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ORIGINAL CONTRIBUTIONS

Effect of Roux-en-y Gastric Bypass on Nonalcoholic Fatty Liver Disease Evaluated Through NAFLD Fibrosis Score: a Prospective Study

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Abstract
Background Nonalcoholic fatty liver disease (NAFLD) is common among subjects who undergo bariatric surgery and its postsurgical improvement has been reported. This study aimed to determine the evolution of liver disease evaluated through NAFLD fibrosis score 12 months after surgery.
Methods It is a prospective cohort study which evaluated patients immediately before and 12 months following Roux-en-Y gastric bypass (RYGB).
Results Mean score decreased from 1.142 to 0.066; surgery led to a resolution rate of advanced fibrosis of 55 %. Resolution was statistically associated with female gender, percentage of excess weight loss, postsurgical body mass index, postsurgical platelet count, and diabetes resolution.
Conclusions As previously reported by studies in which postsurgical biopsies were performed, RYGB leads to a great resolution rate of liver fibrosis. Since postsurgical biopsy is not widely available and has a significant risk, calculation of NAFLD fibrosis score is a simple tool to evaluate this evolution through a noninvasive approach.

Keywords Fatty liver · Gastric bypass · Bariatric surgery · Obesity · Liver function tests

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a common feature among morbidly obese subjects [1]. Several metabolic changes related to obesity are associated with NAFLD, such as the abnormal uptake of fatty acids by the liver, chronic inflammation, insulin resistance, and lipotoxicity [2–5]. NAFLD increases long-time risk for end-stage liver disease and even liver cancer [6–8].

NAFLD fibrosis score was developed as a noninvasive method to estimate fibrosis severity [9]. Several studies have shown its reliability and usefulness as a simple tool in clinical practice [10–12].

Materials and Methods

It is a prospective observational cohort study which enrolled obese subjects aged 18–65 years old who underwent Roux-en-Y gastric bypass (RYGB) at Hospital de Clinicas—UNICAMP—between January 2011 and December 2012. The study was submitted and approved by the local research ethics committee. Surgery was indicated based on the National Institutes of Health Consensus Statement criteria [13]. Sample size estimation was performed through single proportion formula with 95 % confidence interval. Precision was set at 10 % and the calculated sample size was 60. Exclusion criteria for this study were individuals who did not follow up for 12 months, vulnerable groups (mentally ill, institutionalized, or aged below 18 years old), recent or previous abuse of alcohol, antecedents of acute or chronic viral hepatitis, serologic abnormalities regarding hepatitis B or C virus, and previous biliary obstruction.

From 158 subjects who underwent RYGB, 63 who agreed to take part in the study and achieved the 12-month follow-up were included. Main characteristics regarding demographics, anthropometric characteristics, clinical features, and laboratory studies were assessed. Comparisons were made between the periods immediately before and 12 months following surgery, in order to measure the impact of the procedure on

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Table 1 Subjects' characteristics at baseline

Age (years)	40.7±10.3 (range, 21–64)
Gender	Male—13 (20.6 %) Female—50 (79.4 %)
BMI (kg/m^2)	37.4±3 (range, 35–49.9)
Weight (kg)	99.2±12.6 (range, 71.8–125)
Comorbidity profile	Type 2 diabetes mellitus (T2DM)—27 (42.8 %) Hypertension—41 (65.1 %) Dyslipidemia—23 (36.5 %)
Medication usage	Oral antidiabetics—38 (60.3 %) Antilipidemic drugs—4 (6.3 %) Antihypertensives—41 (65.1 %) Insulin—8 (12.7 %)

BMI body mass index

NAFLD liver fibrosis score, which was calculated as described previously by Angulo et al. [9]. Laboratory studies evaluated included fasting glucose (FG), fasting insulin (FI), alanine transaminase (ALT), aspartate transaminase (AST), high density lipoprotein cholesterol (HDL-c), serum triglycerides, total cholesterol, platelet count, and serum albumin. The NAFLD fibrosis score cutoff point considered indicative of advanced fibrosis was above 0.676 [9]. As intraoperative liver biopsy is routinely performed, it was also compared with preoperative NAFLD liver fibrosis score. Significant/advanced fibrosis was achieved when stages equal to or greater than II were observed [2].

Statistical Analysis

The baseline characteristics of patients are described and then compared with postoperative period. Data were examined for normality according to the Pearson's chi-squared test. For univariate analysis of categorical variables, chi-square and Fisher's exact tests were carried out. To identify possible factors associated to the studied outcomes, it was used the multiple logistic regression analysis. To evaluate preoperative diagnostic accuracy of the fibrosis score compared to biopsy (gold standard), sensitivity, specificity, positive predictive value, negative predictive values, and global accuracy were calculated. The significance level adopted was 5 % (p value <0.05). For execution of analysis, Statistical Analysis System (SAS) software for Windows version 9.2 was used.

Results

Of 63 patients selected for the study, 50 (79.4 %) were female and 13 (20.6 %) were male. The mean age at surgery was 40.7 years (range, 21–64 years). Main subject characteristics at baseline are summarized in Table 1.

Mean hospital stay was 4.1±0.3 days. Overall surgical morbidity was 12.7 % and the commonest complication was wound infection (7.9 %). There was no mortality. Patients experienced a significant mean BMI decrease from 37.4±3 to 26.5±3.4 kg/m^2 (p<0.001). Mean weight loss was 28.6±9.5 kg (p<0.0001). Mean percentage of excess weight loss after surgery was 89.9±24.7 %.

Laboratory and clinical features before and after surgery can be observed in Table 2.

Routine liver biopsy was performed during surgery in all the patients. The most observed stages of liver fibrosis were II (39.7 %) and I (36.5 %). Table 3 details the biopsy findings. As liver biopsy is the gold standard method to evaluate liver fibrosis, the results were compared to the those observed in the preoperative NAFLD liver fibrosis score. Sensitivity was

Table 2 Mean clinical and laboratory features

Feature	Presurgical	Postsurgical	Value of p
BMI (kg/m^2)	37.4±3 (range, 35–49.9)	26.5±3.4 (range, 20.7–38.5)	<0.0001
Weight (kg)	99.2±12.6 (range, 71.8–125)	70.6±10.5 (range, 43.6–97.2)	<0.0001
Fasting glucose (mg/dL)	104.5±34.7 (range, 67–251)	81±15.5 (range, 57–174)	<0.0001
Fasting insulin (μU/dL)	11.3±7.1 (range, 2–26.5)	4.6±2.9 (range, 2–12.6)	<0.0001
ALT (mg/dL)	30.7±17.1 (range, 8–97)	20.7±7.2 (range, 7–41)	<0.0001
AST (mg/dL)	25.7±10.6 (range, 12–72)	21.2±5.4 (range, 11–36)	0.0005
HDL-c (mg/dL)	39.6±7.7 (range, 26–64)	53.2±12 (range, 26–94)	<0.0001
Triglycerides (mg/dL)	140.3±93 (range, 38–523)	87.4±45.7 (range, 36–283)	<0.0001
Total cholesterol (mg/dL)	185.7±36.7 (range, 107–290)	144.5±33.8 (range, 90–292)	<0.0001
Platelet count (×10^9/L)	259.2±63.7 (range, 138–396)	245.4±65.5 (range, 136–559)	0.0093
Serum albumin (mg/dL)	4.5±0.3 (range, 3.7–5.1)	4.5±0.2 (range, 3.9–4.9)	0.7414
NAFLD fibrosis score	1.142±1.261 (range, −1.297–3.697)	0.066±1.027 (range, −2.500–2.651)	0.0394

BMI body mass index, *ALT* alanine transaminase, *AST* aspartate transaminase, *HDL*-c high density lipoprotein cholesterol, *NAFLD* nonalcoholic fatty liver disease

Table 3 Intraoperative liver biopsy findings

Histological finding	Number of patients (%)
No fibrosis	6 (9.5 %)
Stage I	23 (36.5 %)
Stage II	25 (39.7 %)
Stages III–IV	9 (14.3 %)

97 %, specificity was 75.9 %, positive predictive value was 82.5 %, negative predictive value was 95.6 %, and global accuracy was 87.3 %.

Mean NAFLD fibrosis score significantly decreased from 1.142±1.261 (range, −1.297–3.697) to 0.066±1.027 (range, −2.500–2.651) (p=0.0394). Preoperatively, 40 subjects (63.5 %) had a score above 0.676 (indicative for advanced fibrosis); postoperatively, 18 (28.6 %) remained at this stage (p<0.0001). Hence, surgery led to a resolution rate of 55 % of severe fibrosis assessed by this method. Multivariate analysis identified factors that showed statistically significant association with this resolution: female gender (p=0.0009), percentage of excess weight loss (p=0.0055), postsurgical BMI (p=0.0286), postsurgical platelet count (p=0.0068), and resolution of T2DM (0.0130). Detailed results of multivariate analysis are shown in Table 4.

Discussion

NAFLD has become a public health issue along with the increase of obesity and overweight prevalence. As it can evolve to severe forms of liver fibrosis, including cirrhosis and liver cancer, NAFLD provides a significant risk for the obese population [14].

This study revealed high prevalence of severe forms of NAFLD at baseline, close to previous findings within the same population of a cross-sectional study which analyzed liver biopsy results [15]. The effect of RYGB on NAFLD was significant, leading to a high resolution rate for advanced fibrosis, as it has been shown by other researchers [16–21].

Table 4 Analysis of factors associated with postsurgical advanced fibrosis improvement

Variable	Improvement	Non-improvement	Value of p
Age (years)	48.3±13.7 (range, 37–64)	42.9±8.5 (range, 23–60)	0.0706
Gender	Male—1 (4.5 %) Female—21 (95.5 %)	Male—9 (50 %) Female—9 (50 %)	0.0009
% EWL	99.9±23.3 % (range, 58.3–138 %)	76.8±21.1 % (range, 36.1–118 %)	0.0055
Presurgical BMI (kg/m^2)	37.5±3.4 (range, 35–50)	37.4±2.5 (range, 35–41.9)	0.9134
Postsurgical BMI (kg/m^2)	25.1±2.9 (range, 20.7–32)	27.3±3.2 (range, 21.8–34.8)	0.0286
Presurgical FG (mg/dL)	110±32.4 (range, 75–185)	111.1±44.8 (range, 77–251)	0.9134
Postsurgical FG (mg/dL)	77.9±4.1 (range, 66–84)	87.3±26.7 (range, 57–174)	0.1783
Presurgical FI (μU/dL)	11±7.2 (range, 2–26.5)	14.1±7.6 (range, 2.1–23.7)	0.2369
Postsurgical FI (μU/dL)	3.9±2.6 (range, 2–12.6)	4.5±2.7 (range, 2–11.2)	0.2952
Presurgical HDL-c (mg/dL)	38±6.3 (range, 32–52)	40.3±8.6 (range, 26–64)	0.8067
Postsurgical HDL-c (mg/dL)	50.7±11.3 (range, 31–64)	54.1±9.9 (range, 38–82)	0.4712
Presurgical triglycerides (mg/dL)	134±94.3 (range, 38–398)	149.3±102.2 (range, 50–523)	0.3277
Postsurgical triglycerides (mg/dL)	82.7±52.5 (range, 36–283)	94.8±43.5 (range, 37–213)	0.1148
Presurgical total cholesterol (mg/dL)	185.4±47.7 (range, 107–290)	184.7±20.7 (range, 152–228)	0.8918
Postsurgical total cholesterol (mg/dL)	136.4±30.4 (range, 90–214)	152.4±42.8 (range, 110–292)	0.1873
Presurgical AST (mg/dL)	26±7.3 (range, 16–46)	26.1±13.6 (range, 14–72)	0.3079
Postsurgical ALT (mg/dL)	21.2±4.2 (range, 16–30)	23.9±6.7 (range, 11–36)	0.1534
Presurgical serum albumin (mg/dL)	4.4±0.3 (range, 3.7–5)	4.4±0.3 (range, 3.8–4.9)	0.4304
Postsurgical serum albumin (mg/dL)	4.5±0.3 (range, 4–4.9)	4.5±0.3 (range, 3.9–4.9)	0.6342
Presurgical platelet count (×10^9/L)	242.5±41.4 (range, 164–341)	217.3±64.8 (range, 138–396)	0.0570
Postsurgical platelet count (×10^9/L)	240±35.7 (range, 210–309)	200.2±55 (range, 138–331)	0.0068
Presurgical T2DM	13 (59.1 %)	13 (72.2 %)	0.5103
Postsurgical T2DM	0	5 (27.8 %)	0.0130
Presurgical hypertension	17 (77.3 %)	12 (66.7 %)	0.4977
Postsurgical hypertension	3 (13.6 %)	4 (22.2 %)	0.6798

% EWL percentage of excess weight loss, *BMI* body mass index, *FG* fasting glucose, *FI* fasting insulin, *HDL-c* high density lipoprotein cholesterol, *AST* aspartate transaminase, *ALT* alanine transaminase, *HOMA-IR* homeostasis model assessment of insulin resistance, *T2DM* type 2 diabetes mellitus

This improvement must be achieved through several not completely understood pathophysiologic pathways, which probably enroll incretin and adipokine activity, decrease of chronic inflammation, reduction of liver fat uptake, and weight loss [22]. On the other hand, a few subjects with refractory postsurgical insulin resistance may have poorer long-term outcomes [23].

Liver biopsy during bariatric surgery has become a mandatory procedure, once it can be safely performed and most obese subjects have any degree of liver disease [24]. As postsurgical liver biopsies may not be widely available and are not free of risk, a noninvasive method should be considered. NAFLD liver fibrosis score has shown to be an easy and adequate way to assess the influence of the surgical procedure on liver disease, and thus its wide utilization should be encouraged. It does not substitute neither is a gold standard by any means as liver biopsy as it does not provide a nuanced evaluation [25], but it has no related morbidity, can be easily and promptly assessed through routine studies, and is very adequate for population studies and clinical follow-up purposes.

Conflict of Interest Everton Cazzo, Laisa Simakawa Jimenez, José Carlos Pareja, and Elinton Adami Chaim declared that they have no conflict of interest.

Statement of Informed Consent Informed consent was obtained from all individual participants included in the study.

Statement of Human and Animal Rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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