diabetes Remission Outcomes in Patients with BMI ≤ 30 kg/m2 Following Sleeve Gastrectomy. *OBES SURG* **30,** 18–22 (2020). https://doi.org/10.1007/s11695-019-04139-1.

5.Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292(14):1724–37.

6. Rutledge R, Walsh T. Continued excellent results with the mini-gastric bypass: six-year study in 2.410 patients. Obes Surg. 2005;15(9):1304–8.

7. Carbajo M, Luque-de-León E, Jiménez J, et al. Laparoscopic one-anastomosis gastric bypass: technique, results, and long-term follow-up in 1200 patients. Obes Surg. 2017;27(5):1153–67.

8.Schauer P, Kashyap S, Wolski K, et al. Bariatric surgery vs. intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012;366:1567–76.

9.ASMBS Clinical Issues Committee. Bariatric surgery in class Iobesity (BMI 30–35 kg/m2). Surg Obes Relat Dis. 2013;9:e1–e10.

10.Bucetto L, Dixon J, De Luca M, et al. Bariatric surgery in class I obesity, a position statement from the International Federation for the Surgery of Obesity and Metabolic Disrorders (IFSO). Obes Surg. 2014;24(4):487–519.

11.Dixon JB, Zimmet P, Alberti KG, et al. Bariatric surgery: an IDF statement for obese type 2 diabetes. Diabet Med. 2011 Jun;28(6):628–42.

12.Rubioa M, Monereoa S, Lecubea A, et al. Posicionamiento de las sociedades SEEN-SECO-SEEDO-SED sobre la cirugía metabólica en la diabetes mellitus tipo-2 Joint. Position Statement of the SEEN-SECO-SEEDO-SED Societies on metabolic surgery for type 2 diabetes mellitus. Endocrinol Nutr. 2013;60(10):547–8.

13.Hu C, Zhang G, Sun D, et al. Duodenal-jejunal bypass improves glucose metabolism and adipokine expression independently of weight loss in a diabetic rat model. Obes Surg. 2013;23(9):1436–44.

14.Li N, Wang HJ, Su H, et al. DJB surgery improves glucose homeostasis by affecting glucose transporter expression levels in different intestinal limbs of type 2 diabetic rats and the possible underlying mechanisms. Diabetes Metab Res Rev. 2017;33.

15.Rubino F, Schauer PR, Kaplan LM, et al. Metabolic surgery to treat type 2 diabetes: clinical outcomes and mechanisms of action. Annu Rev Med. 2010;61:393–411.

16.Rubino F, Forgione A, Cummings DE, et al. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. Ann Surg. 2006;244(5):741–9.

17.Rubino F, R'Bibo SL, del Genio F, et al. Metabolic surgery: the role of the gastrointestinal tract in diabetes mellitus. Nat Rev Endocrinol. 2010;6(2):102–9.

18.Cummings DE, Cohen RV. Bariatric/metabolic surgery to treat type 2 diabetes in patients with a BMI <35 kg/m2. Diabetes Care. 2016;39:924–33.

19.Keidar A, Hershkop KJ, Marko L, et al. Roux-en-Y gastric bypass vs sleeve gastrectomy for obese patients with type 2 diabetes: a randomised trial. Diabetologia. 2013;56(9):1914–8.

20.Nocca D, Guillaume F, Noel P, et al. Impact of laparoscopic sleeve gastrectomy and laparoscopic gastric bypass on HbA1c blood level and pharmacological treatment of type 2 diabetes mellitus in severe or morbidly obese patients. Results of a multicenter prospective study at 1 year. Obes Surg. 2011;21(6):738–43.

21.Murphy R, Clarke MG, Evennett NJ, et al. Laparoscopic sleeve gastrectomy versus banded Roux-en-Y gastric bypass for diabetes and obesity: a prospective randomised double-blind trial. Obes Surg. 2018;28(2):293–302.

22.Oberbach A, Schlichting N, Heinrich M, et al. Gastric mucosal devitalization reduces adiposity and improves lipid and glucose metabolism in obese rats. Gastrointest Endosc. 2018;87(1):288–299.e6.

23.Zhu J, Gupta R, Safwa M. The mechanism of metabolic surgery: gastric center hypothesis. Obes Surg. 2016;26(7):1639–41.

24.Lee WJ, Ser KH, Chong K, Lee YC, Chen SC, Tsou JJ, et al. Laparoscopic sleeve gastrectomy for diabetes treatment in nonmorbidly obese patients: efficacy and change of insulin secretion. Surgery 2010;147:664-9.

25.Ramos-Levi AM, Matia P, Cabrerizo L, et al. Statistical models to predict type 2 diabetes remission after bariatric surgery. J Diabetes 2014;6:472-7.

26.Lee WJ, Chong K, Ser KH, et al. C-peptide predicts the remission of type 2 diabetes after bariatric surgery. Obes Surg 2012;22:293-8.

27. Jones AG, Hattersley AT. The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabet Med. 2013;30:803–817. doi: 10.1111/dme.12159.

28. Kulkarni CM, Patil S. Urinary C-peptide and urine C-peptide/creatinine ratio (UCPCR) are possible predictors of endogenous insulin secretion in T2DM subjects—a randomized study. Int J Pharma Bio Sci. 2016;7:443–446.

29. Steiner DF, Cunningham D, Spigelman L, Aten B. Insulin biosynthesis: evidence for a precursor. Science. 1967;157:697–700. doi: 10.1126/science.157.3789.697.

30.Gjessing HJ, Matzen LE, Faber OK, Frøland A. Fasting plasma C-peptide, glucagon stimulated plasma C-peptide, and urinary C-peptide in relation to clinical type of diabetes. Diabetologia. 1989;32:305–311. doi: 10.1007/BF00265547.

31.Hope SV, Knight BA, Shields BM, et al. Low c-peptide is associated with high glycaemic variability and hypoglycaemia in insulin-treated patients with type 2 diabetes. Diabet Med. 2016;33:144. doi: 10.1111/dme.12907.

32.Rubino F, Marescaux J. Effect of duodenal-jejunal exclusion in a non-obese animal model of type 2 diabetes: a new perspective for an old disease. Ann Surg 2004;239:1-11.

33.Lee WJ, Almulaifi AM, Tsou JJ, et al. Duodenal–jejunal bypass with sleeve gastrectomy versus the sleeve gastrectomy procedure alone: the role of duodenal exclusion. Surg Obes Relat Dis 2015;11:765-70.

34.Zachariah PJ, Chen CY, Lee WJ, et al. Compared to Sleeve Gastrectomy, Duodenal-Jejunal Bypass with Sleeve Gastrectomy gives Better Glycemic Control in T2DM Patients, with a Lower β-Cell Response and Similar Appetite Sensations: Mixed Meal Study. Obesity Surgery 2016;26:2862-72.