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Nonalcoholic steatohepatitis in morbid obese patients: coffee consumption *vs.* disease severity

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ABSTRACT

Introduction. Obesity correlates with nonalcoholic fatty liver disease (NAFLD) and occurs in 90 to 100% of severely obese individuals (body mass index [BMI] > 35 kg/m^2). Coffee consumption (CC) has been associated with reduced progression of fibrosis in both hepatitis C infection and NAFLD; however, this topic is still under discussion when this liver disease affects severely obese individuals. **Objective.** To assess the association between CC, insulin resistance (IR) and histological NAFLD morbid obese patients. **Material and methods.** Cross-sectional study, including obese individuals undergoing bariatric surgery, liver biopsy and histological diagnosis between September 2013 and August 2014. The patients were classified into 3 groups according to their weekly CC: 0- 239.9 mL; 240-2099.9 mL and ≥ 2100 mL. **Results.** A total of 112 obese individuals were included (BMI = 41.9 ± 4.3 kg/m^2), with a mean age of 34.7 ± 7.4 years; 68.6% were women. CC was reported by 72.3% of patients. There were no statistical significant differences between groups regarding the presence of IR (84.8% *vs.* 74.2% *vs.* 75.9%; p = 0.536). Progressively higher percentages of individuals with normal liver histology were observed (14.7% *vs.* 21.9% *vs.* 24.3%). NASH (65.7% *vs.* 70.3% *vs.* 57.5%) were observed among those who consumed greater coffee volumes (p = 0.812). In conclusion, obese individuals with elevated CC exhibited lower frequencies of NASH, although with no statistical significance in this sample.

Key words. NAFLD. NASH. Insulin resistance. Coffee. Liver disease.

INTRODUCTION

Obesity is currently one of the major public health problems in the world, with growing prevalence in all age groups and at all socioeconomic and cultural levels. Therefore, we are observing higher prevalence rates of obesity-related diseases, such as nonalcoholic fatty liver disease (NAFLD), which is considered the hepatic component of metabolic syndrome (MS).[1-4]

One of the main factors responsible for the greater severity of liver tissue damage in obesity is insulin resistance (IR) syndrome and the consequent increases in intrahepatic free fatty acid and cholesterol levels. These factors induce cytotoxicity, mitochondrial dysfunction and oxidative stress, which, when combined with genetic predisposition, favor NAFLD progression to more severe forms, such as cirrhosis.[5-7] In addition to these factors, NAFLD severity is also affected by physical activity, alcohol consumption, fructose intake and smoking.[8-12]

Coffee is one of the most consumed beverages in the world and is part of millions of people's daily diets. Coffee has various components, such as caffeine, triacylglycerol, tocopherols, chlorogenic acid, cafestol, kahweol, and relevant antioxidant and anti-inflammatory properties; thus, it can have beneficial effects on metabolism.[13-16]

Recent studies support the hypotheses that coffee can affect the progression and can reduce the severity of hepatocellular aggression in liver diseases such as chronic hepatitis C and NAFLD.[14,17-19] However, this topic is still under discussion, and it motivated this study, which aimed to assess the correlation between coffee consumption, IR and histological NAFLD severity in morbid obese patients (body mass index [BMI] ≥ 35 kg/m^2).

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MATERIAL AND METHODS

Design and sample population

This cross-sectional cohort study assessed obese patients undergoing bariatric surgery and liver biopsy during surgery between September 2013 and August 2014. This study was conducted according to the guidelines established in the Declaration of Helsinki. The project was approved by the Research Ethics Committee (Comitê de Ética em Pesquisa - CEP) of the School of Medicine of Bahia, and all of the participants signed an informed consent form.

The NAFLD diagnostic criteria included alcohol consumption < 20 g/day for women and < 30 g/day for men, with the exclusion of other liver diseases and histological diagnoses.

Patients' clinical assessment

All patients answered a questionnaire to quantify coffee consumption and to correlate the following variables: gender; age; NAFLD risk factors; alcohol consumption and factors related to other systemic and liver diseases. All patients were subjected to a full physical examination and complementary tests: liver, lipid and glycemic profiles, serum insulin, HBsAg, anti-HCV, ferritin, transferrin saturation index, abdomen ultrasound and liver biopsy.

Insulin resistance (IR) was assessed using the Homeostatic Model Assessment-IR (HOMA-IR).[20] HOMA-IR values ≥ 3 were considered IR.[21] Diabetics were excluded from this assessment. Diabetes mellitus type 2 was defined as blood glucose levels over 126 mg/dL at two different time-points or blood glucose levels over 200 mg/dL after overload with 75 g of anhydrous glucose.[22] High-density lipoprotein (HDL) cholesterol was calculated using the Friedewald equation LDL = total cholesterol – (HDL – triglycerides/5), except for the individuals with TG levels over 400 mg/dL.[23] The diagnosis of MS was established according to the International Diabetes Federation (IDF) criteria.[24]

Histological assessment

Using a Tru-Cut biopsy needle, a single surgeon performed liver biopsies during bariatric surgery. A single liver pathologist analyzed the tissue obtained. The histological diagnosis of NAFLD was established using the NASH Clinical Research Network/2011 criteria.[25]

Coffee and caffeine consumption assessment

Patients were questioned about the consumption of coffee and other foods or beverages containing caffeine during a typical week, two months before surgery, prior to the onset of changes due to the instructions provided regarding the patient's diet and preparation for the surgical procedure.

The amounts of coffee and other foods or of medication ingested were recorded on a table with all of the items about which the patients were asked. These data were used to calculate the amounts of coffee (in milliliters) and caffeine (in milligrams) ingested from coffee and other sources (i.e., tea, chocolate, soft drinks, energy drinks, and medications containing caffeine). The amount of caffeine in each type of coffee and caffeine-containing food was previously determined, considering the different types of coffee, such as expresso, filtered, soluble and decaffeinated.

Patients were classified into three groups according to their coffee consumption, with the amount of ingested coffee varying between 0.0- 239.9 mL, 240-2,099.9 mL and ≥ 2,100 mL/ week.

Statistical analysis

The analyses were conducted using the Statistical Package for the Social Sciences software (SPSS Inc., Chicago, Illinois, USA, Release 16.0.2, 2008). Data were analyzed and are expressed as mean values, standard deviations, medians (Mdns) and interquartile ranges (IQRs) according to the variables' distribution. Coffee consumption was considered the independent variable, and NAFLD was considered the dependent variable. To compare quantitative variables between groups, analysis of variance (ANOVA) or the Kruskal-Wallis test was used; for qualitative variables, Pearson's χ^2 test was used. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

RESULTS

The patients were divided into tertiles for data analysis according to weekly coffee consumption. Clinical and biochemical characteristics and coffee consumption of the 112 obese patients assessed are included in tables 1 and 2.

Coffee consumption was reported by 72.3% (81) of patients. Fasting glucose, serum insulin, total and LDL cholesterol, liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP] and gamma-glutamyltransferase [GGT]) and ferritin levels were not significantly different between groups (Table 2). These variables were similar when analyzing total caffeine consumption too.

There were no significant differences between groups regarding the presence of IR (84.8% *vs.* 74.2% *vs.* 75.9%; $p = 0.536$) (Table 1). Regarding the presence of MS, we observed that 41%[43] of individuals assessed did not meet

the diagnostic criteria. When analyzing the presence of MS according to coffee consumption, we did not note any differences between groups (51.6% *vs.* 33.3% *vs.* 39.5%, p = 0.308).

The table 1 shows the analysis of individual traits of MS in tercis with regard to weekly coffee consumption. Statistic significance was not finding. In descritive analysis arterial hypertention was observed in 42.7% of the patients; diabetes or blood glucose > 99 mg/dL in 37%; HDL cholesterol < 40 mg/dL in men or < 50 mg/dL in women in 61%; and tryglicerides > 150 mg/dL in 39.8%. All severe obese patients presented central obesity.

Comparing the groups to evaluate the relationship between coffee consumption and NASH, it was observed a progressively higher percentage of individuals with normal liver histology (14.7% *vs.* 21.9% *vs.* 24.3%) and a lower percentage of NASH with ou without fibrosis (61.8% *vs.* 62.6% *vs.* 51.3%) among those who consumed a greater amount of coffee, although these differences did not reach statistical significance (Table 3).

The results were similar when total caffeine ingested was considered. There was no difference in caffeine ingestion when analyzing caffeine originating from coffee compared with that from other sources.

Table 1. Clinical and demographic characteristics of 112 obese patients with regard to weekly coffee consumption.

Variables	Weekly coffee consumption			p
	First tertile, 38 (34%)	Second tertile, 36 (32%)	Third tertile, 38 (34%)	
Female	26 (68.4%)	25 (69.4%)	30 (78.9%)	0.530
Age (years)*	33.9 (7.8)	38.1 (9.9)	37.8 (9.6)	0.109
BMI (kg/m^2)*	41.4 (4.1)	40.8 (5.2)	41.1 (4.7)	0.859
Glycemia(mg/dL)†	98.5 (86.8 - 106.5)	93.5 (85.2 - 99.5)	95.5 (87.0 - 117.2)	0.299
Insulin (µU/mL)†	18.75 (14.1 - 26.2)	17.3 (13.9 - 29.5)	18 (13.4 - 23.0)	0.488
HOMA-IR†	5.1 (3.9 - 7.2)	3.7 (2.9 - 6.6)	3.8 (3.0 - 5.4)	0.231
Insulin resistance‡	84.8% 74.2%	75.9%	0.536	
TC (mg/dL)*	193.1 (36.1)	207.8 (36.6)	203.3 (59.6)	0.383
LDL (mg/dL)*	117.2 (31.7)	125.7 (36.0)	129.2 (45.1)	0.378
HDL (mg/dL)†	42.9 (37.2 - 54.5)	42.1 (36.0 - 51.8)	44.8 (38.7 - 52.0)	0.889
TG (mg/dL)†	127.7 (95.5 - 172.5)	151.0 (123.0 - 202.7)	126.0 (84.0 - 191.0)	0.081
Coffee (mL/week)†	0 (0 - 0)	840 (435 - 1680)	3360 (2730 - 3675)	0.000

** Mean values (standard deviations). † Median values (Q_1 - Q_3). ‡ HOMA-IR ≥ 3 was considered insulin resistance.*

Table 2. Patients' liver profiles according to weekly coffee consumption.

Variables	Weekly coffee consumption			p
	First tertile, 38 (34%)	Second tertile, 36 (32%)	Third tertile, 38 (34%)	
Ferritin (ng/mL)*	82.4 (37.0 - 275.2)	140.9 (54.0 - 246.0)	93.3 (44.8 - 162.2)	0.210
ALP (U/L)*	125.5 (71.0 - 199.8)	89.0 (67.0 - 113.0)	84.5 (63.5 - 116.5)	0.555
AST (U/L)*	22.1 (19.0 - 30.5)	27 (17.2 - 39.0)	23.5 (18.5 - 31.5)	0.632
ALT (U/L)*	30.0 (21.6 - 39.5)	28.5 (18.8 - 42.2)	31.0 (22.2 - 49.0)	0.573
GGT (U/L)*	31.6 (25.4 - 61.7)	49.0 (32.0 - 68.5)	39.0 (23.5 - 57.0)	0.189
TB (mg/dL)*	0.50 (0.40 - 0.60)	0.46 (0.37 - 0.61)	0.50 (0.32 - 0.57	0.815
DB (mg/dL)*	0.17 (0.10 - 0.20)	0.13 (0.07 - 0.20)	0.14 (0.04 - 0.22)	0.727

** Median values (Q_1 - Q_3).*

Table 3. Histological diagnosis from severely obese patients and the relationship with coffee consumption.

Liver histology	Weekly coffee consumption			Total, n (%)
	First tertile, n (%)	Second tertile, n (%)	Third tertile, n (%)	
Normal	5 (14.7)	7 (21.9)	9 (24.3)	21 (20.4)
Steatosis	8 (23.5)	5 (15.6)	9 (24.3)	22 (21.4)
NASH	21 (61.8)	20 (62.6)	19 (51.3)	60 (58.3)
Without fibrosis	9 (26.5)	6 (18.8)	6 (16.2)	21 (20.4)
With fibrosis	12 (35.3)	14 (43.8)	13 (35.1)	39 (37.9)

Pearson χ^2 test. p = 0.812. Nine patients with non-specific histopathological abnormalities were excluded from analysis.

DISCUSSION

This study shows that severely obese individuals who reported greater coffee consumption had a less frequent histological diagnosis of steatohepatitis (NASH) with and without fibrosis; however, this difference was not statistically significant.

The protective role of coffee or caffeine in liver diseases is a subject that has garnered interest in the literature. Some studies show that coffee may favorably affect chronic VHC[26] and NAFLD[5] hepatitis evolution. However, few studies have addressed NASH in severely obese individuals (BMI ≥ 35 kg/m^2).

Birerdinc, *et al.*[27] conducted a study of the dietary profiles of NAFLD patients based on data from the National Health and Nutrition Examination Surveys (NHANES) between 2001 and 2008 and suggested that coffee consumption may have a protective effect against NAFLD onset.[13] However, information about coffee and caffeine consumption, demographic data, and clinical and laboratorial parameters were obtained from recall surveys, which may have affected the results. In addition, individuals with high aminotransferase levels were considered as suffering from NAFLD. Finally, the authors observed that Afro-American ethnicity, male gender, obesity and coffee and water consumption were independently associated with NAFLD.

This study diverged from the aforementioned research in several aspects, which could explain the difference in the results. This study considered histological assessments, data collection was performed in person and directly with the patients, and most of the patients were women.

The correlation between the protective effect of coffee and the development of hepatic fibrosis was also assessed in a French study[28] that included 195 obese individuals referred for bariatric surgery and liver biopsy. There was no association between NASH and coffee consumption, and the results suggested a protective effect of coffee on hepatic fibrosis progression. The authors also observed a positive association between AST levels and NASH. However, they questioned the possibility that the common espresso coffee additive sucrose (composed of glucose and fructose) might have affected the results, as the prejudicial effect of fructose on NAFLD has been discussed.

The assessment of aminotransferase levels also did not reveal any significant differences between severely obese subjects when the results were stratified by coffee consumption. However, this finding may not be a relevant datum because severely obese subjects often exhibit normal levels of these enzymes. In addition, aminotransferase levels may be affected by the different diagnostic criteria used for NAFLD: some studies used ultrasonography for diagnosis, and others used liver histology. It is known that these methods have different accuracies in terms of diagnostic assessment.[28-31]

These data differ from those reported by Modi, *et al.,*[32] who observed an association between greater caffeine consumption, lower serum levels of AST, alkaline phosphatase and direct bilirubin, higher serum albumin levels and lower fibrosis severity in chronic liver diseases.

The effect of coffee consumption in IR was not observed in this study. These data differed from those of Catalano, *et al.*[29] and Gutiérrez-Grobe, *et al.,*[30] who observed inverse associations between coffee consumption and obesity, IR and liver steatosis. We should emphasize that NAFLD diagnosis was established by ultrasonography in these studies.

The differences between the results of this and other studies with regard to coffee consumption frequency, IR and hepatic changes may be attributed to the facts that there are several types of coffee from each region and different forms of preparation. In Brazil, e.g., filtered coffee (less concentrated) is more frequently consumed than espresso coffee, which is more concentrated.

Caffeine is the main compound of coffee and is present in other beverages and foods, such as soft drinks, tea and chocolates.[13] Molloy, *et al.* found a negative correlation between hepatic fibrosis severity and coffee consumption and a positive association between the former and IR or diabetes without finding the same association with caffeine. This result suggests that coffee's beneficial properties to the liver are not restricted to the presence of caffeine.[18]

VamDam, *et al.* affirmed that coffee consumption is strongly protective against type 2 diabetes mellitus.[33,34] Improvements in insulin sensitivity were observed in other studies and possibly affected the outcomes related to diabetes. However, it is extremely important to note that there is no uniformity between the HOMA-IR cutoff points used for IR diagnosis.

Therefore, the study shows that severe obese patients with a history of greater coffee consumption exhibited lower frequencies of NASH and fibrosis, although with no statistical significance in this sample.

ABBREVIATIONS

- **BMI:** body mass index.
- **CC:** coffee consumption.
- **CEP:** research ethics committee.
- **IDF:** International Diabetes Federation.
- **IR:** insulin resistance.
- **MS:** metabolic syndrome.
- **NAFLD:** nonalcoholic fatty liver disease.
- **NASH:** nonalcoholic steatohepatitis.

- **NHANES:** National Health and Nutrition Examination Surveys.

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DISCLOSURES

There are no conflicts of interest.

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