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LETTER TO THE EDITOR

Bilobar Hepatic Histological Variability in Obese Individuals Undergoing Bariatric Surgery: an Analysis of Paired Wedge Biopsies

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Introduction

Despite being the most accurate method and considered the gold standard for the assessment of nonalcoholic fatty liver disease (NAFLD), liver biopsy is not without flaws. Due to the heterogeneity of fatty deposition in the liver, variability or sampling error can occur in up to 30% of cases, with no agreement between different sites submitted to biopsy in the same individuals, generating difficulties in the management of this disease, especially the risk of underestimating its real severity [1].

The present study aims at determining the frequency of occurrence of histopathological variability of bilobar wedge liver biopsies collected in obese individuals undergoing bariatric surgery and at identifying factors that may predict the presence of a greater heterogeneity of the liver parenchyma.

Methods

Study Design

A cross-sectional analytical study was carried out enrolling individuals undergoing bariatric surgery (open Roux-en-Y gastric bypass) at a tertiary university hospital. The study protocol was evaluated and approved by the local Research Ethics Committee according to the opinion 3.717.600/Unicamp (Comment #1).

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Study Population

The individuals underwent surgical procedures from July 2017 through December 2019. Data were obtained from medical records and spreadsheets for outpatient care. We included individuals which underwent bariatric surgery indicated according to the National Institutes of Health (NIH) consensus statement (body mass index ≥ 40 kg/m^2 or ≥ 35 kg/m^2 with obesity-related comorbidities, of any gender, aged between 18 and 70 years). Exclusion criteria were past or current history of liver disease of another nature, vulnerable groups, positive serology for viral liver disease, past or current use of alcohol and illicit drugs, and current or recent use of hepatotoxic drugs.From an initial population of 274 individuals, 22 were excluded due to the following reasons: viral liver diseases ($N = 6$); use of hepatotoxic medication ($N = 7$); other liver diseases ($N = 2$); and incomplete data in medical records ($N = 7$), leaving a study population of 252 individuals.

Informed consent was obtained from all participants of this study.

Variables

The biochemical tests analyzed included fasting blood glucose, transaminases (glutamic-pyruvic and glutamic-oxalacetic), alkaline phosphatase, gamma-glutamyltransferase, total bilirubins, triglycerides, and total cholesterol, which were collected in the preoperative preparation of the surgery according to the usual care protocol.Liver biopsies were collected during surgical procedures. Wedge biopsies were performed in both lobes at the end of the procedures, with fragments of about 2.0 cm extracted from segment III of the liver (left biopsy) and segment V (right biopsy). The results were evaluated through histological examination; the changes were classified into categories, according to the classification of the Brazilian Society of Pathology: (1) steatosis (absent, mild, moderate or severe); (2) fibrosis

(according to the Kleiner-Brunt classification: 0, absent; 1, perisinusoidal or periportal isolated; 2, periportal and perisinusoidal; 3, presence of fibrous septa ("bridging fibrosis"); 4, cirrhosis); and (3) steatohepatitis (classified in grades: 0, 1+, 2+, 3 +) [2, 3]. All surgical procedures were performed by the same team, as well as the analyses of all biopsies.

The following variables were also included: age; gender; body mass index (BMI), and presence of comorbidities.

Statistical Analysis

Descriptive analysis was performed with presentation of frequency tables for categorical variables and measures of position and dispersion for numerical variables. To compare proportions, the chi-square test or Fisher's exact test was used, when necessary. To compare continuous measures, the Mann-Whitney test was used. For the analysis of concordance between the results observed in the two assessments (right and left lobes), the Kappa coefficient was calculated. The level of significance adopted for the statistical tests was 5% ($p < 0.05$). The SAS System for Windows (Statistic Analysis System), version 9.2, was used to perform the analyses; SAS Institute Inc., 2002–2008, Cary, NC, USA.

Results

Of 252 patients included, 88.5% (223) were female, with a mean age of 37.8 ± 10.1 years and an average BMI of 37.4 ± 3.2 kg/m^2. There was no biopsy-related morbidity. Among the comorbidities identified, 40.3% were hypertensive, 17.4% were diabetic, and 25.3% were dyslipidemic. The main NAFLD-related histological patterns identified were steatosis in 174 cases (69%), fibrosis in 127 (50.4%), and steatohepatitis in 101 (40.1%). These data are detailed in Table 1.

Sample histological variability was identified in 22 patients (8.7%). Among individuals with histological variability, the right lobe showed more severe changes with greater frequency (77.3%). Comparing the individuals who showed histological variability, there were no significant differences in relation to age, gender, BMI, presence of comorbidities, or preoperative laboratory tests. Regarding histopathological findings, it was observed that the prevalence of liver fibrosis was significantly higher in individuals who presented variability (48% vs. 27.3%; $p = 0.02$). Table 2 shows the comparison of these variables between individuals with or without sample variability.

With regard to the concordance between the biopsies in relation to the histopathological variables, all had a Kappa coefficient greater than 0.8, demonstrating an almost perfect agreement. Table 3 shows the Kappa coefficients for each histopathological variable.

Table 1 Demographic, clinical, and histopathological characteristic of the study population

N	252
Gender	
Male	29 (11.5%)
Female	223 (88.5%)
Age (years)	37.8 ± 10.1
BMI (kg/m^2)	37.4 ± 3.2
Comorbidities	
Hypertension	102 (40.3%)
Type 2 diabetes	44 (17.4%)
Dyslipidemia	64 (25.3%)
Histopathological aspects	
Steatosis	174 (69%)
Fibrosis	127 (50.4%)
Steatohepatitis	101 (40.1%)

N, number of individuals; BMI, body mass index

Discussion

NAFLD diagnosis and staging are fundamental factors for its adequate treatment and follow-up. There have been several proposals for noninvasive tests for this purpose, but the accuracy of these tests is debatable, especially in individual terms [4, 5]. Particularly, the characterization of individuals who are in the early and intermediate stages of NASH remains outside the scope of the majority these tests. Currently, liver biopsy is the only method to accurately assess the extent and pattern of steatosis, steatohepatitis, and fibrosis, confirming the diagnosis of NAFLD and variations in its pathological spectrum. Although not free of risks, liver biopsy assessment remains the gold standard against which other markers and clinical algorithms should be compared and validated. In this context, bariatric surgery presents a unique opportunity to perform a simultaneous and safe liver biopsy [5–8]. Even so, there is previous evidence pointing to a percentage of diagnostic error in relation to a random liver sample, with variation in histological pattern in relation to biopsies from one lobe to another in the same individual at the same surgical time [1, 2, 7–10].

The fat deposition process in the liver usually occurs heterogeneously. Décarie et al. described at least six different patterns of distribution of steatosis in the liver parenchyma: diffuse, geographical, focal, subcapsular, multifocal, and perivascular. The vascular hypothesis postulates that the blood drained through the superior mesenteric vein, which contains lipogenic factors, is preferentially distributed in the right lobe of the liver. Insulin may also be responsible by heterogeneous fat deposition. It was observed that, in patients with chronic renal failure in a peritoneal dialysis program, the insulin added to the dialysis fluid exposes the subcapsular hepatocytes, promoting the esterification of free

Table 2 Comparison of demographic, clinical, biochemical, and histopathological characteristics between individuals with or without histological variability

	Presence of histological variability	Absence of histological variability	Value of *P*
N	22 (8.7%)	230 (91.3%)	NA
Age (years)	35.1 ± 10.2	38.4 ± 9.4	0.07
Gender	F: 20 (90.9%) M: 2 (8.1%)	F: 203 (88.2%) M: 27 (11.8%)	0.7
BMI (kg/m^2)	37.5 ± 2	36.8 ± 3.3	0.3
Comorbidities			
Hypertension	5 (22.7%)	97 (42.2%)	0.08
Type 2 diabetes	1 (4.5%)	43 (18.7%)	0.09
Dyslipidemia	5 (22.7%)	59 (25.7%)	0.7
Glutamic-pyruvic transaminase (U/L)	18.8 ± 5.6	22.5 ± 10.1	0.1
Glutamic-oxaloacetic transaminase(U/L)	23.3 ± 20.6	27.5 ± 20.6	0.06
Alkaline phosphatase (U/L)	61.3 ± 16.3	66.2 ± 18.6	0.2
Gamma-glutamyl transferase (U/L)	21.6 ± 17.3	28.3 ± 34.9	0.3
Total bilirubins (mg/dL)	0.7 ± 0.2	0.8 ± 0.5	0.6
Glucose (mg/dL)	91.4 ± 18.5	89.7 ± 23.6	0.3
Triglycerides (mg/dL)	106.8 ± 79.9	103.7 ± 44.8	0.7
Total cholesterol (mg/dL)	132.4 ± 70.1	141.4 ± 64.5	0.6
Hepatic abnormalities			
Steatosis	19 (86.4%)	155 (67.4%)	0.07
Fibrosis	6 (27.3%)	121 (48%)	**0.02**
Steatohepatitis	11 (50%)	90 (39.1%)	0.3

N, number of individuals; BMI, body mass index

Bold indicates statistical significance

fatty acids in triglycerides. This form of deposition of fatty liver can also be idiopathic [11].

In the present study, it was observed that, in 8.7% of the individuals, there was disagreement between the findings observed between the right and left lobes of the liver in biopsies performed within the same surgical time. Ratziu et al., in a study of 11 individuals, compared biopsies between the right and left lobes and found disagreement in the detection of elementary abnormalities related to NAFLD in 22% of the patient sample [1]. Arun et al. also compared biopsies taken from different sites in the left lobe of 31 patients undergoing bariatric surgery and confirmed the disagreement between the lobes, with the difference varying according to the characteristics of the liver disease [6]. Larson et al., also analyzing 43 patients undergoing bariatric surgery on core needle biopsies, obtained agreement of 93% for steatosis, 74% for inflammation, 84% for ballooning necrosis, and 98% for fibrosis [7].

Table 3 Agreement between findings of bilobar wedge biopsies

Variable	Kappa coefficient (95% CI)	Interpretation
Steatosis	0.81 (0.73–0.88)	Almost perfect concordance
Fibrosis	0.83 (0.76–0.9)	Almost perfect concordance
Steatohepatitis	0.82 (0.75–0.89)	Almost perfect concordance

CI, confidence interval

In the group of individuals in which there was disagreement, the right lobe showed abnormalities with greater frequency and severity. Larson et al. observed that NASH was significantly more frequent in the right lobe, but there was no difference in the prevalence of fibrosis [7]. Merriman et al. also observed significantly more lobular inflammation in the right lobe [8]. The findings of the present study, in association with the previous evidence, allow us to suppose that, in individuals with a high degree of suspicion for established NAFLD, in addition to a high risk of more serious abnormalities in the disease spectrum, wedge biopsy in the right lobe seems to be more useful for an adequate staging of the disease, or even more appropriately, the performance of a bilobar biopsy, if there is safety and possibility. Among individuals with a lower degree of suspicion, a single biopsy can be taken from any of the lobes. No laboratory test was able to predict the degree of steatosis or the possibility of sample disagreement

between the right and left lobes.There is controversy regarding the most appropriate way of obtaining liver biopsy specimens, whether through wedge extraction or through needle core technique. Core biopsies have the advantage of collecting specimens from the deep parenchyma, but wedge biopsies provide fragments of a more significant size [5]. Rawlins et al., comparing both techniques in obese individuals, demonstrated that the findings of the two techniques presented high agreement [9]. On the other hand, Ooi et al., comparing central and bilobar biopsies, observed high disagreement and suggested that the best option would be the combination of both techniques in several locations in the same patients [10].

The current study presents limitations that must be considered. As this is a cross-sectional study developed only in patients with obesity, there is great homogeneity in the population studied. However, the observed findings were significant and may contribute to better practices in choosing the site to be biopsied in obese individuals at high risk of NAFLD and its severe forms.

Conclusion

Histological variability between samples compared between the right and left lobes of the liver occurred in 8.7% of a population undergoing bariatric surgery. Histopathological changes were more commonly found in the right lobe, and the occurrence of fibrosis was significantly higher among individuals with histological variability.

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Compliance with Ethical Standards

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

Ethical Approval The study was approved by the local committee of ethics in research under the reference number 3.717.600/Unicamp, and all participants signed an informed consent form. 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.

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

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