

NONALCOHOLIC STEATOHEPATITIS ON PREOPERATIVE PERIOD OF GASTRIC BYPASS: LACK OF CORRELATION WITH DEGREE OF OBESITY

Esteato-hepatite não-alcoólica em pré-operatório de bypass gástrico: ausência de correlação com grau de obesidade

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ABSTRACT - Background: Metabolic disorders have high correlation with severe forms of nonalcoholic fatty liver disease. However, there is no non-invasive method that promotes its proper stratification and biopsy remains the ideal diagnostic tool. **Aim:** To evaluate the prevalence of this disease in obese in preoperative period of Roux-en-Y gastric bypass and metabolic factors correlated with liver histopathology. **Methods:** From a total of 47 patients, 35 were enrolled in the inclusion criteria and 12 excluded due to liver disease and alcohol intake >80 g/week. Were performed clinical and laboratory evaluation before the surgery and intraoperative liver biopsy. The intensity was ranked in grade of steatohepatitis: I (mild to moderate) and II (diffuse inflammation), III (periportal fibrosis) and IV (cirrhosis). Were compared the following variables: duration of obesity, body mass index, waist-hip ratio, type 2 diabetes mellitus, hypertension and dyslipidemia. **Results:** Thirty-five patients (68.6% women, mean age 37 years) were evaluated. The mean body mass index preoperatively was 53.04 kg/m². Nonalcoholic steatohepatitis was found in 31 patients (88.6%) and 32.2% were in grade I (n=10), grade II 45.2% (n=14), and 25.6% grade III (n=7). The waist-hip ratio was associated with hepatic steatosis; hypertriglyceridemia was the marker that had best correlation with higher grade; there was no correlation between aminotransferase and intensity of the disease; there was correlation of intensity with factors related to insulin resistance. **Conclusion:** Nonalcoholic steatohepatitis is highly prevalent in morbidly obese patients, but there was no positive correlation between aminotransferases and degree of obesity and liver histopathology. Hypertriglyceridemia and waist-hip ratio were positively correlated with the intensity of disease.

HEADINGS - Fatty liver. Gastric bypass. Obesity.

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RESUMO - Racional - Alterações metabólicas têm elevada correlação com formas graves da doença hepática gordurosa não-alcoólica. Todavia, ainda não há método não-invasivo que promova sua adequada estratificação sendo que a biópsia permanece como meio diagnóstico ideal. **Objetivo:** Avaliar a prevalência dessa doença em obesos no pré-operatório de bypass gástrico em Y-de-Roux e correlacionar fatores metabólicos com a histopatologia hepática. **Métodos:** Do total de 47 pacientes, foram incluídos 35 em pré-operatório e excluídos 12 devido à doenças hepáticas e ingestão alcoólica >80 g/semana. Foi realizada avaliação clínico-laboratorial antes da operação e biópsia hepática transoperatória. A intensidade da esteatohepatite foi classificada nos graus: I (leve a moderada), II (difusa e inflamatória), III (fibrose periportal) e IV (cirrose). Foram comparadas as seguintes variáveis: tempo de obesidade, índice de massa corpórea, relação cintura-quadril, diabetes melito tipo 2, hipertensão arterial e dislipidemia. **Resultados:** Trinta e cinco pacientes (68,6% mulheres, média de idade de 37 anos) foram avaliados. O índice de massa corpórea médio pré-operatório foi de 53,04 kg/m². Esteatohepatite não-alcoólica foi encontrada em 31 pacientes (88,6%), sendo grau I 32,2% (n=10), grau II 45,2% (n=14), e grau III 25,6% (n=7). A relação cintura-quadril mostrou associação com esteatose hepática; hipertrigliceridemia foi o marcador que melhor se correlacionou com maior grau; não houve correlação entre aminotransferase e a intensidade da doença; houve correlação da intensidade com fatores relacionados à resistência insulínica. **Conclusão:** Esteatohepatite não-alcoólica tem elevada prevalência em obesos graves, porém não foi observada correlação positiva entre aminotransferases e o grau de obesidade com histopatologia hepática. Hipertrigliceridemia e relação cintura-quadril correlacionaram-se positivamente com a intensidade de doença.

DESCRITORES - Fígado gorduroso. Derivação Gástrica. Obesidade.

INTRODUCTION

It is assumed that 20% of the population presents non-alcoholic fatty liver disease (NAFLD), reaching 90% among obese¹. NAFLD embraces a spectrum of diseases that ranges from benign hepatic steatosis to more severe forms, such as non-alcoholic steatohepatitis (NASH), which demands great interest due to the risk of progression to cirrhosis and hepatocarcinoma⁵.

The degree of insulin resistance and the number of components of metabolic syndrome have higher correlation with the more severe forms of NAFLD^{4,5}. This syndrome is classified by the World Health Organization on basis of criteria or risk factors: waist greater than 102 (men) and 88 (women), dyslipidemia and reduced HDL cholesterol and high blood pressure³.

Bariatric surgery improves simple hepatic steatosis (HS) and NASH in up to 80% of cases, but can lead to cirrhosis or worsening of histology in 6.7 to 11.6%^{8,11,17}. There is difficulty in evaluating clinical parameters due to the lack of correlation between clinical and laboratory intensity of SS and elevated liver enzymes (Table 1). Boza et al. published a study in 2007 showing an increase of these enzymes in more severe cases of HS⁶. Most studies do not reveal this association, which makes the liver biopsy the gold standard for diagnosis of more severe forms of NAFLD. However, it must be considered that it is an invasive diagnostic method and with risks⁹.

TABLE 1 - Correlation between the advanced levels of aminotransferases and degrees of NAFLD

Authors	Year	N	NASH(%)	BMI	DM	AST/ALT
Abrams et al. ⁴	2004	195	36	48	20	25/29
Dixon JB et al. ⁵	2004	36	100	47	56	31/37
Mattar ⁶	2005	70	31	56	50	31/37
Ong et al. ⁷	2005	212	37	26	23	35/44
Boza et al. ⁸	2005	127	26	43	30	67/38
Merriman et al. ⁹	2006	41	31	50	24	22/24
Mathurin P et al. ¹⁰	2009	381	27	50	25	=/31
Ribeiro ¹¹	2010	437	38	48	65	29/37
Weingarten ¹²	2011	340	58	46	33	28/37
Pulzi ¹³	2011	66	40	19	62	31/44
Salgado Júnior et al. ¹⁴	2011	259	89	38	=	30/32

Thus, the objective is to assess the prevalence of NAFLD in obese preoperative Roux-en-Y gastric bypass, and to correlate metabolic factors with liver histopathology by assessing the following variables: body mass index (BMI), waist-hip ratio, type 2 diabetes mellitus, hypertension and dyslipidemia.

METHODS

This study had ethic approval from the institution specific committee.

Forty-seven patients with a BMI ≥ 40 kg/m² or BMI > 5 kg/m² with comorbidities, as outpatients in General Surgery Service at Hospital das Clínicas, Universidade Federal de Pernambuco, Recife, PE, Brazil, took part in this prospective case series. Was performed preoperative clinical and laboratory evaluation and intraoperative liver biopsy (Figure 1), being 12 patients excluded after histopathologic analysis. In preoperative consultation, the following measures were taken: weight, height, waist and hip circumferences, BMI and waist-hip ratio (normal values: woman < 0.8 and man < 1.0). Laboratory tests were performed, being collected 10 ml of blood after 12 h fasting to determine: fasting glucose, total cholesterol and its fractions, HDL and LDL cholesterol, triglycerides, aspartate aminotransferase and alanine aminotransferase, markers of viral hepatitis B and C, alkaline phosphatase, total bilirubin and fractions, prothrombin time and enzyme activity. The severity of NAFLD was graded as follows: 7 grade 0 – normal; grade I – mild to moderate steatosis; grade II – steatosis with ballooning; grade III – periportal fibrosis; grade IV – cirrhosis.

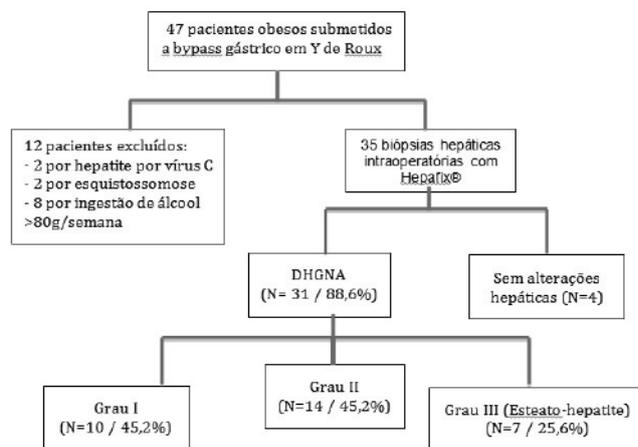


FIGURE 1 - Flowchart of the study

The descriptive statistics and analytical analysis were performed using the Mann-Whitney test. For the association analysis were applied the chi-square and Fisher tests.

RESULTS

Thirty-five patients were analyzed (68.6% women, mean age 37) pre-operatively, with a mean time of obesity of 18 years (range 5-42y), and mean BMI of 53.04 kg/m² (40 kg/m² to 71.7 kg/m²). Regarding risk factors for metabolic syndrome, the following distribution was found: 35.2% (1-2 factors), 41.2% (3-4 factors) and 17.6% (5-6 factors). There was no statistically significant association.

Thirty-one patients (88.6%) had NAFLD, 10

(32.2%) classified as grade I, 14 (45.2%) as grade II, and seven (25.6%) as grade III. There was no grade IV (cirrhosis) (Table 2).

TABLE 2 - Distribution of severe obesity in pre-operative gastric bypass Roux-en-Y depending on the frequency of non-alcoholic fatty liver disease and the degree of liver injury

	N	%
NAFLD		
Yes	31	88,6
No	04	11,4
Grade of the NAFLD		
Grade I	10	32,2
Grade II	14	45,2
Grade III	07	25,6
Total	35	100,0

Patients with grade III NAFLD had a mean age of 33 years, inferior to the average found in HS patients, which was 37 years. There was an inverse association between duration of obesity: 20.3 years for patients with HS versus 14.1 years for patients with NASH (Figure 2). There was no significant difference related to BMI and aminotransferase levels in both groups.

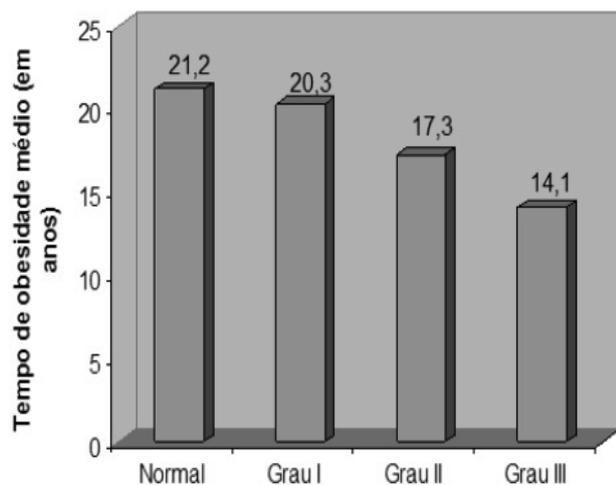


FIGURE 2 - Distribution of the degree of non-alcoholic fatty liver disease according to the average time of obesity in severely obese patients undergoing

The waist-hip ratio correlated significantly ($p=0.05$) with patients with more advanced degrees of disease (grade II and III). As far as, triglyceride levels in patients with NASH was elevated in 83.3% versus 25% of patients with grade I and II of NAFLD. The levels of total cholesterol, HDL cholesterol, LDL cholesterol, hypertension and type 2 diabetes showed no statistic significant association with different degrees of NAFLD (Table 3).

TABLE 3 - Distribution of all grades of NAFLD in obese pre-operative Roux-en-Y, according waist-hip ratio, total cholesterol, HDL, LDL, triglycerides, diabetes and hypertension

Clinical condition	Absent		Present		χ^2	p
	n	%	n	%		
Waist-hip					2,51	0,083
Normal	02	100,0	05	23,8		
Increased	00	0,0	16	76,2		
Cholesterol					1,49	0,315
Normal	03	75,0	11	42,3		
Raised	01	25,0	15	57,7		
HDL					0,01	0,930
Normal	03	100,0	19	79,2		
Low	00	0,0	05	20,8		
LDL					0,37	0,541
Normal	02	66,7	12	48,0		
Raised	01	33,3	13	52,0		
Triglycerides					0,01	0,9841
Normal	03	75,0	15	60,0		
Raised	01	25,0	10	40,0		
Intolerance and diabetes						
Absent	00	0,0	04	100,0	0,42	0,686
Present	03	9,7	28	90,3		
SAH						
Absent	01	25,0	03	75,0	1,56	0,237
Present	18	58,1	13	41,9		

DISCUSSION

Liver biopsy remains the procedure of choice for diagnosis of severe forms of NAFLD. However, due to the high prevalence of this disease, particularly when associated with severe obesity, routine use of this method has been questioned⁹. Clinical scores as SteatoTest noninvasive tests have been developed and FibroTest to predict the existence of fibrosis, steatosis and, respectively, but with low accuracy for routine use^{15,16}.

In this study, the association between waist-hip ratio and triglyceride elevation as factors that correlated most with grade III fibrosis. Meanwhile, BMI or duration of obesity occurred more frequently in grade I and II of NAFLD. In terms of age, a lower mean age in cases of NASH was observed. According to the National Cholesterol Education Program, the main change related to metabolic syndrome is increased waist/hip ratio, being more important than BMI².

Hyperinsulinemia and insulin resistance play a central role in the pathogenesis of HS and NAFLD¹⁰. The presence of hepatic fat, increases resistance to insulin action and reduces suppression of hepatic glucose production, resulting in hyperglycemia and worsening insulin resistance. HS is also associated with poor distribution of Free Fatty Acids leading to the emergence of type 2 diabetes, hypertension and dyslipidemia.

Marceau et al. published a study demonstrating the association between HS and some components of the metabolic syndrome¹³. In this study, 56.8% of patients with HS had more than two risk factors. There was no statistical significance probably due to the small sample size. Treatment of hyperinsulinemia appear to improve

the liver enzyme abnormalities found in NAFLD and, in some cases, lead to histopathological regression, as demonstrated by Luyckx et al. in a cohort study¹². This study involved 505 patients who underwent liver biopsy during bariatric surgery, and second biopsy performed 27±15 months after surgery in 69. After weight loss of 32±19 kg remarkable regression in scores of hepatic fat was observed¹².

A meta-analysis involving 15 studies and 766 paired biopsies, the average percentage reduction in BMI after bariatric surgery ranged from 19.11 to 41.76%. The proportion of patients with improvement or resolution of hepatic steatosis was 91.6%; in steatohepatitis, 81.3%; in fibrosis, 65.5%; and complete resolution of NAFLD, in 69.5%.⁸ In 6.7 to 11.6% of patients there may be worsening or progression of HS mainly related to the weight speed loss^{11,14}.

The present study had small sample size as a limiting factor, once the liver biopsy involves risks, and, besides that, the high number of alcohol-related liver disease, hepatitis C and schistosomiasis were also limiting factors.

This study indicates a high prevalence of asymptomatic liver disease (NAFLD and NASH) in obese patients in Roux-en-Y gastric bypass preoperative period. There was a strong association between NASH and insulin resistance and features of metabolic syndrome.

CONCLUSION

Nonalcoholic steatohepatitis is highly prevalent in morbidly obese patients, but there was no positive correlation between aminotransferases and degree of obesity and liver histopathology. Hypertriglyceridemia and waist-hip ratio were positively correlated with the intensity of disease.

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