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Original Article

Nonalcoholic fatty liver disease in severely obese individuals: The influence of bariatric surgery

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Abstract

Background: **Obesity is the most frequent risk factor associated with NAFLD, and bariatric surgery (BAS) is traditionally indicated for the treatment of severely obese individuals. Here, we discuss the behavior and prognosis of this liver disease following post-surgical weight loss.** ***Aim:*** **To evaluate the influence of the BAS on the clinical and biochemical parameters of NAFLD in severely obese patients.** ***Methodology:*** **An intervention study included obese individuals (BMI≥ 35kg/m^2), who had been submitted to liver biopsy during BAS and had NAFLD. HAIR (hypertension, ALT and insulin resistance and BAAT (BMI, ALT, age and triglycerides) scores and FLI (Fatty Liver Index) were used to compare the patients at the time of surgery, and 12-30 months following weight loss.** ***Results:*** **From October 2004 to September 2007, 122 patients were diagnosed with NAFLD, 40 of whom agreed to participate in the study. The mean age was 37.7 ± 12.5 years, 60% were women and 80% had steatohepatitis (NASH) with fibrosis upon analysis of the liver biopsy performed during BAS. Mean weight loss was 46.0 ± 2.0 kg. After 21 ± 5.8 months of follow-up, a significant improvement was found in all the variables analyzed (79.3% according to the HAIR scores, 95.2% as measured by the BAAT score and 72.5% by the FLI.** ***Conclusion:*** **The results suggest that treatment of obesity by bariatric surgery may influence the prognosis of NAFLD. In addition to weight loss, we observed improvement in the clinical and biochemical parameters related to NAFLD, such as anthropometrics index, hypertension, aminotransferases, triglycerides and insulin resistance.**

Key words: Nonalcoholic steatohepatitis (NASH), morbid obesity, metabolic syndrome, insulin resistance, obesity.

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Abbreviations:
NAFLD: Nonalcoholic Fatty Liver Disease, NASH: Nonalcoholic Steatohepatitis, MS: Metabolic Syndrome, BMI: Body Mass Index, IR: Insulin Resistance, BAS: Bariatric Surgery, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma Glutamyl Transpeptidase, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, SPSS: Statistical Package for Social Sciences, ROC curve: Receiver Operating Characteristic Curve, FIOCRUZ – BAHIA: Fundação Osvaldo Cruz - Bahia- Brazil.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is currently considered one of the most common diseases of the liver. It is characterized as a broad spectrum clinical pathological condition that includes steatosis, nonalcoholic steatohepatitis (NASH) with or without fibrosis, cirrhosis, and hepatocellular carcinoma. It may progress insidiously and asymptomatically to terminal liver disease.[1,2]

NAFLD is multifactorial and may result from primary causes such as clinical conditions associated with insulin resistance (obesity, diabetes mellitus and hyperlipidemia) or from secondary causes such as the use of medications, bowel resection surgery and exposure to chemical products.[3] NAFLD (steatosis and steatohepatitis) is currently considered the hepatic component of metabolic syndrome (MS).[4]

In obese individuals, submitting to liver biopsy, a prevalence of NAFLD is estimated in more than 90%.[5] Bariatric surgery (BAS) has been indicated for the treatment of severely obese with NAFLD.[6,7] and the present study aimed to evaluate the behavior of this liver disease following post-surgical weight loss in these obese individuals.

Patients and methods

Study Design and Patient Selection:

An intervention study was carried out in a population of severely obese individuals (BMI ≥ 35 kg/m^2) from October 2004 to September 2007. Among 122 obese patients with a histological diagnosis of NAFLD during BAS, 40 agreed to participate of the study. Clinical and laboratory data at baseline were compared to those at 12 to 30 months following surgery.

This study was performed in accordance with a protocol approved by the Ethics Committee for Medical Research of Gonçalo Muniz Research Center – FIOCRUZ – Bahia. All the patients included in the study gave their signed, informed consent prior to enrollment.

Inclusion criteria: Severely obese (BMI ≥ 35 kg/m^2), men or women ≥ 18 years old, with a histological diagnosis of NAFLD in a biopsy carried out during bariatric surgery were included in the study.

Criteria for NAFLD: NAFLD was diagnosed in those with a history of alcoholic consumption d» 20 g/day, upon exclusion of other forms of liver disease such as hepatitis B and C, autoimmune disease or metabolic liver disease, and histological diagnosis.

Histological diagnosis: each sample was analyzed by a single pathologist and classified into histological subtypes: isolated steatosis and steatohepatitis (steatosis, ballooning of hepatocytes and inflammation) without and with fibrosis and cirrhosis.

The pattern of alcohol consumption was obtained from medical consultations with physicians and interviews with patient relatives.

Patient evaluation:

Prior to surgery, the patients were evaluated by a multidisciplinary medical team composed of a surgeon, an endocrinologist, a cardiologist and a gastroenterologist, as well as a psychologist and a nutritionist.

A questionnaire was used to obtain medical history, demographic data, to evaluate alcohol consumption, and the use of medications. All the data were obtained prior to surgery and following weight loss.

All patients underwent a complete physical exam, including anthropometric measurements (height, weight, and waist circumference).

Laboratory tests carried out prior to and following BAS consisted of serum measurements of ALT, AST, GGT, fasting glucose, insulin, and a lipid profile (triglycerides, total cholesterol, HDL-C, LDL-C). Serological tests for hepatitis B and C were also performed.

Liver biopsy was performed during BAS.

Systemic arterial hypertension was defined as arterial pressure ≥ 130/85 mmHg and/or continuous use of antihypertensive medication. Type 2 diabetes mellitus was defined as a fasting glucose measurement ≥ 126 mg/dL, a prior history of type 2 diabetes mellitus and/or use of oral hypoglycemic agents or insulin.

Insulin resistance (IR) was evaluated by calculating the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR).[8] To apply HOMA-IR to the insulin resistance index, HOMA-IR ≥ 3 was used.[6,9]

Metabolic syndrome was defined as the presence of three or more of the following factors: abdominal obesity (waist circumference > 102 cm for men and > 88 cm for women), dyslipidemia (triglycerides e» 150 mg/dL, HDL < 40 mg/dL for women and < 50 mg/dL for men), increased blood pressure and glucose intolerance (fasting glucose ≥ 110 mg/dL).[10]

HAIR, BAAT and FLI criteria were used to compare the patients at the time of surgery and following weight loss.

The HAIR (hypertension, raised ALT and raised insulin resistance) score was originally proposed by Dixon *et al* in 2001.[11] The combination of two or three of these predictors resulted in a sensitivity of 0.8 and a specificity of 0.89 for NASH. The BAAT score (BMI, ALT, age and triglycerides), defined by Ratziu *et al* in 2000,[12] refers to the presence of at least two of these factors as being predictive of the severity of NAFLD. The FLI (Fatty Liver Index) created by Bedogni *et al* in 2006,[13] using predictors of fatty liver (BMI, WC, GGT and triglycerides), established that FLI ≥ 60 have 85% chance of there is fat liver injury.

For the purpose of analysis, the study sample was divided into three groups (G) with respect to the time of follow-up evaluation after bariatric surgery: G1: 12-18 months (13 patients); G2: 18-24 months (13 patients); G3: 24-30 months (14 patients).

Statistical analysis: The Statistical Package for Social Sciences (SPSS) software program, version 12.0, was used to analyze the data in this study. The variables are expressed as means ± standard deviations, frequencies and percentages. P-values < 0.05 were considered statistically significant.

Results

Forty obese patients were included in the study. The mean age of these patients was 37.7 ± 12.5 years and 24 (60%) were female. Mean BMI was 45.9 ± 5.7 kg/m^2 (range 36.7–62.5 kg/m^2). Mean waist circumference was 125 ± 17 cm (range 99-169 cm).

Table I shows improvement of all the clinical conditions following surgery (arterial hypertension, diabetes mellitus, dyslipidemia and metabolic syndrome).

Pre-surgical evaluation

The following findings were recorded: metabolic syndrome (MS) in 12 patients (27.5%), elevated ALT in 12 (30.0%), elevated GGT in 10 (25.0%) and elevated AST in 4 (10.0%). Insulin resistance (HOMA-IR e» 3) was found in 66.7% of the subjects. Twenty-nine patients (72.5%) fulfilled the criteria for BAAT, 21 patients (53.9%) the criteria for HAIR and 40 patients (100%) the criteria for FLI.

Hepatic steatosis was found on ultrasonography in 21/40 patients (52.5%).

Histological diagnosis: steatosis in 5%, steatohepatitis (NASH) without fibrosis in 15%, and steatohepatitis with fibrosis in 80% of cases.

Post-surgical evaluation

After a mean period of 21 ± 5.8 months (range 12-30 months) following surgery, we found no difference between the three groups with respect to the time of follow-up evaluation: G1:12-18; G2: 18-24; G3: 24-30 months. A statistically significant reduction was found in all the anthropometric and laboratory parameters except for serum AST levels *(Table II)*.

Following weight loss 87.5% of patients did not present criteria for diagnosis of MS. The *figure 1* shows relevant reduction of all components of this syndrome after BAS.

Insulin resistance was found in only 2.5% (1/40) of the patients after surgery and weight loss.

When evaluated according to the BAAT parameters, 24/29 patients (85%) no longer fulfilled the severity criteria for NAFLD. With respect to the HAIR score, only one patient still fulfilled the severity criteria for NAFLD following surgery and FLI, 11/40 (27.5%) had FLI ≥ 60. All scores were indicative of severe disease in more than 50% of cases (BAAT–72.5%, HAIR–53.9% and FLI–100%).

Liver biopsy was performed only during the BAS and the clinical parameters of the patients were also compared considering the results of the histological diagnosis (steatosis or steatohepatitis (NASH) with and without fibrosis. It was not observed influence of the histological diagnosis, when clinical and biochemical parameters of obese were compared.

An analysis of the abdominal ultrasonography before and following surgery was observed that 79% of the cases did not have signs suggestive of hepatic steatosis.

Table I. Clinical conditions in severely obese patients with NAFLD prior to and following bariatric surgery (n = 40).

Variables	Prior to surgery		Following surgery	
	N	%	N	%
Systemic arterial hypertension	29	72.5	10	25.0
Diabetes mellitus	5	12.5	2	5.0
Dyslipidemia	20	50.0	5	12.5
Metabolic syndrome	25	62.5	3	7.5

Discussion

Bariatric surgery (BAS) has been considered to treat obese patients and NAFLD.[14,15] Given modern technological advances, BAS results in fewer complications, such as malabsorptions and nutritional deficiency.[16]

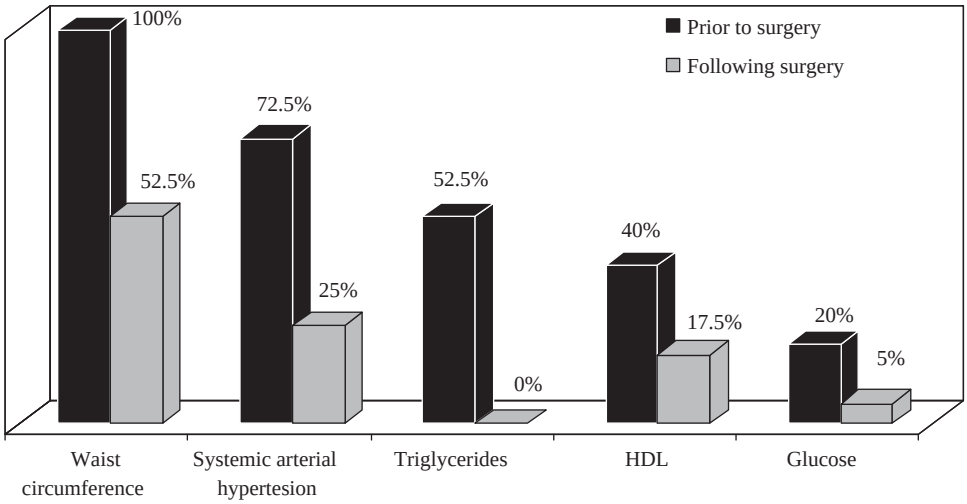
The present study compared clinical and biochemical parameters of NAFLD before and after a mean period of 21 ± 5.8 months following bariatric surgery in a severely obese population.

No clinical or biochemical differences were found between the groups of patients with respect to the time of follow-up evaluation (from 12 to 30 months). This suggests that the improvement found in the clinical vari-

Table II. Comparative analysis of the clinical and laboratory variables of severely obese patients with NAFLD prior to and following bariatric surgery (n = 40).

Variables	Prior to surgery (mean ± SD)	Following surgery (mean ± SD)	*p*
Weight loss (kg)	129.0 ± 24.0	82.6 ± 18.0	< 0.001
BMI (kg/m^2)	45.9 ± 5.7	29.47 ± 23.0	< 0.001
Waist circumference (cm)	125.0 ± 7.0	94.5 ± 13.0	< 0.001
Fasting glucose (mg/dL)	103.0 ± 44.0	85.0 ± 23.0	< 0.001
Serum insulin (μU/mL)	19.5 ± 13.8	5.5 ± 3.9	< 0.001
HOMA-IR	5.2 ± 5.3	1.2 ± 1.2	< 0.001
Total cholesterol (mg/dL)	206.0 ± 40.0	169.0 ± 36.0	< 0.001
HDL-C (mg/dL)	45.0 ± 12.0	57.0 ± 8.0	< 0.001
LDL-C (mg/dL)	128.0 ± 40.0	90.0 ± 15.0	< 0.001
Triglycerides (mg/dL)	167.0 ± 79.0	81.0 ± 46.0	< 0.001
AST (UI/L)	27.0 ± 10.0	22.5 ± 13.0	0.017
ALT (UI/L)	40.0 ± 10.0	28.0 ± 7.0	< 0.001
GGT (UI/L)	66.3 ± 10.0	24.0 ± 14.0	< 0.001

Abbreviations: BMI: Body mass index/HOMA-IR: Homeostasis model assessment of insulin resistance/HDL-C: High-density lipoprotein cholesterol/LDL-C: Low-density lipoprotein cholesterol/ALT: alanine aminotransferase/AST: aspartate aminotransferase/GGT: Gamma glutamyl transpeptidase



HDL: High-density lipoprotein

Figure 1. Frequency of the components of metabolic syndrome prior to and following weight loss in severely obese patients with NAFLD submitted to BAS (n = 40).

ables for NAFLD is present one year after surgery (the time at which weight stabilizes) and remains unchanged over the following eighteen months.

A statistically significant improvement was found in all the clinical and laboratory parameters evaluated in this sample. Patients showed improved arterial hypertension, aminotransferases levels, insulin resistance and dyslipidemia (hypertriglyceridemia improved in 100% of cases, and HDL-cholesterol in 56.5%). Similar results have previously been reported in relation to dyslipedemia.[17,18]

Aminotransferases profiles have not yet been well-defined in severely obese patients.[19] In this study, 30 and 40% of patients had abnormal ALT and AST levels, respectively. After weight loss, decreased levels of ALT, GGT, and AST were observed.

Ong *et al*.[5] used a similar cut-off level (ALT > 40 UI/L), and found abnormal ALT measurements in 56% of patients with steatohepatitis and fibrosis and 35% without fibrosis. Abnormal AST levels were found in 15 and 6% of patients with and without fibrosis, respectively. Barker *et al*[18] found elevated aminotransferases levels in only 2% of patients.

Metabolic syndrome has been diagnosed in up to 64% of patients with NAFLD.[6,9] Some studies have reported significant improvement in all the components of the MS in patients undergoing bariatric surgery.[6,19-22] Similar results were observed in this study and may be relevant. NAFLD has been considered a hepatic component of MS, and it is reasonable to postulate that NAFLD may be under control as a result of the BAS and weight loss in severely obese patients.

Insulin resistance (IR) has been considered synonymous with MS,[23,24] and both are related to NAFLD.[1] In this study, insulin resistance (HOMA) disappeared following weight loss in the majority of the cases. IR is an important factor in the pathogenesis of NAFLD, and weight reduction by BAS decreases insulin resistance. These observations suggest that bariatric surgery may be an effective form of treatment for NAFLD.

In order to evaluate clinical improvement of NAFLD, and to define patients with more advanced disease some scores have been used (11-13, 24-26). They were created using a combination of variables defined as predictors of the disease in its more severe stages. In this study we used the scores proposed by Ratziu *et al*,[12] defined BAAT (BMI, ALT, age and triglycerides) criteria, and that proposed by Dixon *et al*[11] or HAIR criteria (hypertension, raised ALT and raised insulin resistance), because they are easier to apply.

In our samples the results were similar as far as concerning the BAAT score and different for the HAIR score: after weight loss, we found a statistically significant reduction of both scores, with an higher sensitivity and specificity of the BAAT score in respect to the HAIR score.

It also was observed improvement of all parameters , when we apply the FLI index (13) before and after surgery in our patients.

These results suggest that no simple score yet exists as an alternative to liver biopsy even if either of these scores may help to diagnose NAFLD.

The liver biopsy, performed during the bariatric surgery, showed that the majority of the patients already presented NASH with fibrosis, but the histological stage of NAFLD did not influence the degree of improvement in both clinical and biochemical parameters analyzed after surgery.

In conclusion, the present study suggests that treatment of severely obese individuals by bariatric surgery has a favorable impact on the prognosis of NAFLD. In addition to weight loss, the results showed improvement in the clinical and biochemical parameters related to NAFLD such as the anthropometrics index, arterial hypertension, aminotransferases, triglycerides and insulin resistance. However, prior to indicating bariatric surgery in obese patients with NAFLD, the characteristics of each patient should be taken into consideration.

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