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Original Article

OBESE PATIENTS WITH DIABETES MELLITUS TYPE 2 UNDERGOING GASTRIC BYPASS IN ROUX-EN-Y: ANALYSIS OF RESULTS AND ITS INFLUENCE IN COMPLICATIONS

Obesos diabéticos tipo 2 submetidos à derivação gástrica em y-de-roux: análise de resultados e influência nas complicações

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ABSTRACT – Background: About 90% of type 2 diabetic patients are obese or overweight. The obvious clinical improvement observed with surgeries, such as Roux-en-Y gastric bypass, has opened space for research by different factors than only weight loss, as responsible for the return to euglycemia and reduction of medication use. ***Aim***: To evaluate the efficacy and safety of surgical treatment of diabetes in obese patients with BMI above 35 kg/m2 underwent to gastric bypass, for the control of diabetes, weight loss, improvement of laboratory findings and complications of diabetes. ***Method -*** The protocol was implemented in three stages: initial, after losing 10% of weight, and after a year. ***Results*** - Seventeen patients who have lost weight in 10% were included in the surgical protocol. From the total, 11.8% continued needing medication (p <0.001). The time for weight loss was a month with significant reduction in fasting glucose, HOMA-IR index, insulin, HbA1c, hemoglobin, AST, urea and C-peptide and there was no variation in hematocrit, albumin, ALT and creatinine. With a year of monitoring, the surgical group showed a significant difference in weight, BMI, blood glucose, HbA1c, C-peptide, insulin and HOMA-IR. The percentage of patients with neuropathy (31.3%) was lower than the number of cases at baseline (52.9%) (p> 0.05). ***Conclusion***: Gastric bypass with Roux-en-Y derivation is a safe procedure, with good results in control of diabetes type 2 in obese patients with BMI above 35 kg/m2.

HEADINGS - Obesity. Bariatric surgery. Gastric bypass. Diabetes mellitus.

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RESUMO – *Racional*: Cerca de 90% dos diabéticos tipo 2 são obesos ou têm sobrepeso. A evidente melhora clínica observada com o tratamento cirúrgico, como a derivação gástrica em Y-de-Roux, abriu caminhos para a pesquisa de outros fatores, que não somente a perda de peso, como responsáveis pelo retorno à euglicemia ou redução no tratamento medicamentoso. ***Objetivo***: Avaliar a eficácia e segurança do tratamento cirúrgico do diabete melito em obesos com IMC acima de 35 Kg/m2 submetidos ao by-pass visando o controle do diabetes, perda de peso, melhora nos parâmetros laboratoriais e complicações do diabete. ***Métodos***: O protocolo do estudo foi aplicado em três momentos: o inicial; após perda de 10% do peso; e após um ano. ***Resultados:*** Foram analisados 17 pacientes que perderam 10% de peso; 11,8% continuaram com necessidade de medicamento (p<0,001). O tempo para perda de peso foi de um mês, quando ocorreu redução significante da glicemia de jejum, do índice HOMA-IR, insulina, HbA1c, hemoglobina, AST, peptídeo C e uréia; não ocorreu variação do hematócrito, albumina, ALT e creatinina. Com um ano de acompanhamento, a série apresentou diferença significativa nas variáveis peso, IMC, glicemia, HbA1c, peptídeo C, insulina e o HOMA-IR. O percentual de pacientes com neuropatia (31,3%) foi menor que o número de casos no início do estudo (52,9%) (p>0,05). ***Conclusão***: A derivação gástrica em Y-de-Roux é procedimento seguro, com bons resultados no controle do diabete em obesos com IMC acima de 35 Kg/m2.

DESCRITORES - Obesidade. Cirurgia bariátrica. Derivação gástrica. Diabete melito.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by hyperglycemia, deficient secretion of insulin by the β-cells of the pancreas and/or increased peripheral resistance to insulin action. The progression of the disease is the most common cause of blindness, amputations and renal failure in adults, and increases the incidence of acute myocardial infarction and

cerebrovascular accidents[1].

The association between obesity and diabetes is well established. The US National Health and Nutrition Examination Survey showed that the incidence of diabetes in men aged 25–54 years with a body mass index (BMI) between 30 and 34.9 kg/m^2 is 10.1-fold higher[17].

Patients with severe obesity, i.e., BMI greater than, or equal to, 40 kg/m^2 carry an even higher risk of developing comorbidities[15]. For these individuals, as well as for those whose BMI is equal to, or greater than, 35 kg/m^2 and who already manifest associated diseases, bariatric surgery has shown efficacy in improving these comorbid conditions, including T2DM[19]. The evident clinical improvement achieved by type 2 diabetics observed after surgical procedures such as Roux-en-Y gastric bypass and biliopancreatic diversion has opened the way to research on a variety of factors, in addition to weight loss, that could be responsible for the euglycemia and reduction in medication use found in 80–100% of these patients. A number of studies have demonstrated the action of intestinal peptides with both peripheral and central action in the control of glycemia and regulation of food intake[23].

Vetter et al.[28] in a review study on the correlation between the intestine and pancreas - termed enteroinsular axis - reported that it was first mentioned in 1902, when Bayliss and Starling[28] identified a compound in the intestinal mucosa that they named secretin. It would function via bloodstream by stimulating pancreatic secretion in such a way that any disruption in the enteroinsular axis would trigger diabetes. Sixty-five years later, Perley and Kipnis[28] demonstrated that ingested food elicits insulin release more intensely than a parenteral glucose solution. In 1979, incretins were identified as the gastrointestinal hormones that stimulate the release of insulin.

Two theories have been proposed to explain the beneficial effect of surgery in T2DM. One theory holds that diabetes control is the result of the delivery of chyme nutrients directly into the distal intestine, thus amplifying a physiologic signal that enhances glucose metabolism, with GLP-1 as the major mediator in this process. This incretin hormone is secreted by the L cells of the distal intestine in response to the presence of nutrients; it stimulates the secretion of insulin and shows proliferative and antiapoptotic effects on β-cells. The second hypothesis is based on the exclusion of the duodenum and proximal jejunum from the transit of nutrients, possibly preventing the secretion of a specific signal that promotes insulin resistance and T2DM. The latter theory has been verified in experimental studies and, later, in humans[23]. Bariatric surgery interferes with the enteroinsular mechanism by positively affecting the production of the hormones acting directly on the pancreatic β-cells; this promotes insulin production. Diabetes reduces this incretin effect through mechanisms not fully understood. Two effects are produced: decreased insulin secretion in response to GIP and decreased GLP-1. One of the possible explanations for the decrease in insulinogenic activity is defective expression of receptors. Studies of GIP levels in diabetic patients have been inconsistent to date - some authors have detected normal levels, while others found elevated fasting and post-prandial levels[8,22]. The mechanism of reduced GLP-1 secretion has not been fully explained; a decrease is known to occur in GLP-1 levels in obesity and an even greater reduction in diabetic patients; however, the target tissues respond normally[18].

The Diabetes Surgery Summit defined the criteria for choosing surgical therapy for T2DM. Obese patients (BMI≥30 kg/m^2) with T2DM are candidates for surgery with duodenal-jejunal bypass, coupled or not with a restrictive gastric procedure. A consensus approved Roux-en-Y gastric bypass as the technique of choice, with biliary bypass as a possible alternative.

Dixon et al.[10] reported the results of a study developed by an International Diabetes Federation group of endocrinologists, surgeons and public health experts, who reviewed the proper role of surgery in the treatment and prevention of T2DM. The authors point out that new techniques should be rigorously evaluated for efficacy and safety, and prove equivalence or improved benefit compared with the established surgical procedures after studies with humans following pre-clinical trials. Randomized studies are needed to evaluate and compare the different procedures for the treatment of diabetes, including a number of emerging nonsurgical treatment modalities.

The objective of the present study was to evaluate the efficacy and safety of Roux-en-Y gastric bypass in the surgical treatment of T2DM in obese patients in relation to weight loss and the influence of this procedure on the complications of the disease.

METHODS

This prospective, non-randomized study was approved by the Research Ethics Committee of the Universidade Federal do Tocantins (Technical Opinion 075/2009). Informed consent comprised verbal clarification and a signed consent form.

Patients with T2DM (n=17) spontaneoulsy presented to, or were referred to, the Bariatric Surgery Service of the Gastrocentro in the municipality of Palmas, Tocantins state, Brazil, with the intent of undergoing surgical treatment. All of them underwent Roux-en-Y gastric bypass.

The study included obese individuals with a BMI greater than 35 kg/m^2 and T2DM; elevated fasting plasma glucose; glycosylated hemoglobin (HbA1c) above 6.0; adequate endocrinological care; age between 18 and 60 years; ability to understand the procedures; weight variation of less than 5% over the previous three

months; diagnosis and clinical follow-up for T2DM at least over the past six months; serum C-peptide level greater than 1 ng/ml; a maximum of eight years of disease duration and, when on insulin therapy, for no longer than five years, and voluntary participation in the study, with provision of signed informed consent.

The exclusion criteria were: type 1 and 2 diabetics on insulin therapy for more than five years; history of liver disease with alterations in alanine transaminase (ALT) and/or aspartate transaminase (AST) three times the normal values; use of anticoagulant therapy, except for antiplatelet agents; congenital or acquired anomalies of the digestive tract; pregnancy or willing to become pregnant within the following 12 months; history of cancer less than five years ago; use of oral or injected corticosteroids for more than 14 consecutive days in the past three months; lab test results pointing to likely insulin production failure (C-peptide levels of less than 1 ng/ml); alcohol or substance abuse; history of autoimmune disease; HIV-positive, and decompensated psychiatric diseases.

The group underwent complete endocrinological and metabolic laboratory testing; routine preoperative laboratory tests; endocrinological, nutritional, psychological, cardiological, pulmonary and vascular evaluations; upper endoscopy and abdominal ultrasound, and assessment of ophthalmological, renal or neurologic complications.

Subsequent follow-up was conducted at a specialized outpatient clinic. On the 30th postoperative day, a weight loss of approximately 10% was noted in relation to preoperative weights. Fasting plasma glucose, HbA1c, insulin, C-peptide, albumin, AST, ALT, hematocrit, hemoglobin, and the homeostasis model assessment - insulin resistance (HOMA-IR) were quantified.

After that, follow-up was conducted every three months up to the end of the first year, with measurements of fasting plasma glucose and HbA1c.

At the end of the first year, the laboratory tests were reviewed and the diabetes-related complications, reassessed.

Statistical analysis

The postoperative course, clinical benefit regarding T2DM, clinical improvement of comorbidities and occasional complications were analyzed statistically. The database was created using Excel® 2007 for Windows® software. The statistical analyses were performed with the statistical package PASW® 18 for Windows®. Potential associations between variables were assessed using the chi-square test (χ^2). For the analysis of 2 × 2 tables, Fisher's exact test was used. The distribution of the data for each variable within the group was analyzed using the Kolmogorov-Smirnov test to determine the parametric or nonparametric conditions. Some variables were evaluated at two timepoints. The analysis of possible differences between means at each timepoint was conducted using the paired t-test. Mixed-design ANOVA was used for the analysis of each outcome variable. The post hoc analyses were performed using multiple comparisons or the paired t-test as needed. The Bonferroni method was applied for the correction of the level of significance. Violations of sphericity were corrected using the Greenhouse-Geisser method; however, when reporting the results, the original values of the degrees of freedom were given.

The values were expressed as mean±standard deviation. Statistical significance was set at 5% ($p \leq 0.05$). All tests were two-tailed.

RESULTS

The mean age of the 17 patients - 10 female (58.8%) and seven male (41.2%) - was 44.9 years. Two patients were on insulin, and all 17 were using oral antidiabetic drugs. Regarding the presence of diabetes-related complications, nine patients had neuropathy (52.9%), none presented with retinopathy, creatinine clearance was reduced in five (29.4%), and elevated microalbuminuria was found in nine (52.9%) patients. All the17 patients lost 10% of their body weight for initial assessment. The time of progression of diabetes was 29.7±7.9 months on average, and the time of insulin use was 36±0 months.

Results after 10% weight loss

On study entry, all participants were using oral antidiabetic agents and two, insulin. After the initial weight loss, 15 patients (88.2%) were able to discontinue the oral medication; the two who were on insulin no longer needed it. The mean length of time for the 10% weight loss was one month. With that weight loss, a significant reduction was noted in glucose levels, which reached a mean concentration of 104.1 mg/dl ($p<0.001$). Baseline C-peptide concentration was significantly superior to the mean after weight reduction ($p=0.009$). At all three timepoints, C-peptide levels stayed above 1 ng/ml. HbA1c decreased significantly ($p<0.001$); its mean concentration after weight loss was significantly lower (6.3%) than that on study entry. For insulin and HOMA-IR, the time factor had a statistically significant effect ($F1, 26=14.381$, $p=0.001$). Baseline plasma concentrations were significantly superior to those found after the 10% weight loss timepoint. A significant effect was also noted in the interaction between these two factors ($F1, 26=7.275$, $p=0.012$). Post hoc analyses showed significant differences between the concentrations at baseline and after the 10% weight loss ($p=0.001$), with a mean difference of 13.5±3.3; the mean for insulin values was 12.2 micro U/ml after weight loss. In addition, a significant decrease in HOMA-IR was found. The post hoc analyses demonstrated a significant reduction in mean HOMA-IR values ($p=0.001$), with a mean difference of 9.0±2.2. As expected, these two variables behaved in a similar manner, since the latter derives from the former (mean HOMA-IR, 3.1). No significant variation was found in the hematocrit means after the 10% weight loss. However, initial hemoglobin

concentrations were greater than those measured after the weight reduction (p=0.039). It is important to note that these two variables remained within the normal range at all times. With respect to liver function, mean albumin concentration showed no significant variation (p=0.087). The analysis of the plasma concentration of the liver enzymes revealed that the weight loss exerted a significant effect on the AST mean (p=0.042). The concentration of this enzyme fell significantly after weight loss; nevertheless, it remained in the normal range. On the other hand, the plasma concentration of ALT was not affected by the weight reduction (p=0.091). By contrast, urea and creatinine levels decreased after the 10% weight loss. The post hoc analyses demonstrated a difference between baseline urea concentration and after weight loss (p=0.003), with values within the normal range at all timepoints. For the variable creatinine, however, the effect was not statistically significant (p=0.343).

Results after one year

One patient died at nine postoperative months of causes unrelated to the surgery.

The variables weight, BMI, plasma glucose, HbA1c, C-peptide, insulin and HOMA-IR showed statistically significant differences across timepoints (p<0.001). The baseline values decreased up to 30 days following surgery, and were found to be even lower in the one-year evaluation. Of note, at one year, mean plasma glucose had reached normal levels and mean HbA1c was 5.6%; the mean for the HOMA-IR index after the 10% weight loss was within the normal range.

A summary of the analyses performed is presented in Table 1.

TABLE 1 - Results of the laboratory tests in the patient group

Variable	Timepoint		
	Baseline	10% weight loss	One year
Weight	123.3 ± 6.8	106.5 ± 5.5	79.2 ± 4.4
BMI	44.3 ± 1.3	38.7 ± 1	28.9 ± 1.1
Plasma glucose	188.4 ± 14.5	104.1 ± 4.6	88.7 ± 2
C-peptide	4.3 ± 0.4	3.4 ± 0.4	2.5 ± 0.3
HbA1C	7.6 ± 0.5	6.3 ± 0.4	5.6 ± 0.3
Insulin	26 ± 3.9	12.2 ± 1.8	6.6 ± 1.2
HOMA	12.5 ± 2.4	3.1 ± 0.4	1.6 ± 0.3
Hematocrit	39.7 ± 0	38 ± 1	39 ± 0
Hemoglobin	13.3 ± 0.3	12.6 ± 0.5	12.8 ± 0.4
Albumin	4 ± 0.1	3.9 ± 0.1	3.9 ± 0.1
AST	31.6 ± 3.5	32.3 ± 4	22 ± 2
ALT	39.1 ± 4.6	36.6 ± 5.1	20.9 ± 2.5
Urea	29.3 ± 1.3	22.9 ± 1.7	27.1 ± 1.8
Creatinine	0.9 ± 0	0.9 ± 0	0.9 ± 0.1
Proteinuria	270.2 ± 62.7	-	99.2± 11.7
Clearance	89.1 ± 4.6	-	81.4 ± 6.4
Microalbuminuria	120.8 ± 46,9	-	39.7 ± 21.4

Remission of diabetes was defined as a dichotomous variable (remission or no remission) for each evaluation timepoint (10% weight loss and after one year). The category "remission criterion" included partial and complete remission. The potential association between the treatment and the remission criterion was tested using the chi-square test. A statistically significant association was found both at the 10% weight loss timepoint (χ^2=24.157, df=1, p<0.001), and after one year (χ^2=27.000, df=1, p<0.001). The group of surgical therapy had one patient without remission and 16 with remission, seven of whom achieved partial remission, while nine patients had complete remission. At one year, four patients attained partial remission and 12, complete remission. It should be noted that only one of the patients had a remission "reversal", i.e., after the 10% weight loss, this patient had complete remission, which became partial in the one-year evaluation. All the other patients remained stable or exhibited improvement in biochemical parameters.

DISCUSSION

The course of T2DM brings macrovascular complications, such as acute myocardial infarction, and microvascular complications, such as nephropathy, retinopathy and neuropathy[3]. Diabetic retinopathy is a complication strongly related to the duration of the disease. It is the most frequent cause of new cases of blindness among adults aged between 20–74 years. Diabetic retinopathy progresses from mild proliferative abnormalities (when an increase in blood vessel permeability occurs) to moderate and severe nonproliferative diabetic retinopathy (characterized by vascular obstruction), and to proliferative diabetic retinopathy (marked by the growth of new blood vessels in the retina and posterior surface of the vitreous). Up to 21% of the patients present with retinopathy on diagnosis of diabetes. The duration of diabetes is probably the strongest predictor for the onset and progression of retinopathy. The prevalence of any retinopathy was 8%, 25%, 60% and 80% in three, five, 10 and 15 years, respectively[3]. In the present study, for a mean time of diagnosis of 29 months, no patient had developed retinopathy.

All the patients in the present study were in use of different oral antidiabetic agents, and two of them were also on insulin; the use of medical therapy after weight loss was significantly reduced, and the percentage of patients who used insulin decreased after the weight loss. This was corroborated by other authors[20,21]. In the present study, the 10% weight loss occurred in 30 days, by which time a significant decrease in the levels of insulin, HOMA-IR and HbA1c was observed. The levels of C-peptide decreased significantly with that weight reduction. This measurement allows for the evaluation of β-cell secreting capacity and, especially, enables the distinction between cases of type 1 from type 2 diabetes. In some instances, C-peptide concentrations can be used to evaluate

individuals with metabolic syndrome[15]. In the present study, the decrease in the levels of C-peptide followed that observed in insulin during the period of weight loss. This fact was noted by Lee et al.[14], who studied 205 morbidly obese type 2 diabetics who underwent surgical treatment at the same three timepoints adopted herein. The mean values for albumin, hematocrit and hemoglobin showed no statistically significant differences between the evaluation timepoints, which proves that no malnutrition occurred, and that both vitamin replacement and nutritional guidance were adequate. The variables weight, BMI, plasma glucose, HbA1c, C-peptide, insulin and HOMA-IR showed statistically significant differences across timepoints. There was a decrease in the initial values up to 30 days postoperatively; these values were found to be further reduced in the evaluation conducted at one year.

A study by Boza et al.[5] analyzed the efficacy of T2DM control with Roux-en-Y gastric bypass in 30 obese patients with a BMI below 35 kg/m^2 and with diabetes duration of 4±2.9 years; 12 months after the procedure, remission was noted in 83.3% with HbA1c falling from 8.1±1.8% to 5.9±1.1%.

Weight loss induces a reduction in visceral fat and increased sensitivity to insulin[13,27]. In the present study, the weight loss at the three timepoints totalled 123.3 kg, 106.5 kg and 79.2±4.4 kg and was found to be significant, which reflected in the improvement in insulin action according to the HOMA-IR index (12.5±2.4, 3.1±0.4 and 1.6±0.3 respectively).

Buse et al.[6], in a review article, sought to establish criteria to define "cure of diabetes". Cure would be the restoration of health; partial remission, fasting glucose of 100-125 mg/dl for one year without antidiabetic medication, and complete remission, normal plasma glucose and HbA1c levels for more than one year without medication. Prolonged remission was defined as more than five years without medication. Such criteria, which have been cited in a number of studies, have been updated by the American Diabetes Association[3,7,11,16].

Nondiabetic glycemia resulting from ongoing medications or repeated procedures, such as bariatric surgery, would not fulfill the definition of remission, considering that those interventions are regarded as treatment. Remission could be characterized following surgical procedures or the use of endoluminal devices only after the patient has achieved stability, with no need for further adjustments and/or replacements of devices. Prolonged remission is that which lasts for more than five years and could operationally be regarded as cure. The period of five years was chosen arbitrarily, since no actuarial data exist indicating the likelihood of relapse over long periods of time from the onset of normoglycemia.

In the present study, in the analysis conducted after 30 days, one patient remained diabetic, with no remission, while 16 achieved remission levels - seven patients attained partial, and nine, complete remission. By one year, four patients showed levels consistent with partial remission and 12, with complete remission. It is worth noting that only one of the patients had a "reversal" of remission, i.e., after loss of 10% of body weight, this patient had complete remission, which turned to partial remission in the one-year evaluation. All the other patients remained stable or showed improvement in their biochemical parameters.

Bringing HbA1c values to less than, or around, 7% has been shown to reduce microvascular and neurologic complications; however, for microvascular disease prevention, it is necessary to maintain HbA1c below that level. A number of controlled studies, based on the fact that clinical treatment usually yields unsatisfactory results with respect to the control of cardiovascular complications, have established dietary modification and implementation of physical activity programs as part of their protocols. The aim of such measures is to maintain HbA1c at levels closer to normal with the help of adequate care and stringent guidance[3].

All type 2 diabetic patients should be evaluated for distal symmetric neuropathy on diagnosis, and at least once a year after that[3,26,29]. Neuropathies can be focal or diffuse, sensory, motor and autonomic. Glycemic control can attenuate the progression of a lesion, yet it will not revert neuronal injury to a previous condition[4]. In the present study, the percentage of patients who developed neuropathy after one year (31.3%) was lower than the number of patients who presented with neuropathy at baseline (52.9%). However, the small number of patients in the group limited the analysis and it was not possible to demonstrate a statistically significant reduction in the prevalence of neuropathy ($p>0.05$). It is important to note that none of the patients developed neuropathy after the treatment, as those who exhibited that condition after one year had already manifested it initially.

Overall, nephropathy develops in 20-40% of the patients with diabetes, and albuminuria between 30-299 mg/24 h has been the marker of its progress. Progression to macroalbuminuria (>300 mg/24 h) heralds a course toward renal failure[12]; however, treatment could slow the progression of the renal disease.

In the present study, the variables creatinine clearance ($p=0.503$) and microalbuminuria ($p=0$) showed no statistically significant differences between the evaluation timepoints. Although measurements of proteinuria are not the best parameter for the diagnosis of renal disease, they were significantly lower at one year after the initiation of the study.

Despite the fact that evidence supporting surgery in the treatment of diabetes has been published[4,9,12,25,30], this concept meets resistance from specialists who regard the disease as one of exclusively clinical treatment. These experts raise the argument of surgery-related morbidity and mortality, even though studies have demonstrated safety with 0.28% mortality, as described by DeMaria et al.[9] in 58,000 operated patients.

Parameters should be found that could discriminate which patients will have a better, or worse, response to surgical therapy. In view of this, it is unquestionable that randomized studies are needed to compare the best clinical and surgical treatments, evaluate improvements in the parameters of T2DM control, and, especially, monitor the course of complications[2,20]. The BMI falls short as a cut point for indication of surgery, given that this index is not predictive of metabolic risk.

CONCLUSION

The Roux-en-Y gastric bypass is a safe procedure, with good results in the control of diabetes in obese patients with a BMI greater than 35 kg/m^2.

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