Biliopancreatic diversion with duodenojejunal exclusion associated with truncal vagotomy. A new proposal for type 2 diabetes mellitus treatment[1]

Derivação biliopancreática com exclusão duodeno-jejunal associada à vagotomia troncular. Uma nova proposta para o tratamento do diabetes melito tipo 2

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ABSTRACT

PURPOSE: To evaluate the effectiveness of the biliopancreatic diversion surgery with duodenojejunal exclusion in combination with truncal vagotomy in type 2 diabetes mellitus (T2DM) patients with overweight or class I or II obesity.

METHODS: The study included ten patients with T2DM and class I or II obesity or overweight who were subjected to biliopancreatic diversion with duodenojejunal exclusion in combination with truncal vagotomy. The blood glucose levels during the pre- and postoperative periods were compared using the Friedman test. The significance level adopted was 5%.

RESULTS: There were significant differences between preoperative and postoperative blood glucose levels at three months (p=0.01), six months (p=0.001) and 12 months (p=0.001). There was also a significant difference between one month postoperative blood glucose and six months postoperative blood glucose (p=0.01). Glycosylated hemoglobin levels decreased in 80% of patients, there was marked improvement in their lipid profiles, and the average BMI reduction was 7.0±1.5 kg/m² at 12 months after the surgery.

CONCLUSION: In patients with type 2 diabetes mellitus associated with class I/II obesity or overweight, performing biliopancreatic diversion with duodenojejunal exclusion in combination with truncal vagotomy resulted in glycemic control, reduction of excess weight, and improvement of lipid profile 12 months after the surgery.

Key words: Diabetes Mellitus, Type 2. Biliopancreatic Diversion. Vagotomy, Truncal. Overweight. Bariatric Surgery. Obesity.

RESUMO

OBJETIVO: Avaliar a eficácia da operação de derivação biliopancreática com exclusão duodeno-jejunal associada com vagotomia troncular em doentes com diabetes tipo 2 com sobrepeso ou obesidade classe I ou II.

MÉTODOS: Foram estudados dez doentes com diabetes melito tipo 2 e sobrepeso ou obesidade grau I ou II submetidos à derivação biliopancreática com exclusão duodeno-jejunal associada à vagotomia troncular. Os valores de glicemia no pré e no pós-operatório foram comparados pelo teste de Friedman. O nível de significância adotado foi de 5%.

RESULTADOS: Houve diferença significante (p=0,01) nas glicemias pré e pós-operatórias de três meses, de seis meses (p=0,001) e de 12 meses (p=0,001). Houve diferença significante entre a glicemia pós-operatória de um mês e glicemia pós-operatória de seis meses (p=0,01). O nível de hemoglobina glicosilada reduziu-se em 80% dos doentes, houve melhora acentuada do perfil lipídico e a média da redução do IMC foi de 7,0±1,5 kg/m² após 12 meses da operação.

CONCLUSÃO: No paciente com diabetes melito tipo 2 associado com sobrepeso ou obesidade grau I/II, a realização da derivação biliopancreática com exclusão duodeno-jejunal associada à vagotomia troncular proporcionou controle glicêmico, redução do excesso de peso e melhora do perfil lipídico após 12 meses da operação.

Descritores: Diabetes Mellitus Tipo 2. Desvio Biliopancreático. Vagotomia Troncular. Sobrepeso. Cirurgia Bariátrica. Obesidade.

Introduction

A high body mass index (BMI) is an important risk factor for the progression of type 2 diabetes mellitus (T2DM) due to its association with metabolic syndrome, which is responsible for complications such as systemic arterial hypertension and dyslipidemia[1,2].

In the approach proposed for greater control of T2DM, bariatric surgery is highly regarded, as it may prevent or cure T2DM in morbidly obese patients[3-6].

All disabsortive methods of bariatric surgeries have demonstrated a marked impact on T2DM, although with varying degrees of effectiveness[7,8]. Among bariatric procedures, two techniques are considered the most effective: the Roux-en-Y gastric bypass (mixed technique) and the biliopancreatic diversion (disabsortive technique)[9].

Patients who have undergone gastrectomy for benign conditions do not develop obesity and remain thin for life. Furthermore, morbidly obese patients who undergo biliopancreatic diversion, Roux-en-Y gastric bypass procedures, and vertical banded gastroplasty plus truncal vagotomy lose more weight compared to patients subjected to vertical banded gastroplasty alone[10,11].

Pinkney and Kerrigan[12] observed that the patient often exhibits glycemic control a few days after surgery, long before the weight loss becomes significant, although the weight loss is directly correlated with decreases in insulin resistance and blood glucose level[13-15].

Kashyap *et al*.[16] studied the early effects of bariatric surgery on beta cell function and insulinotropic hormone action in obese patients with T2DM before the weight loss occurred. They observed that gastric bypass resulted in better T2DM control before the weight loss occurred, with most patients suspending the use of antidiabetogenic medication, probably due to an increase in the endocrine response of beta cells, an event that is attributed to the action of incretins due to the increase in glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) levels caused by the surgery.

Furness *et al*.[17] showed that truncal vagotomy alone is able to reduce food intake and consequently leads to weight loss in humans and animals. These authors also found that rats subjected to vagotomy reduced their daily food intake and exhibited a fat mass reduction of 20% at 4 weeks after the vagotomy, an effect that is attributed to the loss of vagal afferent pathways responsible for stimulating appetite.

The objective of this study was to evaluate the effectiveness of the biliopancreatic diversion surgery with duodenojejunal exclusion in combination with truncal vagotomy in T2DM patients with overweight or class I or II obesity.

Methods

The research protocol for this study was approved by the Research Ethics Committee of the Institute for Medical Assistance to State Public Servant (IAMSPE) (protocol number 063/09).

Ten adult patients of both genders from Candido Rondon Hospital (Ji-Parana-RO, Brazil) with diagnosis of T2DM were selected for the study. The average age was 51.9 years (range, 42 to 62 years). Seven patients were females, and three were males. All patients were either overweight or had class I or class II obesity according to the World Health Organization (WHO) criteria[10,15,18] and had an average preoperative BMI value of 34.5 kg/m² (range 27 to 39 kg/m²).

All patients were operated upon by the same surgeon (EA) and underwent biliopancreatic diversion with duodenojejunal exclusion and truncal vagotomy. The inclusion criteria were adult patients with BMI<40 kg/m², C-peptide serum levels >1 ng/mL, anti-glutamic acid decarboxylase (anti-GAD) serum levels <1 U/mL, and acceptance of the terms of informed consent. The exclusion criteria were the presence of malignancy in any location, pediatric age, C-peptide serum levels ≤1 ng/mL, anti-GAD serum levels ≥1 U/mL, and the rejection of the terms of informed consent.

The average preoperative fasting blood glucose was 173.9±52.4 mg/dL. Before the surgery, seven patients used hypoglycemic agents: Four used metformin or glibenclamide, and the other three used insulin to control the blood glucose levels.

During the preoperative period, the average C-peptide level was 2.9 ng/mL (range, 1 to 5.3 ng/mL), and all patients had C-peptide levels greater than or equal to 1 ng/mL. The average anti-GAD level was 0.6 U/mL (range, 0.1 to 1.0 U/mL). The average glycosylated hemoglobin was 8.2% (range, 6.2% to 11%).

The following laboratory tests were obtained in the preoperative and postoperative periods: plasma levels of fasting glucose (mg/dL), C-peptide level (ng/mL), anti-GAD (U/mL), glycosylated hemoglobin (%), hemoglobin (g/dL), hematocrit (%), total cholesterol (mg/dL), high-density lipoprotein fraction cholesterol (HDL cholesterol – mg/dL), low-density lipoprotein fraction cholesterol (LDL cholesterol – mg/dL), triglycerides (mg/dL), calcium (mg/dL), iron (mg/dL), total protein (g/dL), albumin (g/dL), globulins (g/dL), and vitamin B12 (pg/mL). Dyslipidemia was defined as an increase >160 mg/dL in LDL cholesterol and/or >150 mg/dL in triglycerides and/or reduction <50 mg/dL in

HDL cholesterol. The prevalence of systemic arterial hypertension was defined by considering the presence of arterial hypertension when the systolic blood pressure was >135 mmHg or the diastolic pressure was >85 mmHg.

The following values were obtained for the average preoperative patient lipid profile: total cholesterol, 202.5±38.2 mg/dL; HDL cholesterol, 44.3±8.1 mg/dL, LDL cholesterol, 136.1±31.9 mg/dL; and triglycerides, 172.7±67.5 mg/dL. The values for average preoperative serum levels were as follows: calcium, 9.3±0.3 mg/dL; iron, 76.2±13.7 µg/dL; total protein, 7±0.5 g/dL; albumin, 3.9±0.2 g/dL; globulin, 3±0.3 g/dL; and vitamin, B12 229±68.3 pg/mL.

The average time of diabetic disease was 4.7 years (range 2 to 14 years). The comorbidities identified in the preoperative period were systemic arterial hypertension in seven patients, dyslipidemia in three, cholecystopathy in two, hypothyroidism in two, and hepatic steatosis in one.

Operation procedures

A median supraumbilical incision was used. The truncal vagotomy was performed first. The cecum was then located, and an 80-cm-long common channel was measured from the ileocecal valve and marked. The alimentary limb was measured to 170 cm from where the common limb was marked and was cut using a linear stapler with white load. The biliopancreatic limb was anastomosed at 80 cm from the ileocecal valve with manual latero-lateral anastomosis, thus forming the common channel. Subsequently, the duodenal bulb was sectioned with a linear cutting stapler at approximately 2 cm from the pylorus and was reinforced with continuous sutures. A wide latero-lateral anastomosis of the alimentary limb with the greater curvature of the stomach close to the pylorus was performed with an 80-mm linear cutting stapler with blue load (Figure 1). After confirmation that hemostasis was adequate, the closing of the abdominal wall was performed by layers.
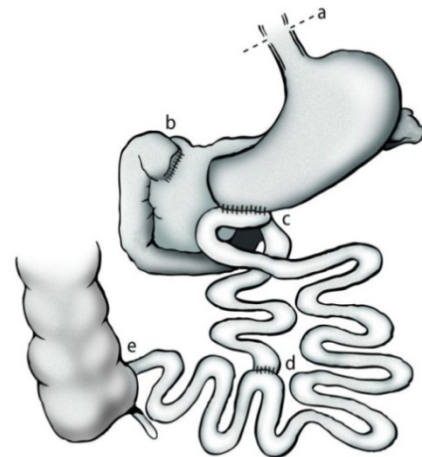
FIGURE 1 - Illustration of biliopancreatic diversion with duodenojejunal exclusion in combination with truncal vagotomy. **a** = Truncal vagotomy; **bd** = biliopancreatic limb; **cd** = alimentary limb (170 cm); **de** = common channel (80 cm).

Postoperative treatments

During the first 30 postoperative days, the patients were subjected to capillary blood glucose tests every 6 hours. In the subsequent 60 days, the test was performed twice a day.

After hospital discharge, the patients were monitored at the outpatient clinic with scheduled follow-ups at one, three, six, nine and 12 months. All patients received the same dietary guidelines. Initially, the patients were on a liquid diet plan until food was reintroduced during the postoperative period. At 17 days after the surgery, the patients were given a liquid and soft diet, and 30 days after the surgery, solid foods, proteins, iron, and calcium were added to the diet plan. Control laboratory tests were conducted at one, three, six, and 12 months after the surgery.

Statistical analysis

In the descriptive analysis of the data obtained, the means, standard deviations, frequencies as percentages, and minimum and maximum values were used. For the comparison and confirmation of possible significant differences between the preoperative blood glucose values and each of the postoperative values, the Friedman test was used. The significance level adopted was 5% ($p \leq 0.05$). The statistical programs used were BioEstat 2.0 (Brazil) and Microcal OriginTM 4.10 (Origin Lab., MA, USA).

Results

The mean operation time was 90 minutes. There were no intra-operative complications. The average length of hospital stay after surgery was 33.6 hours (range 24 to 72 hours). There were no cases of gastroparesia, increased gastroesophageal reflux, or anastomotic ulcers in the patients participating in this study.

There were two complications during the early postoperative period: one patient had bleeding at the gastroenteric suture line, and another patient had a subphrenic abscess. Both complications occurred seven days after hospital discharge. The first patient was treated by endoscopic sclerosis with monoethanolamine oleate on the suture line and transfusion of two units of whole blood. The subphrenic abscess was treated by intercostal drainage and antibiotic therapy, which resulted in clinical improvement.

All patients used subcutaneous insulin during the postoperative period for no more than two months. A continuous and progressive reduction in fasting glucose levels was observed. The blood glucose levels were normalized in all patients at the end of 12 months after the surgery, and there was no need for the use of medications after this period (Table 1).

At 12 months after surgery, glycosylated hemoglobin was reduced in 80% of patients (Table 2); the average BMI reduction was 7.0±1.5 kg/m² (range, 5 kg/m² to 12 kg/m²) (Table 3). The patient lipid profile had the following average values: total cholesterol, 157.3±29.3 mg/dL; HDL cholesterol, 43.2±10 mg/dL; LDL cholesterol, 87.8±23.2 mg/dL; and triglycerides 126.8±57.4 mg/dL. During the same postoperative period, the average serum levels of calcium (8.9±0.9 mg/dL), iron (86.7±19.6 ug/dL), total protein (7.0±0.6 g/dL), albumin (3.9±0.3 g/dL), globulin (3.1±0.4 g/dL), and vitamin B12 (265.3±127 pg/mL) remained within normal limits.

TABLE 1 - Means and standard deviations of fasting blood glucose values during the preoperative and postoperative period of biliopancreatic diversion with duodenal exclusion in combination with truncal vagotomy.

Case	Preoperative blood glucose (mg/dL)	Postoperative blood glucose – 1 month (mg/dL)	Postoperative blood glucose – 3 months (mg/dL)	Postoperative blood glucose – 6 months (mg/dL)	Postoperative blood glucose – 12 months (mg/dL)
1	242	105	102	102	80
2	160	80	80	76	87
3	162	127	82	86	86
4	121	137	107	110	90
5	289	186	78	90	90
6	169	105	80	72	72
7	153	130	120	110	102
8	167	127	100	100	104
9	156	114	102	90	98
10	120	120	99	100	100
Mean/SD	173.9±52.4	123.1±27.5	95.0±14.2	93.6±13.1	90.9±10.2

SD – Standard deviation

TABLE 2 - Preoperative and postoperative glycosylated hemoglobin levels of patients who underwent biliopancreatic diversion with duodenal exclusion in combination with truncal vagotomy.

Case	Preoperative glycosylated hemoglobin (%)	1-year postoperative glycosylated hemoglobin (%)
1	8.7	8.5
2	11	7.8
3	8.7	6
4	7.5	6.2
5	10.8	7.8
6	8.5	7.9
7	8.4	8.4
8	8.3	7.8
9	6.2	6.5
10	8.5	6.1
Mean /SD	8.6±1.4	7.3±0.9

SD – Standard Deviation

TABLE 3 - Means and standard deviations of BMI during the preoperative period and one year after biliopancreatic diversion with duodenal exclusion in combination with truncal vagotomy.

Case	Preoperative BMI (kg/m$^{2)}$)	BMI 1 year after surgery (kg/m$^{2)}$)
1	27	24
2	31	25
3	38	29
4	35	30
5	35	25
6	39	27
7	31	27
8	38	31
9	33	27
10	39	34
Mean /SD	(34.6±4)	28±3.1

BMI – Body mass index   SD – Standard deviation

When the preoperative blood glucose level was compared to the blood glucose levels at different postoperative periods, significant differences were found between the following averages: preoperative and three months postoperative blood glucose levels (p=0.01); preoperative and six months postoperative blood glucose levels (p=0.001); and preoperative and 12 months postoperative blood glucose levels (p=0.001). Additionally, a significant difference was identified between blood glucose levels at 1 month and 6 months after the surgery (p=0.01).

There were also significant differences in the preoperative and 1-year postoperative levels of glycosylated hemoglobin (p=0.01), BMI (p=0.005), total cholesterol (p=0.006), LDL cholesterol (p=0.005), and triglycerides (p=0.02). There were no significant differences between the preoperative and 1-year postoperative levels of HDL cholesterol (p=0.7), calcium (p=0.06), iron (p=0.1), total protein (p=0.9), albumin (p=0.5), globulin (p=0.7), or vitamin B12 (p=0.5).

Discussion

One of the greatest benefits of bariatric surgery is the resolution of T2DM in approximately 50% to 80% of cases[18]. The changes in the secretion of incretin hormones produced in the small intestine and their effects on insulin and glucagon production may be a mediator of the significant improvement in blood glucose levels after gastric bypass surgery, which would not show the same effects when compared to weight loss caused by diet or restrictive surgeries[19-21].

GIP and GLP-1 are secreted by K cells in the duodenum and L cells in the ileum, respectively. These two incretins are responsible for approximately 50% of postprandial secretion of insulin[21,22].

Laferrère *et al.*[19,20] found that patients subjected to gastric bypass exhibited a significant 5- to 10-fold increase in postprandial GLP-1 or after the oral intake of glucose. However, the GIP levels did not show significant changes after the same surgical procedure was performed. Nevertheless, the increase in GLP-1 levels observed soon after gastric bypass surgery remained constant 3 years after the surgical procedure.

It has been shown that bariatric surgery promotes the control or improvement of T2DM[9,12,15,16,18,23]. Among the variations of this type of surgery, the disabsortive techniques are considered the most effective[23]. Conventional gastrointestinal surgeries for obesity also have yielded marked improvements in T2DM, resulting in the normalization of blood glucose and glycosylated hemoglobin levels and the subsequent suspension of hypoglycemic drug use[14,24].

It was observed that the improved glycemic control resulting from surgeries that exclude the duodenum and jejunum occurs very fast (approximately five to six days after the procedure), when significant body weight loss or reduction in calories intake still has not occurred[23].

While investigating the mechanisms of action for gastrointestinal diversion procedures using duodenojejunal bypass, it was suggested that the exclusion of the duodenum and proximal jejunum would change nutrient movement, thus preventing the stimulation of the inappropriate signal that would promote insulin resistance[13,25,26]. Rubino *et al.*[25] reported that duodenal exclusion of nutrient movement is the critical component for this reduction and subsequent control of diabetes mellitus.

Geloneze *et al.*[26] compared the potential advantages of the duodenojejunal exclusion surgery. Thus, a group of patients was operated upon using this technique and was compared to another paired control group that received the standard medical treatment for T2DM. At the end of 24 weeks after the surgery, the patients who were operated upon exhibited a significant decrease in blood glucose and a lower average daily insulin requirement (93% vs. 29% of the control group). These authors concluded that duodenojejunal exclusion is an effective and superior method to the standard treatment for the control of T2DM.

In this study, using this technique, which was used in conjunction with truncal vagotomy in patients with T2DM and overweight or class I or II obesity, resulted in a significant proportion (80%) of patients with decreased blood glucose levels in the first month after the surgery, with one patient reaching normal levels.

Kindel *et al.*[27] stated that the duodenojejunal exclusion in diabetic patients increases GLP-1 secretion, which would result in improved glucose tolerance. The results of that study showed that, despite the weight profiles being similar in the preoperative period and a period of 4 weeks after the surgery, there was a significant improvement in the oral glucose tolerance test and a significant increase in plasma GLP-1 levels. Those results provide direct evidence of improvement in glucose tolerance as a result of gastric bypass, an event that would be mediated by increasing GLP-1 action.

In this study, glycemic control was achieved by all patients at 12 months after surgery; additionally, these patients no longer required hypoglycemic drugs for glycemic control. The average fasting blood glucose level went from 173.9±52.4 mg/dL during the preoperative period decreased to 90.9±10.2 mg/dL at 1 year after surgery. The reduction in blood glucose levels from the

preoperative period to 12 months after the surgery was significant (p=0.001).

Ramos *et al.*[28] found that patients who underwent duodenojejunal exclusion exhibited a decrease in BMI up to 3 months after surgery, and their weights stabilized between 3 and 6 months after surgery. There was a significant reduction (p<0.001) in fasting blood glucose (43.8%) and HbA1c (22.8%) levels up to the sixth month.

In the case series described in this report, all patients exhibited a significant reduction in their average BMI value, which decreased from 35±4.0 kg/m² to 28±3.1 kg/m² over 1 year. Thus, as occurs in vagal blocking, the weight loss was ready expected due to the truncal vagotomy. All patients experienced early satiety and reduced their volume of caloric intake.

Roux *et al.*[29] observed that the transection of the vagus nerve abolished the orexigenic effect of ghrelin. These authors observed that the administration of peripheral ghrelin leads to increased food intake and GH release in humans. Thus, it is believed that ghrelin increases appetite. These authors also observed that after a gastrectomy, the plasma levels of ghrelin are reduced to at least 50% of the initial values.

Souza *et al.*[30], in a study conducted on the effect of truncal vagotomy in rats with monosodium glutamate injected in the neonatal phase, which induces a lesion in the hypothalamus and subsequent obesity, concluded that truncal vagotomy caused hypophagia in the first month after surgery and significant reduction in the percentage of perigonadal fat. It can be inferred that, at least in the first 4 weeks, the reduction of fat mass in these animals occurred as a result of reduced food intake and by the interruption of the vagal stimulus of the pancreas, reducing hyperinsulinemia and fat deposition.

In this case series, during the follow-up period the positive impact of the surgery was observed, with significant postoperative reductions in the levels of total cholesterol, triglycerides, and LDL cholesterol. However, HDL cholesterol levels did not show any significant change.

The results obtained in this study demonstrate that duodenojejunal exclusion in combination with truncal vagotomy in patients with T2DM and with class I or II obesity provided greater glycemic control, reduction of excess body weight, and improvement of lipid profile at 12 months after surgery.

Conclusions

The biliopancreatic diversion with duodenojejunal exclusion technique in combination with truncal vagotomy in

patients with T2DM and overweight or class I or II obesity has the potential to be an option for the treatment of T2DM. However, controlled clinical studies are still required, including a control group that does not undergo truncal vagotomy, and with an adequate number of patients to confirm the encouraging results obtained in this case series.

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