BYPASS VS. SLEEVE AND ITS EFFECTS IN NON-ALCOHOLIC FATTY LIVER DISEASE: WHAT IS THE BEST TECHNIQUE?

Bypass vs. sleeve e seus resultados na doença hepática gordurosa não alcoólica: Qual a melhor técnica?

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ABSTRACT - Background: Strongly associated with obesity, non-alcoholic fatty liver disease is considered the hepatic manifestation of the metabolic syndrome. It presents as simple steatosis and steatohepatitis, which can progress to cirrhosis and its complications. Among the therapeutic alternatives is bariatric surgery. Aim: To compare the effect of the two most frequent bariatric procedures (sleeve and bypass) on liver disease regarding to epidemiological, demographic, clinical and laboratory parameters. Methods: The results of intraoperative and 12 months after surgery liver biopsies were used. The NAFLD activity score (NAS) was used to assess and compare the stages of liver disease. Results: Sixteen (66.7%) patients underwent Bypass procedure and eight (33.3%) Sleeve. It was observed that the variation in the NAFLD activity score was significantly greater in the Bypass group than in Sleeve (p=0.028) and there was a trend regarding the variation in fibrosis (p=0.054). Conclusion: Both surgical techniques were effective in improving the hepatic histology of most operated patients. When comparing sleeve and bypass groups, bypass showed better results, according to the NAS score.

RESUMO - Racional: Fortemente associada à obesidade, a doença hepática gordurosa não alcoólica é considerada a manifestação hepática da síndrome metabólica. Ela apresenta-se como estatose simples e estatose-hepatite, podendo evoluir para cirrose e suas complicações. Entre as alternativas terapêuticas está a cirurgia bariátrica. Objetivo: Comparar o efeito sobre a doença hepática dos dois procedimentos bariátricos mais frequentes - sleeve e bypass - e comparar dados epidemiológicos, demográficos, parâmetros clínicos e laboratoriais. Métodos: Utilizou-se o resultado das biópsias hepáticas realizadas no intra-operatório e 12 meses após a operação. O NAFLD activity score foi utilizado para avaliar e comparar os estágios da doença hepática. Resultados: Dezesseis (66,7%) pacientes foram submetidos ao bypass e oito (33,3%) ao sleeve. Observou-se melhoria significativa no IMC e glicemia nas duas técnicas cirúrgicas enquanto que os níveis de fosfatase alcalina, ferritina, Gama-GT e TGP reduziram com significância apenas no grupo bypass. A redução no NAFLD activity score foi significativamente maior no grupo bypass que no sleeve (p=0,040). Conclusão: Ambas as técnicas foram eficazes em promover a melhora da histologia hepática da maior parte dos pacientes operados. Quando comparadas o bypass apresentou melhores resultados.

HEADINGS: Bypass. Sleeve. Non-alcoholic fatty liver disease. Morbid obesity. Bariatric surgery.
INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has a global distribution and is considered nowadays the most common liver disease in the West industrialized countries, probably because of the association with obesity, type 2 diabetes (DM2), dyslipidemia and metabolic syndrome. The prevalence of NAFLD is reported as 6–35%, with an average of 20%, in the general population.31

There is a strong evidence that NAFLD represents the hepatic component of the metabolic syndrome, characterized by obesity, hyperinsulinemia, insulin resistance (IR), DM2, hypertriglyceridemia and systemic arterial hypertension (SAH). Obesity is a common and well-documented risk factor for NAFLD. In patients with severe obesity undergoing bariatric surgery, the prevalence of NAFLD can exceed 90%, with up to 50% of patients presenting steatohepatitis (NASH) and 5% cirrhosis.25

Abdominal ultrasound is widely used as the first line in the investigation of NAFLD and evidence the accumulation of fat when more than 33% of hepatocytes have steatosis. Liver biopsy is the gold standard method for the diagnosis of NAFLD, being able to assess the degree of fatty infiltration, hepatocellular damage, inflammation and fibrosis. The presence of hepatocellular ballooning in association with steatosis is the key to the differential diagnosis between simple steatosis and NASH.29

All patients with NAFLD should undergo interventions to promote a healthier lifestyle and strict control of the metabolic risk factors associated with NAFLD. Weight loss is the most important factor. Relatively small losses of approximately 7–10% of body weight in 12 months seem to be effective in improving NAFLD already.12,20

Obesity and DM2, isolated or linked by metabolic syndrome, are among the most important risk factors in the genesis of NAFLD. The role of bariatric surgery comes up in this context. Several consistent studies over the past few years, culminating in the publication of Philip Schauer in 2017, have shown that surgical treatment is more effective in weight loss and in the control of glycemia and metabolic syndrome than intensive and optimized clinical treatment in the short, medium and long terms.

Although there are still no randomized clinical trials evaluating the role of bariatric surgery in the treatment of NAFLD, there are several retrospective and prospective studies in the literature, in addition to a few meta-analyses, which evaluate the effect of surgical treatment on NAFLD.1,5,6,10,12–14,16,20,21,23,26,52,54

The AASLD and EASL guidelines define bariatric surgery as a therapeutic option in NAFLD, mainly in those patients who did not respond to conservative clinical treatment.11,20

Roux-en-Y bypass (bypass) and vertical gastrectomy (sleeve) have been compared in several studies to determine which one has the greatest benefit in weight loss or in resolving obesity-related comorbidities. However, there is few knowledge about which of these techniques is associated with the best results on NAFLD. There are few comparative studies and these are small series with a large number of biases, such as heterogeneity of groups and assessment systems.13,15,28

In a group of obese patients, the main objective of the present study was to compare the bariatric sleeve and Roux-en-Y bypass techniques and their effects on NAFLD, also in epidemiological, demographic, clinical and laboratory parameters.

METHODS

The study was submitted to and approved by the Ethics Committee of the institution, where it was carried out. CAAE: 9047521550005335.

Patients selection

A retrospective study that evaluated patients undergoing bariatric surgical procedures by the same surgical team, between 2014 and 2016, at Irmãode da Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, RS, Brazil.

Only patients with intraoperative and postoperative liver biopsy were included. The average time between biopsies was 12 months.

Demographic characteristics (gender and age), clinical parameters (weight, height, BMI, SAH, weight loss, excess weight lost) and laboratory (platelets, ALP, ferritin, GGT, AST, ALT), histopathological analysis and NAS score16 were collected and analyzed.

Operative technique

All procedures were performed laparoscopically.

The sleeve surgery was made with the dissection of the greater gastric curvature 3 cm from the pylorus to the esophagogastric flexure. The gastric transection was calibrated with a 36F bougie and reinforcing the staple line with continuous suture with Caprofly® 2.0.

In the bypass surgery, a 4 cm gastric pouch was done using a 36F bougie. The Roux limb used to be 100cm and the biliopancreatic limb used to be 150 cm. Gastroenteric anastomosis was performed laterally with a linear stapler calibrated by a 36F bougie.

Histopathological evaluation

All liver samples were analyzed in the hospital’s pathology laboratory by a single professional experienced in liver pathology. The NAFLD activity score (NAS) was used to assess and compare the stages of liver disease.18 It proposes the characterization of NAFLD regarding the degree of steatosis, the presence of ballooning and inflammation activity. NAS scores the histological analysis from 0 to 3: degree of steatosis (0–3), lobular inflammation (0–3) and ballooning (0–2). The degree of fibrosis was assessed semi-quantitatively with a scale of 0 to 4.

Statistical analysis

Categorical results were presented using frequency and percentage and were analyzed using the X² test (chi-square). The likelihood-ratio test was performed in comparisons when there were more than 20% of the cells with an expected value below 20%. Quantitative results were displayed using means ± standard deviations and when data followed normal distribution it was analyzed using Student’s t tests for paired and independent samples; when non-parametric, the Wilcoxon and Mann-Whitney tests were used. The normality of the data was verified using the Shapiro-Wilk test. The variation in the NAS score was calculated using the difference between the postoperative and the intraoperative score. The analyses were performed using SPSS software, version 21 and significant results were considered when p < 0.05.

RESULTS

Twenty-four obese patients who underwent bariatric surgery were evaluated, of which 16 (66.7%) undergoing bypass and eight sleeve, with a mean segment time of 21.3±16 months and 15.5±12.5 months, respectively (p=0.380). 68.8% of patients undergoing bypass were women, on the sleeve group, 75% (p=0.571); 31.3% were hypertensive vs. 37.5% in the sleeve (p=0.553); in the bypass group, age and maximum weight were 38.6±11.3 years and 119.1±13.5 kg respectively vs. 36.7±8.4 years, p=0.692 and 119.1±14.1 kg respectively vs. 36.7±8.4 years, p=0.180, respectively.

In the bypass group, age and maximum weight were 38.6±11.3 years and 119.1±13.5 kg respectively vs. 36.7±8.4 years, p=0.692 and 119.1±14.1 kg respectively vs. 36.7±8.4 years, p=0.180, respectively.

Table 1 shows the results of the clinical and laboratory
parameters in the preoperative period and after the surgical procedures. In both periods and in all parameters analyzed, no difference was found between the techniques with statistical significance. However, there were significant reductions in BMI and glycemia in the two techniques analyzed, while reductions in alkaline phosphatase, ferritin, GGT and ALT were significant only in the bypass group.

**TABLE 1** - Pre and postoperative clinical and laboratory parameters according to the type of operation performed.

| Parameter       | Technique | Pre-op | Post-op | p   |
|-----------------|-----------|--------|---------|-----|
| **BMI (kg/m²)** | Bypass    | 44.3±4.2 | 27.9±1.1 | <0.001 |
|                 | Sleeve    | 42.1±4.1 | 28.6±5.8 | <0.001 |
| **Platelets (x1000)** | Bypass    | 270±59 | 239±66 | 0.170 |
|                 | Sleeve    | 273±45 | 279±71 | 0.832 |
| **ALP (U/L)**   | Bypass    | 92.2±30.7 | 72.8±16.8 | 0.010 |
|                 | Sleeve    | 105.5±20.6 | 103.0±70.3 | 0.910 |
| **Ferritin (ng/ml)** | Bypass    | 227±150.3 | 121.1±86.4 | 0.011 |
|                 | Sleeve    | 232±67.6 | 133.6±103.1 | 0.069 |
| **GGT (U/L)**   | Bypass    | 55.9±31.1 | 19.1±10.8 | 0.000 |
|                 | Sleeve    | 111.0±151.8 | 64.5±116.3 | 0.123 |
| **Glycemia (mg/dl)** | Bypass    | 99.4±17.2 | 82.1±9.8 | 0.001 |
|                 | Sleeve    | 102.7±10.2 | 90.2±8.6 | 0.007 |
| **AST (U/L)**   | Bypass    | 30.8±16.2 | 25.5±6.9 | 0.038 |
|                 | Sleeve    | 33.5±12.2 | 39.0±27.9 | 1.000 |
| **ALT (U/L)**   | Bypass    | 42.1±20.6 | 28.3±10.6 | 0.023 |
|                 | Sleeve    | 39.9±12.5 | 31.6±13.2 | 0.207 |

BMI = body mass index; ALP = alkaline phosphatase; GGT = gamma-glutamyl transpeptidase; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Evaluating the evolution of the NAFLD degree on the second biopsy compared to the first, 19 (79.2%) patients showed improvement, two (8.3%) remained in the same degree and three (12.5%) worsened. There was a significant association between the evolution of NAFLD and the surgical procedure performed (p=0.024). In the sleeve group, three (37.5%) worsened the level of NAFLD vs. no patient in the bypass group (Figure 1).

**FIGURE 1** - Evolution of NAFLD degree

Table 2 shows the differences in the NAS classification between the first and second biopsies. In all categories, a significant reduction was observed when the technique was bypass. However, in the sleeve group, only steatosis and the NAS score showed significant reductions.

**FIGURE 2** - Comparison of the mean variation of the NAS score

The intensity of variations was compared between groups with no significant difference between them (p>0.05), except for the NAS score shown in Figure 2, whose reduction observed in the bypass was significantly higher than in the sleeve (-3.81±1.80 vs. -1.87±2.10, respectively; p=0.040).

| TABLE 2 - Comparison between the first and second liver biopsies |
|---------------------------------------------------------------|
| **NAS classification** | **First** | **Second** | **Change** | **p** |
|------------------------|-----------|-----------|------------|------|
| Steatosis              | 2.0±0.8   | 0.2±0.4   | -1.8±0.91  | <0.001 |
| Inflammation           | 1.2±0.7   | 0.5±0.5   | -0.7±0.77  | 0.005 |
| Ballooning             | 1.5±0.9   | 0.2±0.7   | -1.3±1.00  | 0.002 |
| Fibrosis               | 0.9±1.0   | 0.2±0.7   | -0.6±0.87  | 0.015 |
| NAS score              | 4.8±1.7   | 0.9±1.3   | -3.8±1.80  | <0.001 |

DISCUSSION

In our country, bypass is still the most performed bariatric technique; but, in recent years, there has been an important increase in the number of vertical gastrectomy, which follows the worldwide trend of technical preference nowadays^4^.

Historically, patients with morbid obesity or those with clinical signs and symptoms of metabolic syndrome had in the operations of mixed character (bypass) - with restrictive and disabsorptive component -, their most frequent indication. Purely restrictive procedure - vertical gastrectomy - a relatively newer technique, was initially indicated for patients with grade II obesity or very high BMI levels greater than 60 kg/m², those in which the necessary weight loss was not too much or those that mixed operations has became impractical due to the great excess of weight. Thus, sometimes it becomes difficult to compare the results between the techniques, since the patients generally presented important clinical and epidemiological differences, making statistically different groups.

In the present study, evaluating the demographic characteristics of both groups - bypass and sleeve - it was noticed that there were no statistical differences between them. Gender, breed and age were similar. SAH was present in approximately 30% of patients. There were no diabetic patients and the mean blood glucose was practically the same in both groups, 100 mg/dl. Regarding weight, BMI, laboratory tests - platelets, alkaline phosphatase, ferritin, gamma-GT, glycemia, AST and ALT preoperatively - the groups also showed similarity. This parity between the groups...
contributes to a more reliable comparative analysis with a lower incidence of bias.

In the present study, we observed that in the purely restrictive operation (sleeve) and in the mixed operation using baros system. ABCD, Arq. Bras. Cir. Dig. 2018; 32(4): e1474.

However, unlike the previous findings published by Froylich et al., Billeret et al., Billeter et al., Kirkil et al., Karcz et al., Deitel et al., Beymer et al., Chaves et al., Caiazzo et al., and Angrisani et al., the observational nature of the study, the small number of patients, the potential selection bias, and the lack of randomized control groups limit the generalizability of these results. Furthermore, the long-term follow-up is necessary to confirm the findings and evaluate the durability of the effects.

**REFERENCES**

1. Algooneh A, Almazeeni S, Al-Sabah S, et al. Nonalcoholic fatty liver disease resolution following Sleeve gastrectomy. Surg Endosc. 2016;30(5):1985-7.
2. Almogy G, Crookes PF, Anthone GI. Longitudinal gastrectomy as a treatment for the high-risk super-obese patient. Obes Surg. 2004;14(4):492-7.
3. Angrisani L, Santonicola A, Iovino P, et al. Bariatric surgery and endoluminal procedures: IFSOWorldwide survey 2014. Obes Surg. 2017;27(9):2279-89.
4. Angrisani L, Santonicola A, Iovino P, et al. Bariatric surgery and endoluminal procedures: IFSOWorldwide survey 2014. Obes Surg. 2017;27(9):2279-89.
5. Barros F, Negrão M, Negrão G. G. Weight loss comparison after Sleeve and Roux-en-Y Gastric Bypass: systematic review. ABCD, Arq. Bras. Cir. Dig. 2019; 32(4):e1474.
6. Beyemer C, Kowley KV, Larson A, et al. Prevalence and predictors of asymptomatic liver disease in patients undergoing gastric bypass surgery. Arch Surg. 2003;138(11):1240-4.
7. Billeret AT, Senft J, Gotthardt D, et al. Combined non-alcoholic fatty liver disease and type 2 diabetes mellitus: Sleeve gastrectomy or gastric bypass? - a controlled matched pair study of 34 patients. Obes Surg. 2016;26(8):1687-76.
8. Bowler G, Athanasiou T, Iqbal A, et al. Bariatric surgery and nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol. 2015;27(7):755-68.
9. Caiazzo R, Lassailly G, Leteurtre E, et al. Roux-en-Y gastric Bypass versus adjustable gastric banding to reduce nonalcoholic fatty liver disease: a 5-year controlled longitudinal study. Ann Surg. 2014;260(5):893-8; discussion 898-9.
10. Cazzo E, Jimenez LS, Pareja JC, Chaim EA. Effect of Roux-en-Y gastric Bypass on nonalcoholic fatty liver disease evaluated through NAFLD fibrosis score: a prospective study. Obes Surg. 2015;25(6):982-5.
11. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology, vol 67, no 1, 2018.
12. Chaves-Tapia NC, Tellez-Avila FJ, Barrientos-Gutierrez T, et al. Bariatric surgery for non-alcoholic steatohepatitis in obese patients. Cochrane Database Syst Rev. 2010; 20(1):CD007340.
13. Clark JM, Alkhuriashi AR, Solga SF, et al. Roux-en-Y Gastric Bypass improves liver histology in patients with non-alcoholic fatty liver disease. Obes Res. 2005;13(7):1180-6.
14. Deitel G, Magner G, Erickson AL, Crosby RD. Third international summit: current status of sleeve gastrectomy. Surg Obes Relat Dis. 2011;7:749-759.
15. Froylich D, Corcelles R, Daigle C, et al. Effect of Roux-en-Y Gastric Bypass and Sleeve gastrectomy on nonalcoholic fatty liver disease: a comparative study. Surg Obes Relat Dis. 2016;12(1):127-31.
16. Karnick WK, KrawczykowskI K, Kuesters S, et al. Influence of Sleeve gastrectomy on NASH and type 2 diabetes mellitus. J Obes. 2011;2016:765473.
17. Kirkil C, Aygen E, Korkmaz M, Bozan M. Quality of life after laparoscopic Sleeve gastrectomy using baros system. ABCD, arq. bras. cir. dig. 2018; 31(3):e1385.
18. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005;41(6):1313-21.
19. Lassailly G, Caiazzo R, Buob D, et al. Bariatric surgery reduces features of non-alcoholic steatohepatitis in morbidly obese patients. Gastroenterology. 2015;149:377-88.
20. Marchesini G, Roden M, Vettor R, et al. The management of non-alcoholic fatty liver disease. EASL, EASD, EASO Clinical Practice Guidelines. The Journal of Hepatology, vol 64, 2016.
21. Mattar SG, Velcu LM, Rabinovitz M, et al. Surgically-induced weight loss significantly improves nonalcoholic fatty liver disease and the metabolic syndrome. Ann Surg. 2005;242(4):610-7; discussion 618-20.
22. Moretto M, Kupsic C, da Silva VD, et al. Effect of bariatric surgery on liver fibrosis. Obes Surg. 2012;22(7):1044-9.
23. Mottin CC, Moretto M, Padoin AV, et al. Histological behavior of hepatic steatosis in morbidly obese patients with obesity after weight loss induced by bariatric surgery. Obes Surg. 2005;15(6):788-93.
24. Mummadi RR, Kasturi KS, Chennareddyari S, Sood GK. Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2008;6(12):1396-402.
25. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet. 2016;387:1377-96.
26. Palermo M, Serra E, Duza G. N-Sleeve gastrectomy: an option for obesity and GERD. ABCD, arq. bras. cir. dig. 2019; 32(4): e1482.
27. Peterli R, Wölnerhanssen BK, Peters T, et al. Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss in Patients With Morbid Obesity: The SM-BOSS Randomized Clinical Trial. JAMA, 2018 Jan 16;319(3):255-265.
28. Praveen Raj P, Gomes RM, Kumar S, et al. The effect of surgically induced weight loss on nonalcoholic fatty liver disease in morbidly obese Indians: "NASHOST" prospective observational trial. Surg Obes Relat Dis. 2015;11(6):1315-22.
29. Saadeh S, Younossi ZM, Remer EM, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology. 2002;123(3):745-50.
30. Salminen P, Helimo M, Ovaska J, et al. Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss at 5 year among patients with morbid obesity: the Sleevepass randomized clinical trial. JAMA 2018 Jan 16;319(3):241-254.
31. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy for diabetes – 5 year outcomes. N Engl J Med. 2017;376:641-51.
32. Vargas V, Allende H, Lecube A, et al. Surgically induced weight loss by gastric bypass improves non-alcoholic fatty liver disease in morbid obese patients. World J Hepatol. 2012;4(12):382-8.
33. Williams CD, Stengel J, Asike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology. 2011; 140(1):124-31.
34. Zilberstein B, Santo M A, Carvalho M H. Critical analysis of surgical treatment techniques of morbid obesity. ABCD, arq. bras. cir. dig. 2019; 32(3): e1450.