



# Non-Alcoholic Fatty Liver Disease Is Associated with Impairment of Ejection Fraction Among Individuals with Obesity Undergoing Bariatric Surgery: Results of a Cross-Sectional Study

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Published online: 16 September 2019

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## Abstract

**Background** The relationship between non-alcoholic fatty liver disease (NAFLD) and myocardial function seems to be more than just the effect of mutual metabolic risk factors.

**Objective** To determine whether there is a significant association between NAFLD assessed by means of liver biopsy and left ventricular function expressed by the estimated ejection fraction among individuals with obesity.

**Methods** This is a cross-sectional study which enrolled individuals who consecutively underwent bariatric surgery. NAFLD was assessed by means of liver biopsies which were systematically collected during the procedures. The estimated ejection fraction was obtained by means of transthoracic echocardiograms. The main outcome evaluated was a possible association between NAFLD features and ejection fraction. The results of liver biopsies and the respective degrees of severity of each NAFLD feature were also correlated with the ejection fraction and main anthropometric, biochemical, and clinical variables.

**Results** Of 112 individuals, 86.6% were female and the mean age was  $38.5 \pm 9.3$  years. It was observed that the average estimated ejection fraction (EEF) was significantly lower among individuals with liver fibrosis ( $67.6 \pm 5.5\%$  vs.  $70.8 \pm 4.9\%$ ,  $p = 0.008$ ). After adjustment for confounding variables in a multivariate model, the degree of liver fibrosis was independently associated with the EEF ( $R = -0.3$ ,  $p = 0.02$ ).

**Conclusion** Among individuals with morbid obesity, the findings of this study are suggestive that liver fibrosis confirmed by histopathological examination is associated with a slight impairment of left ventricular function. Further studies are needed to confirm this association.

**Keywords** Obesity · Fatty liver · Bariatric surgery · Echocardiography · Liver diseases

## Introduction

Non-alcoholic fatty liver disease (NAFLD) is the commonest liver disease and its growing occurrence is closely related to the obesity epidemics [1]. NAFLD is characterized by a large spectrum of histological abnormalities that range from simple steatosis through liver fibrosis, cirrhosis, and even cancer. It is

expected that, by 2030, NAFLD turns into the major indication for liver transplantation [2, 3].

The gold standard method for the assessment of NAFLD is the histological examination, once it provides an accurate and nuanced analysis of the liver tissue architecture, with information on fat deposition, inflammatory activity and occurrence of fibrosis and/or cirrhosis [4]. However, a potential relationship between NAFLD and myocardial function was previously suggested in studies that used non-invasive estimates of liver fibrosis and the estimation of myocardial function provided by echocardiogram scans. From these studies, the association between the liver and heart morbid conditions seems to be more than just the effect of mutual metabolic risk factors since several studies have independently linked both conditions regardless of other metabolic abnormalities [5, 6]. Nonetheless, to date, there is scarce evidence of the

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association between NAFLD assessed by histological examination and myocardial function [7].

This study aims to determine whether there is a significant correlation between NAFLD assessed by means of liver biopsy and left ventricular function evaluated through echocardiogram scan among morbidly obese individuals.

## Methods

### Study Design and Setting

This is a cross-sectional study which enrolled individuals who consecutively underwent bariatric surgery at a tertiary university hospital from June 2017 through July 2018. The study was structured according to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) Guidelines. [8]

### Compliance with Ethical Standards

The study protocol was analyzed and approved by the local Research Ethics Board under the reference number 3.173.474/2019 (CAAE: 05571019.3.0000.5404). All participants provided informed consent.

### Study Population

Sample size estimation was performed using the T statistic and non-centrality parameter; the parameters considered were a 5% type I error rate ( $\alpha$ ), a 20% type II error rate ( $\beta$ ), a proportion of 70% of exposed individuals based on previous epidemiological studies [3], and an effect size of 0.6. The calculated minimum sample size was 108. This protocol included individuals with morbid obesity, of any gender, aged from 18 through 70 years old who underwent Roux-en-Y gastric bypass (RYGB) which was indicated according to the National Institutes of Health consensus statement [9]. Exclusion criteria were the following: vulnerable groups (mentally ill, institutionalized, or aged below 18 years old); history of any alcohol consumption in the last 6 months; use of hepatotoxic drugs; history of chronic viral hepatitis, previous or actual diagnosis of bile duct obstruction; any previous surgical liver intervention; unrelated myocardial disease; electrocardiographic abnormalities; smoking; and incomplete medical reports.

Of 148 individuals who underwent RYGB, 112 who agreed and matched the criteria to take part in the study were included. The main reasons for exclusion were the following: history of alcohol abuse (16), viral hepatitis (6), use of hepatotoxic drugs (4), unrelated myocardial disease (3), history of main bile duct obstruction (2), age under 18 (2), and incomplete medical reports (3).

## Variables

Main characteristics regarding anthropometric characteristics and clinical features were assessed. The anthropometric characteristics assessed were weight, waist circumference, and body mass index (BMI). Patients were weighted using a digital scale properly assessed, with a maximum capacity of 300 kg and a resolution of 100 g, and height was verified by a wall stadiometer. After that, the body mass index (BMI) in kilogram per square meter was calculated. Waist circumference was determined with the tape surrounding the individual in the natural waistline, in the narrowest area between the chest and hip, at the midpoint between the last rib and the iliac crest. The reading was done at the end of expiration.

Biochemical variables analyzed were fasting glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-c), and triglycerides. These examinations were collected during the preoperative period.

NAFLD was assessed by means of liver biopsies which are systematically collected during the procedures. All the histological examinations were performed by the same pathologist. Liver abnormalities were classified into 3 categories as follows: (1) steatosis; (2) fibrosis; (3) steato-hepatitis. Each category was divided accordingly as absent or present. The severity of each abnormality was stratified into 4 categories as follows: absent (0), mild (1), moderate (2), or severe (3). Left ventricular function was estimated by means of transthoracic echocardiogram scans which are routinely performed as a part of the preoperative evaluation of this service. The variable used to express left ventricular function was the estimated ejection fraction (EEF). All scans were performed by the same team. The association between the results of liver biopsy and their respective degrees of severity with the main anthropometric, clinical, and left ventricular function variables was evaluated.

### Preoperative Assessment Routine

All subjects who undergo bariatric surgery at this institution take part in a preoperative weight loss program which lasts 4 to 12 weeks and are comprehended by weekly consultations carried out by a multidisciplinary team. Individuals undergo surgery once a minimum 10% weight loss is achieved or whenever they achieve the minimal body mass index (BMI) according to the NIH criteria (35 kg/m<sup>2</sup> for subjects with obesity-related morbidities or 40 kg/m<sup>2</sup> for those free of comorbidities). Individuals with any use of alcohol in the last 6 months are not selected for surgery until this withdrawal time is reached [10]. Echocardiograms are routinely performed on all candidates to bariatric surgery as a requirement by the anesthesiology team.

## Statistical Analysis

Data were expressed as means  $\pm$  standard deviation. For comparison of proportions, chi-square and Fisher's exact tests were carried out. The Mann-Whitney test was used for comparison of continuous variables between independent groups. For comparison of continuous variables among more than two groups, the Kruskal-Wallis test was used; Tukey's post-test was performed to identify which groups significantly differed. To assess the correlation between continuous or ordinal variables with the studied outcome (EEF), linear and multiple regression models with adjustment for possible confounding variables were performed. The significance level adopted was 5% ( $p$  value  $< 0.05$ ). For the execution of analysis, it was used Statistic Analysis System (SAS) software for Windows version 9.2.

## Results

Of 112 individuals, 86.6% were female and the mean age was  $38.5 \pm 9.3$  years. The mean weight was  $100 \pm 13.4$  kg and the average BMI was  $37.6 \pm 3.1$  kg/m<sup>2</sup>. In regard to clinical characteristics, 14.3% presented diabetes, 44.6% hypertension, and 36.6% dyslipidemia. In relation to NAFLD features, 91.1% of the individuals presented steatosis, 75.9% fibrosis, and 50.9% steato-hepatitis. The average EEF of the study population was  $68.3 \pm 5.5\%$  and there was no individuals with an EEF lower than 50%.

Analyzing the myocardial according to the NAFLD features, it was observed that the average EEF was significantly lower among individuals with liver fibrosis ( $67.6 \pm 5.5\%$  vs.  $70.8 \pm 4.9\%$ ,  $p = 0.008$ ). On the other hand, steatosis and steato-hepatitis were not associated with significantly different values of EEF. Table 1 summarizes the results observed for each NAFLD category.

Correlating the degrees of severity of each NAFLD feature with the EEF, it was observed a significant negative correlation between the severity of liver fibrosis and EEF, i.e., the higher the intensity of fibrosis, the lower the EEF ( $R = -0.3$ ,  $p = 0.006$ ). There were no significant correlations between other NAFLD features (steatosis and steato-hepatitis) and EEF. The complete regression analyses are presented in Table 2. After adjustment for confounding variables (age, gender, waist circumference, BMI, HDL-c, total cholesterol, triglycerides, and fasting glucose) in a multivariate model, the degree of liver fibrosis was independently correlated with the EEF ( $R = -0.3$ ,  $p = 0.02$ ).

Comparing the EEF in each group according to fibrosis severity, the individuals with no fibrosis presented a significantly higher EEF than those with moderate/severe fibrosis ( $70.8 \pm 4.9\%$  vs.  $66.6 \pm 6.9\%$ ,  $p < 0.01$ ). There were no

significant differences between both groups and the individuals with mild fibrosis, whose mean EEF was  $68 \pm 4.8\%$ .

## Discussion

The relationship between liver damage and impairment of myocardial function has been previously hinted by some studies which utilized non-invasive methods to assess NAFLD. Mantovani et al. have observed that NAFLD assessed by ultrasound scan is independently associated with early left ventricular diastolic dysfunction in type 2 diabetic patients with preserved systolic function [11]. Trovato et al., also by means of ultrasound scan, have demonstrated that NAFLD is associated with lower systolic function in lean non-diabetic subjects, independently of BMI, dietary profile, physical activity, and insulin resistance [12]. Using magnetic resonance spectroscopy to assess NAFLD, Houghton et al. observed that cardiac and autonomic impairments appear to be dependent on the level of liver fat, metabolic dysfunction, inflammation and fibrosis staging, and to a lesser extent alcohol intake. [13]

To our knowledge, a single study that included NAFLD evaluation by means of liver biopsy has correlated its features with cardiac function to date. In a cross-sectional study which enrolled 36 participants, Canada et al. have observed that, among individuals with NAFLD, the severity of diastolic function impairment is directly related to the severity of fibrosis stage in pre-cirrhotic stages of NAFLD [7]. The findings of the current study reinforce this observation in a larger sample of individuals with morbid obesity with and without NAFLD, showing that the severity of liver fibrosis assessed by histopathological examination was directly correlated with EEF, regardless of age, gender, weight, BMI, and comorbidities. The current study demonstrated a slight negative correlation between the intensity of liver fibrosis, which is a feature that indicates a severe hepatic impairment in the spectrum of NAFLD, and left ventricular function. Although statistically significant, the relatively mild effect observed may be due to the relative homogeneity of the sample evaluated (all obese individuals with a high prevalence of NAFLD and free of known heart diseases); it is possible to hypothesize that different and even more significant results may be observed in populations with more severe liver disease and cardiac impairment. Nonetheless, our findings point towards a direct relationship between advanced NAFLD and some degree of impairment of left ventricular function.

The current study presents some limitations that should be taken into consideration. Its cross-sectional design does not permit to draw ultimate conclusions in regard to nature (cause or consequence) of the association found. The assessment of left ventricular function by means of transthoracic echocardiography is far from perfect; however, the transesophageal approach is more expensive and not easily available. Moreover, the required

**Table 1** Comparison of clinical, anthropometric, and biochemical characteristics and cardiac function according to non-alcoholic fatty liver disease features

	Presence	Absence	Value of P
<b>Steatosis</b>			
<i>N</i> (%)	102 (91.1%)	10 (8.9%)	NA
Gender	Male 13 (12.7%)	Male 2 (20%)	0.4
	Female 89 (87.3%)	Female 8 (80%)	
Age (years)	38.8 ± 9.5	35.6 ± 6.2	0.3
BMI (kg/m <sup>2</sup> )	36.7 ± 2	35.9 ± 0.9	0.2
Waist circumference (cm)	111.2 ± 9.1	111.2 ± 7.1	1.0
Hypertension	48 (47.1%)	2 (10%)	0.1
Type 2 diabetes	16 (15.7%)	0	0.3
HDL-c (mg/dL)	31.2 ± 5.2	50.2 ± 5.1	< 0.001
Total cholesterol (mg/dL)	164.9 ± 22.9	139.2 ± 7.3	< 0.001
Triglycerides (mg/dL)	172.2 ± 29.3	99.8 ± 14.6	< 0.001
Fasting glucose (mg/dL)	88.9 ± 9.5	81.9 ± 3.3	0.02
Ejection fraction (%)	68.1 ± 5.7	71.1 ± 3.1	0.1
<b>Fibrosis</b>			
<i>N</i> (%)	85 (83.3%)	27 (16.7%)	NA
Gender	Male 12 (14.1%)	Male 3 (11.1%)	0.7
	Female 72 (85.9%)	Female 24 (89.9%)	
Age (years)	38.8 ± 9.8	37.4 ± 7.8	0.5
BMI (kg/m <sup>2</sup> )	36.8 ± 2	36.1 ± 1.4	0.1
Waist circumference (cm)	111.3 ± 9.4	110.9 ± 7.5	0.9
Hypertension	38 (44.7%)	12 (44.4%)	0.9
Type 2 diabetes	14 (16.5%)	2 (7.5%)	0.3
HDL-c (mg/dL)	29.9 ± 4.1	42.2 ± 8	< 0.001
Total cholesterol (mg/dL)	166.9 ± 23.6	149 ± 15.4	< 0.001
Triglycerides (mg/dL)	178.8 ± 25.8	124.7 ± 28.1	< 0.001
Fasting glucose (mg/dL)	89 ± 9.6	85.7 ± 8.1	0.1
Ejection fraction (%)	67.6 ± 5.5	70.8 ± 4.9	0.008
<b>Steato-hepatitis</b>			
<i>N</i> (%)	57 (51%)	55 (49%)	NA
Gender	Male 6 (10.5%)	Male 9 (16.4%)	0.4
	Female 51 (89.5%)	Female 46 (83.6%)	
Age (years)	40 ± 7.6	36.9 ± 7.6	0.08
BMI (kg/m <sup>2</sup> )	37 ± 2.1	36.2 ± 1.6	0.07
Waist circumference (cm)	110.5 ± 8.1	111.9 ± 9.8	0.4
Hypertension	25 (43.9%)	25 (45.5%)	0.8
Type 2 diabetes	12 (21.1%)	4 (7.3%)	0.06
HDL-c (mg/dL)	28.7 ± 4.1	37.2 ± 7.7	< 0.001
Total cholesterol (mg/dL)	174.4 ± 20.5	150.3 ± 19.1	< 0.001
Triglycerides (mg/dL)	176.2 ± 28.7	154.9 ± 37.9	0.001
Fasting glucose (mg/dL)	91 ± 10.2	85.4 ± 7.4	0.001
Ejection fraction (%)	68.3 ± 6.2	68.4 ± 4.8	0.9

*N*, number of individuals; *NA*, not applicable; *BMI*, body mass index; *HDL-c*, high-density lipoprotein cholesterol. Values in italics indicate statistical significance

preoperative weight loss may have influenced the results observed since it may be associated with histological changes in the liver. In line with this observation, the strict inclusion and exclusion criteria of this study, along with the specificities of a population comprised of surgical patients whose EEF was mostly

within the normal range, could also narrow the meaning of these findings. Therefore, the findings of the current cannot be extrapolated to the general population without further research.

Interventions aimed at the control of obesity and NAFLD will also likely contribute to decrease the evolution of left ventricular

**Table 2** Linear regression analysis of the relationship between variables and the study outcome (estimated ejection fraction)

	Beta coefficient	Value of <i>p</i>
Age	− 0.1	0.3
BMI	− 0.01	0.9
Waist circumference	− 0.002	1.0
Triglycerides	− 0.1	0.2
Total cholesterol	− 0.08	0.4
HDL-c	− 0.02	0.7
Fasting glucose	− 0.04	0.6
Severity of steatosis	− 0.1	0.3
Severity of fibrosis	− 0.3	0.006
Severity of steato-hepatitis	− 0.05	0.6

NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; HDL-c, high-density lipoprotein cholesterol. Values in italics indicate statistical significance

dysfunction, even in individuals with the pre-clinical disease [14–16]. Hence, bariatric surgery, which has been previously reported to lead to the improvement and even regression of several NAFLD features, including advanced fibrosis, should play a crucial role in diminishing the late cardiovascular burden of individuals with morbid obesity.

## Conclusion

Among individuals with morbid obesity, the findings of this study are suggestive that liver fibrosis confirmed by histopathological examination is associated with a slight impairment of left ventricular function. Further studies are needed to confirm this association.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

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

**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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