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ORIGINAL CONTRIBUTIONS

The Correlation Between Obesity-Related Diseases and Non-alcoholic Fatty Liver Disease in Women in the Pre-operative Evaluation for Bariatric Surgery Assessed by Transient Hepatic Elastography

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Abstract

Background Non-alcoholic fatty liver disease (NAFLD) is a common, severe disease in obese patients. However, NAFLD is usually underestimated by ultrasonography. Liver biopsy is not routinely done in bariatric surgery or during the follow-up. This study therefore examined the correlation between metabolic syndrome and NAFLD in morbidly obese patients based on an assessment using transient hepatic elastography (THE).

Material and Methods This study involved 50 female patients in the pre-operative phase for bariatric surgery. Before surgery, we collected clinical, laboratory, and anthropometric variables. THE measurements were obtained using a FibroScan® device (Echosens, Paris, France), and steatosis was quantified using Controlled Attenuation Parameter software (CAP). Statistical analyses were done using linear correlation and the Kruskal-Wallis test.

Results The mean of THE and CAP values were 7.56 ±4.78 kPa and 279.94±45.69 dB/m, respectively, and there was a significant linear correlation between the two measurements ($r=0.651$; $p<0.001$). The numbers of metabolic syndrome parameters did not influence the THE ($p=0.436$) or CAP ($p=0.422$) values. HbA1c and HOMA-IR showed a strong linear correlation with CAP ($r=0.643$, $p=0.013$ and $r=0.668$, $p=0.009$, respectively) and a tendency to some linear correlation with THE ($r=0.500$, $p=0.05$ and $r=0.500$, $p=0.002$, respectively).

Conclusion Morbidly obese women submitted to FibroScan® presented a high prevalence of severe steatosis and advanced

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fibrosis in our sample. Insulin resistance parameters were correlated with steatosis, but less with fibrosis.

Keywords Bariatric surgery · Fatty liver · Metabolic syndrome X · Morbid obesity · Non-invasive test · Transient elastography

Introduction

Non-alcoholic fatty liver disease (NAFLD) is estimated to affect up to 20 % of the general population and can reach values of up to 90 % in morbidly obese patients [1]. NAFLD involves a wide spectrum of hepatic damage, including steatosis, hepatitis, and fibrosis. Frequently, these three entities are present in the same patient, and in the presence of fibrosis, progression to cirrhosis and hepatocellular carcinoma may occur in 20 and 10 % of cases, respectively [2, 3]. Some prospective studies using biopsies to investigate cryptogenic cirrhosis have shown that NAFLD related to diabetes and/or obesity is present in 73 % of cases [4]. Several factors associated with metabolic syndrome have been linked to liver damage, including type 2 diabetes mellitus (T2DM) [5], insulin resistance [6], dyslipidemia [7], and hypertension [8].

In the preoperative phase for bariatric surgery, NAFLD is frequently assessed only with routine ultrasonography, a procedure that is operator-dependent and does not provide enough information about the severity of liver injury mainly regarding the initial stages of fibrosis. Some authors have been reported a poor correlation between ultrasound and NAFLD with low accuracy in obese patients [9, 10]. So far, the gold standard for the diagnosis of NAFLD is liver biopsy for histological analysis based on Kleiner's classification [11]. However, liver biopsy is a surgical procedure and may involve complications such as hematomas, fistulas, and biliomas. In addition, NAFLD-related lesions may be unevenly distributed in the liver parenchyma, leading to false interpretation of inaccurate diagnosis and staging [12].

Transient hepatic elastography (THE) using a FibroScan® device (Echosens, Paris, France) is a non-invasive and painless procedure for measuring liver elasticity based on the emission of elastic waves. With this approach, it is possible to average several measurements (shots) and estimate the degree of fibrosis that is expressed as a continuous variable in kilopascals (kPa) [13]. A new XL probe was recently developed for obese patients [14]. The values of these measurements can vary from 3.5 to 75 kPa, depending on the degree of hepatic fibrosis. The use of THE for obese patients was recently evaluated with good results compared to liver biopsies [15].

The FibroScan® can also assess liver steatosis using Controlled Attenuation Parameter software (CAP), with the results being expressed in decibels per meter (dB/m) [16, 17]. CAP is sufficiently sensitive to identify as little as 5 % steatosis and can evaluate a volume corresponding to a sample 2 cm deep; this specimen size is 100 times larger than that removed in a liver biopsy and therefore reduces the chance of a flawed liver tissue sample [18]. The CAP values can vary from 150–400 dB/m, depending on the severity of liver steatosis.

The main objective of this study was to investigate the relationship between THE/CAP measurements and the comorbidities in morbidly obese patients in the preoperative phase for bariatric surgery.

Material and Methods

Study Population

This study involved female patients in the preoperative phase for bariatric surgery in the Department of Bariatric and Metabolic Surgery of Andaraí Federal Hospital in Rio de Janeiro City. During preparation for surgery, all patients were examined and followed by the same multidisciplinary team that consisted of a bariatric surgeon, endocrinologist, nutritionist, psychologist, physiotherapist, dentist, and social worker.

Morbidly obese patients with grade II or grade III obesity (BMI > 35) were considered eligible for the study. The exclusion criteria were as follows: an age <18 or >65 years old, chronic diseases (heart failure, chronic liver disease), alcohol abuse (abuse was defined as the consumption of >14 drinks per week), long-term consumption of hepatotoxic drugs, positive screening results for hepatitis (positive tests for hepatitis B surface antigen and hepatitis C virus antibodies), and impossibility of acquiring THE and CAP measures by FibroScan®.

Clinical Evaluation

All anthropometric variables were collected by the same surgeon and included weight, height (measured with *Welm*® weighing scales), body mass index (BMI), and waist circumference (WC; measured from the bottom edge of the last rib and the iliac crest). Blood samples were also collected for analyses that included total cholesterol, triglycerides (TG), gamma-glutamyl transpeptidase (GGT), fasting blood glucose (FBG), glycated hemoglobin (HbA1c), and insulin and homeostasis model assessment (HOMA). The HOMA-IR and HOMA-BETA indexes were used as a simple surrogate indicator of insulin resistance. HOMA-IR was calculated as [(fasting insulin in μU/mL) × (FBG × 0.0555)] ÷ 22.5 (assuming normal values ≤3.40) and HOMA-BETA was calculated as [(20 × fasting insulin in milliunits per liter) ÷ (FBG × 0.0555)] − 3.5 (assuming normal values of 167.0–175.0) [19]. The fatty liver index (FLI) was calculated using the formula: FLI = [(e 0.953 x loge (triglycerides) + 0.139 x BMI + 0.718 x loge (GGT) + 0.053 x

waist circumference − 15.745)] ÷ [(1 + e 0.953 x loge (triglycerides) + 0.139 x BMI + 0.718 x loge (GGT) + 0.053 x waist circumference − 15.745)] x 100 [20].

The metabolic syndrome parameters were defined as follows: waist circumference ≥94 cm for men and ≥80 cm for women; hypertension, use of antihypertensive or blood pressure ≥130/85 mmHg; T2DM, use of any medication, glycated hemoglobin (HbA1c) >6.0 %, or FBG >126 mg/dl; dyslipidemia, total cholesterol >200 mg/dl; and TG >150 mg/dl and HDL <40 mg/dl for men and <50 mg/dl for women [21, 22].

Transient Hepatic Elastography

The patients underwent THE with FibroScan® device in accordance with the manufacturer's instructions and training. The operators were trained and have performed more than 50 exams in this new approach in obese patients as recommended by the manufacturer and blind to all clinical and biological data or diagnoses of the patients. Measurements were assessed on the right lobe of the liver through the ninth intercostal space with the patient lying supine and the right arm in maximal abduction. Ten successful acquisitions were obtained for each patient, first with the M probe and then with the XL probe if the exam was not possible to perform or was unreliable with the M probe.

The THE measurements were expressed in kilopascals (kPa) and the CAP in decibels per meter (dB/m). Measurements were considered valid when the interquartile range (IQR) was <30 % and the success rate was ≥60 %. The correlation between THE/CAP vs. metabolic syndrome was assessed using these parameters as continuous variables. We also analyzed CAP as a categorical variable for four different cutoff points as defined by: <214, 214–251, 252–295, and >296 dB/m. These four cutoffs were chosen based on previous work that included the diagnosis of hepatic steatosis and yielded a sensitivity of 90 % for detecting steatosis of at least 5 % [23].

Statistical Analysis

In descriptive analyses, continuous variables were expressed as the mean ± standard deviation and categorical variables as percentages. Pearson or Spearman's linear correlation was used to examine the relationship between each variable and THE/CAP. The number of parameters associated with metabolic syndrome was analyzed using the Kruskal-Wallis test. A strong, significant linear correlation was defined as $r > 0.6$ and $p < 0.05$, whereas a tendency towards a linear correlation was defined as $0.5 < r < 0.6$ and $p < 0.05$. All analyses were done using SPSS IMB® statistical software version 20.0.0, with $p < 0.05$ indicating significance.

Informed Consent

Informed consent was obtained from all subjects who participated in this study.

Results

We assessed 73 female obese patients. Fifty patients had reliable FibroScan® measurements and were included in the study (68 % of patients). We summarized the baseline, clinical, and biological characteristics of the patients (Table 1). Forty-two percent of the patients had T2DM, 28 % had hypertension, and 26 % had dyslipidemia. Two patients (4 %) had one of the parameters associated with metabolic syndrome, 14 (28 %) had two, 21 (42 %) had three, 9 (18 %) had four, and 4 (8 %) had five. The number of metabolic syndrome parameters was not directly correlated with higher THE or CAP values ($p = 0.436$ and $p = 0.422$, respectively), although there was an increase in the mean values in relation to the number of comorbidities (Fig. 1). Patient's with one parameter had a mean THE of 3.75 ± 0.49 kPa, while those with two parameters had a THE of 7.06 ± 3.33 kPa, and those with three, four, and five parameters had values of 8.37 ± 5.75, 7.60 ± 5.49, and 6.85 ± 2.61 kPa, respectively. Patients with one parameter (4 %) had a mean of CAP of 238 ± 9.89 dB/m, while those with two parameters (28 %) had 268.5 ± 35.2 dB/m, those with three parameters (42 %) had 285.6 ± 8.3 dB/m, those with four parameters (18 %) had 294.7 ± 32.1 dB/m, and those with five parameters (8 %) had 277.2 ± 24.3 dB/m.

The mean THE was 7.56 ± 4.78 kPa (range 3–21.6 kPa), and the mean CAP was 279.9 ± 45.7 dB/m (range 203–398 dB/m) (Fig. 2a, b). Ten patients (20 %) had THE measures of 9.6 kPa or higher, suggesting advanced fibrosis. Besides that, significant fibrosis, defined as fibrosis stage less than stage 2, could be excluded by THE results in 36 (72 %) patients, considering those with THE < 7.9 kPa as defined by Wong et al. [13]. Eighteen patients (36 %) had a CAP 296 dB/m (mean THE of 11.33 ± 6.12 kPa), 17 (34 %) had between 252 and 295 dB/m (mean THE of 6.19 ± 1.67 kPa), 13 (26 %) had between 214 and 251 dB/m (mean THE of 4.01 ± 0.67 kPa), and 2 (4 %) had <214 dB/m (mean THE of 3.45 ± 0.99 kPa). There was an analyses of CAP classified into four ranges and THE showed significance ($p = 0.006$) (Fig. 2c). THE and CAP measurements were also significantly correlated with each other ($r = 0.651$; $p < 0.001$), as shown in Fig. 2d.

The WC, BMI, FBG, HOMA-BETA, TG, LDL, and HDL showed no linear correlation with CAP ($r = -0.064$, 0.132, 0.450, 0.031, 0.284, −0.183, and 0.172, respectively) or THE ($r = -0.046$, 0.024, −0.033, 0.031, 0.456, −0.061, and −0.093, respectively). However, as shown in Fig. 3, HbA1c and HOMA-IR were strongly correlated with CAP ($r = 0.643$, $p = 0.013$ and $r = 0.668$, $p = 0.009$, respectively), and there was

Table 1 Baseline, clinical, and laboratory data, as well as transient hepatic elastography and controlled attenuation parameter measurements for morbidly obese patients submitted to FibroScan®

Parameters	Mean±SD (n=50)	Range
Age (years)	40.96±9.87	25–63
Weight (kg)	125.52±17.54	93.6–159.5
BMI (kg/m^2)	47.34±5.34	37.3–58.3
FBG (mg/dl)	125.3±48.26	65–345
HbA1c (%)	6.24±1.19	4.4–10.3
Insulin (U/ml)	22.39±15.55	2.0–77.6
HOMA-IR	6.72±4.55	0.6–20.29
HOMA-BETA	208.65±324.42	12.0–2232.56
Triglycerides (mg/dl)	116.36±109.86	38–780
Total cholesterol (mg/dl)	196.32±40.03	136–331
HDL cholesterol (mg/dl)	50.60±9.79	29–74
LDL cholesterol (mg/dl)	132.8±38.39	70–244
Uric acid (md/dl)	5.11±0.84	3.3–6.8
FLI	97.75±2.89	85.15–99.85
THE (kPa)	7.56±4.78	3.0–21.6
CAP (dB/m)	279.94±45.69	203–398

BMI body mass index, *CAP* controlled attenuation parameter, *FBG* fasting blood glucose, *FLI* fatty liver index, *HbA1c* glycated hemoglobin, *HOMA-IR* homeostasis model assessment insulin resistance, *HOMA-BETA* homeostasis model assessment beta-cells, *THE* transient hepatic elastography

a tendency to some linear correlation with THE (r=0.500, p=0.05 and r=0.500, p=0.002, respectively).

Discussion

The main goals of this study were to investigate the association between obesity, metabolic syndrome, and NAFLD in morbidly obese women using a non-invasive and promisor device in obese population, FibroScan®, and mainly to evaluate his applicability in morbidly obese patients. The limited amount of information available on the use of non-invasive methods to evaluate NAFLD and obesity-related diseases led us to examine this relationship in detail. NAFLD is currently the most common chronic liver disease in Western countries and is expected to increase along with the worldwide epidemic of obesity and T2DM [24]. Indeed, this increase in the prevalence of obesity, insulin resistance, T2DM, dyslipidemia,

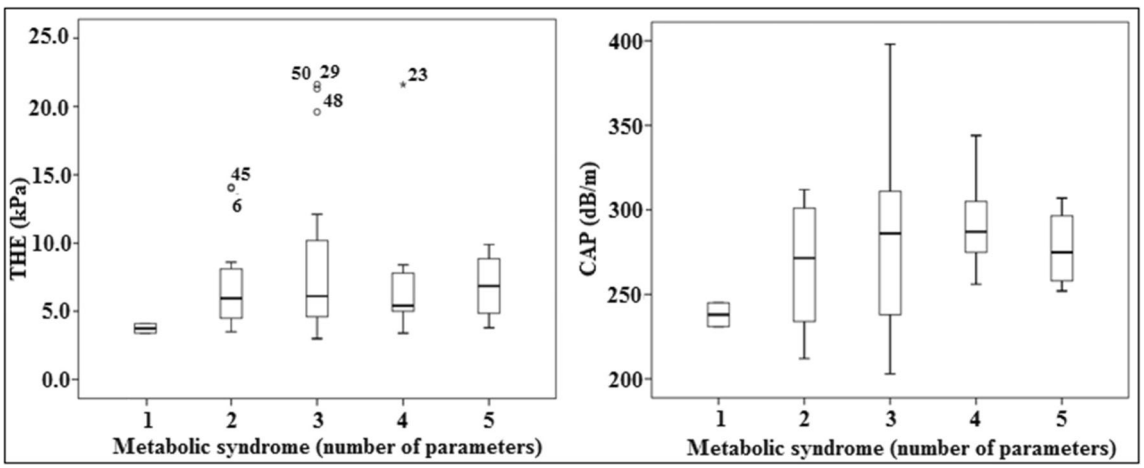

Fig. 1 THE and CAP values according to the number of metabolic syndrome parameters. The results are shown as box plots for the 50 subjects enrolled in the analysis. The *points* and *numbers* in the *left panel* indicate individual subjects in the study group. Although the mean and median values for THE and CAP tended to increase with increasing number of parameters, there was no significant difference among the THE or CAP values in relation to the parameters examined (p = 0.436 and p = 0.422, respectively; Kruskal-Wallis test)

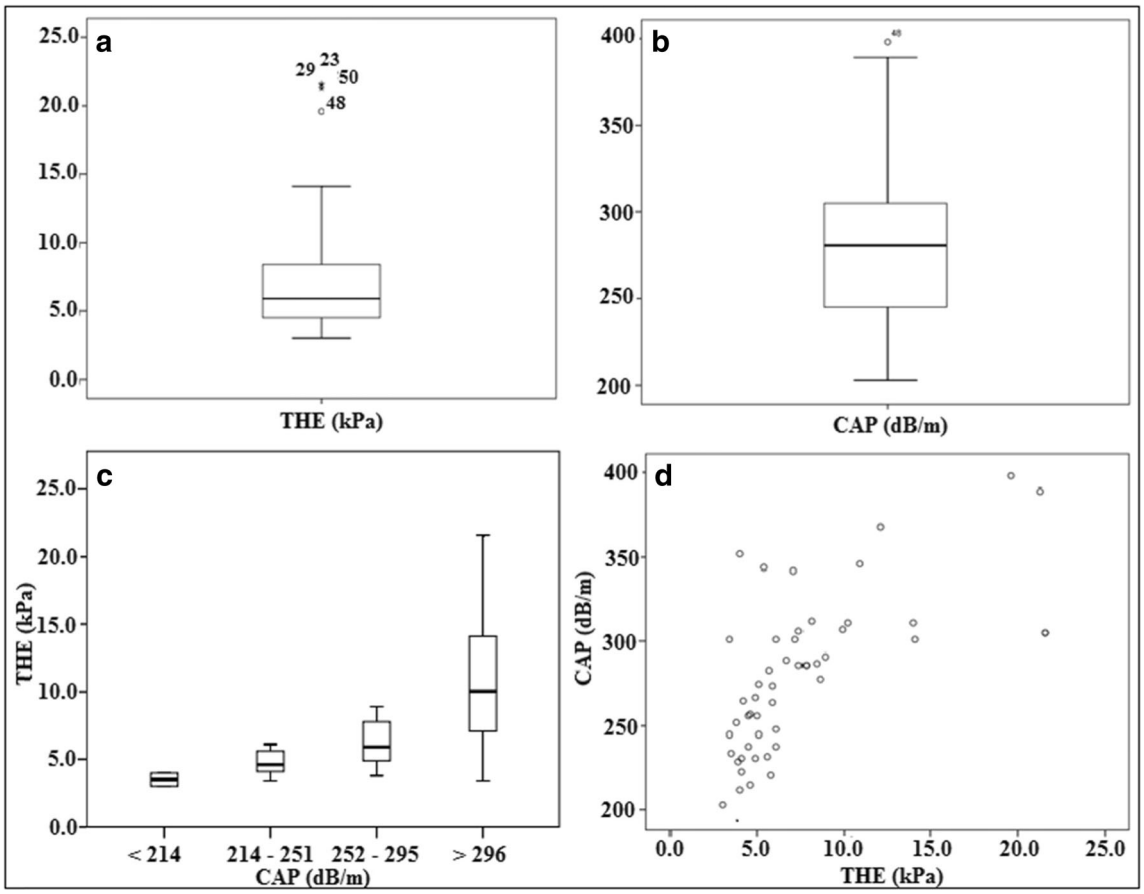

Fig. 2 Correlation between transient hepatic elastography (THE) and controlled attenuation parameter (CAP). **a**–**c** Box plots of the THE (**a**), CAP (**b**) values, and the CAP values classified in four ranges in relation to THE values (**c**) ($p = 0.006$). **d** Scattergram of the relationship between the THE and CAP data. These two measurements were significantly correlated ($r = 0.651$; $p < 0.001$). Linear correlation was assessed using the Pearson coefficient (r), with a strong correlation and significance being defined as $r > 0.6$ and $p < 0.05$, respectively

hypertension, and metabolic syndrome is rapidly changing the scenario in the field of hepatology. To determine the epidemiology and natural history of NAFLD, Verno et al. [25] undertook a systematic review of all studies of NAFLD published from 1980 to 2010 and showed that T2DM had a particularly close relationship with NAFLD.

Benotti et al. [26] recently reported outcomes from more than 150,000 patients recorded in the Bariatric Outcome Longitudinal Database. Evidence of liver disease was significantly associated with 30-day mortality after gastric bypass. However, the diagnosis and true severity of steatohepatitis and/or advanced fibrosis associated with fatty liver infiltration are a challenge and have important prognostic and therapeutic implications for obese patients. Furthermore, there is increasing evidence to suggest that NAFLD is a new and increasingly relevant risk factor for the development of hepatocarcinoma [27]. In general, this population is evaluated by abdominal ultrasound before bariatric surgery, which can detect in general a minimum of 30 % steatosis but is not able to evaluate incipient grades of fibrosis [10]. In morbidly obese patients, ultrasound may also be a challenge owing to the high BMI presented by these patients which might also limit the accuracy of the ultrasound [9].

Recently, a study showed that CAP, evaluated with FibroScan®, could efficiently evaluate steatosis grades [16]. This physical parameter has been developed using the ultrasound propagation in the fat liver. It has a higher sensitivity to detect steatosis as low as 11 % compared to ultrasound, and furthermore, CAP can define different grades of steatosis allowing classifying in different categories according to de Ledhighen et al. [23]. Hence, it can be a relevant tool when evaluating obese patients since liver biopsy (the gold standard) may be challenging in this population. Fibrosis also can be assessed with acceptable accuracy in obese patients as first documented by Naveau et al. [15]. As in this study, many obese patients (20 %) already presented advanced fibrosis stage (THE > 9.6 kPa) and, hence, are at high risk of developing related complications such as hepatocarcinoma. In view of this, Verna [28] strongly suggested that all obese patients should have a liver biopsy.

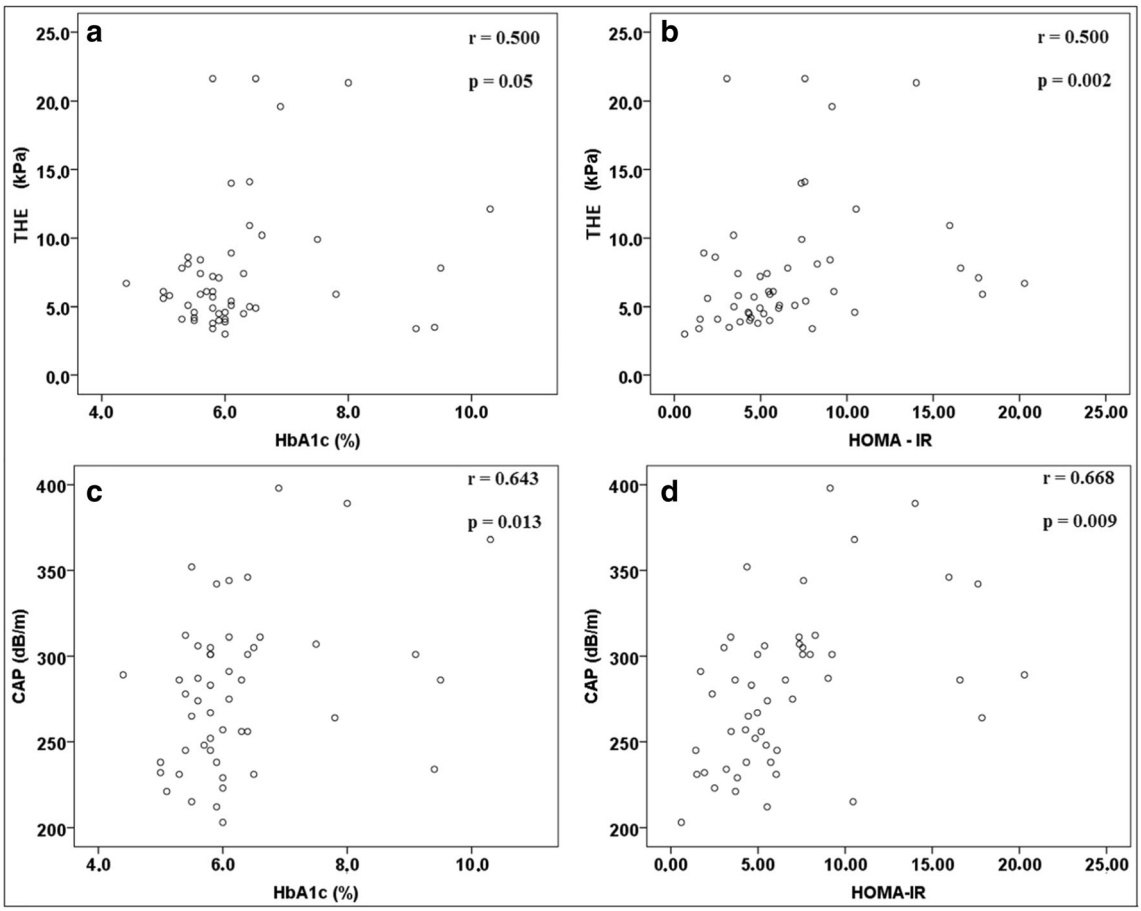

Fig. 3 Correlation of transient hepatic elastography (THE) and controlled attenuation parameter (CAP) with HbA1c and HOMA-IR. **a**, **b** Scattergrams for THE vs. HbA1c and THE vs. HOMA-IR, respectively, showing a trend towards linear correlation ($r = 0.500$, $p = 0.05$, and $r = 0.500$, $p = 0.002$). **c**, **d** Scattergrams for CAP vs. HbA1c and CAP vs. HOMA-IR, respectively, showing strong linear correlation ($r = 0.643$, $p = 0.013$, and $r = 0.668$, $p = 0.009$). Linear correlation was assessed using the Pearson coefficient (r), with strong correlation and significance being defined as $r > 0.6$ and $p < 0.05$, respectively. A trend towards linear correlation was defined as $0.5 = r = 6$ and $p < 0.05$

Because of the enormous prevalence of NAFLD worldwide and the invasiveness of liver biopsy, much effort is being expended on developing non-invasive alternatives for assessing this condition. Based on that, our group has started a study with obese patients using THE. This study is the first one that evaluates fibrosis and steatosis using THE and CAP in this population to compare comorbidities. Elastography performed with the FibroScan® in morbidly obese patients has some limitations that must be considered. In our study, we had a high prevalence of unreliable acquisition that was discarded. This is an intrinsic limitation of the FibroScan® device that was largely overcome by the use of the XL probe. In the present study, a reliable exam was possible in 68 % of patients. Overall, the failure of 32 % of exams, which included exclusive morbidly obese patients, was higher than generally expected in obese patients, which is usually around 5–15 % [29]. Although steatosis might overestimate the degree of fibrosis as recently described by Petta et al. [30], it is a non-invasive and easy-to-perform device that can be applied to identification and follow-up of obese patients with NAFLD. In addition, it is worth mentioning that with the development of the CAP for the XL probe, the frequency of unreliable exams will decrease.

In the last few years, THE, initially developed to detect cirrhosis in patients with virus C [31], has been increasingly used to assess NAFLD [13]. The development of a new XL probe has made it easier to assess THE in obese patients [14, 32]. Some authors recently evaluated the diagnostic value of THE in 100 bariatric surgery candidates with suspected NAFLD and showed that the FibroScan® device can be used for the early diagnosis of fibrosis in patients with severe obesity [15]. In the present study, the agreement of histology and elastography data was not performed; this way, the sensitivity and specificity of THE in morbidly obese patients are still a relevant question not answered so far. It is noteworthy that studies that perform liver biopsy during the procedure are required.

Some authors showed that the prevalence of NAFLD can increase in parallel with the components of metabolic

syndrome [17] and can be present in patients without symptoms, signs, or enzymatic abnormalities. However, in the present study, there was no relationship between the number of metabolic syndrome parameters and THE or CAP values ($p=0.436$ and $p=0.422$, respectively). However, the mean values of both THE and CAP had a trend to increase in relation to the number of comorbidities. It is possible that the small number of patients included might have hindered this association.

As we know, some studies have already showed a high prevalence of NAFLD in diabetic patients based on liver biopsy [33, 34]. Ratziu et al. [35] observed a correlation between HOMA and the amount of steatosis ($r=0.35$, $p<0.001$) and fibrosis ($r=0.34$, $p<0.001$) in a large European population, with HOMA on its own being a predictor of advanced disease ($p=0.001$). In a prospective study of 105 consecutive liver biopsies taken as a routine part of the operative procedure, Dixon et al. [36] identified HOMA as a factor with a significant independent predictive effect in steatohepatitis ($p<0.001$), with indirect measures of HOMA showing the best correlation with steatosis ($r=0.47$, $p<0.001$). Naveau et al. [13], in the only study to combine data on HOMA with FibroScan® measurements, found that HOMA was correlated with the amount of steatosis ($p<0.00001$) and liver stiffness, independently of fibrosis ($p<0.02$); these authors also suggested that THE could identify a subgroup with NAFLD that had a high risk of progressing to end-stage liver disease. We also found a significant correlation between CAP and HOMA ($r=0.668$, $p=0.009$), and a trend towards linear correlation between THE and HOMA ($r=0.500$, $p=0.002$). The absent correlation between THE and HOMA may be missed owing to a beta error since only 50 patients were included in this study.

Dixon et al. [34] identified T2DM as a clinical predictor of steatosis, inflammation, and fibrosis ($p=0.004$, $p<0.001$, and $p<0.001$, respectively), whereas HbA1c levels were not predictive ($p=0.36$, $p=0.34$, and $p=0.35$, respectively). However, Bae et al. [37] observed an increased risk for NAFLD with high levels of HbA1c (odds ratio (OR) 1.44, 2.62, and 7.18) when compared with the lowest quartile (HbA1c≤4.9 %). In a cross-sectional biopsy study with 949 patients, Ma et al. [38] found that NAFLD patients had significantly higher serum HbA1c levels (HbA1c≥6.5 %) than controls ($p<0.001$). In the present study, we observed a significant linear correlation between HbA1c and CAP ($r=0.643$, $p=0.013$) and a tendency towards linear correlation with THE ($r=0.500$, $p=0.05$).

The presence of dyslipidemia (hypercholesterolemia, hypertriglyceridemia, or both) has been reported in 20–80 % of cases associated with NAFLD [39]. Hence, it is not surprising that many studies have reported an association between NAFLD and metabolic syndrome, especially abdominal obesity, and glucose and lipid metabolism [40]. Dixon et al. [36] found that TG levels were a predictor of steatohepatitis ($p=0.047$). However, other studies did not confirm this association for hyperlipidemia and fibrosis ($p=0.4$) [13]. In this study, lipid levels showed no correlation with THE measurements (HDL $r=-0.093$; LDL $r=-0.061$; TG $r=0.456$) or CAP values (HDL $r=0.172$; LDL $r=-0.183$; TG $r=0.284$).

Although BMI is one of the most useful predictive factors for the onset of NAFLD [41] it is probably not a reliable parameter for assessing the severity of damage [15, 36]. Indeed, we found no relationship between BMI and both THE and CAP measures ($r=0.024$ and $r=0.132$, respectively). However, based on multiple regression analysis, Hyogo et al. [42] reported that waist circumference (inversely, $p<0.01$) was independently correlated with the level of advanced glycation products ($r^2=0.176$) that in turn was related to liver damage [43]. Waist circumference showed no correlation with THE and CAP in our subjects ($r=-0.046$ and $r=-0.064$, respectively), probably because most waist circumference are high enough to determine significant association in THE and CAP measures. It is possible that in morbid obese patients, waist circumference per se might not be a parameter of advanced fibrosis.

Conclusion

In conclusion, in this study including young morbidly obese women who had fibrosis and steatosis evaluated by THE and CAP, high prevalence of advanced fibrosis and severe steatosis was observed and directly correlated with each other. In addition, diabetes and insulin resistance parameters were strongly correlated with steatosis and had a moderate correlation with fibrosis. The number of metabolic syndrome parameters showed no direct correlation with the values obtained with the FibroScan® device, although the mean values tended to increase in relation to the number of comorbidities.

Compliance with Ethical Standards

Ethical Approval 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.

The Ethics and Research Committee of the Fluminense Federal University, Niteroi, Brazil, approved this study (protocol no. 363.683). The ClinicalTrials.gov identifier is NCT02394353 (Ministry of Health, Brazil).

Conflict of Interest The authors declare that they have no competing interests.

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

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