Most patients with severe obesity has liver fibrosis even without Metabolic Syndrome

A maioria dos pacientes com obesidade grave apresenta fibrose Hepática mesmo sem Síndrome Metabólica

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ABSTRACT

BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) is a condition commonly associated with metabolic syndrome (MS). This association is frequently found in people with severe obesity, yet some who are diagnosed with NAFLD do not fulfill the criteria for MS. We aimed to compare the clinical and histological characteristics of NAFLD in patients with obesity with and without MS.

METHODOLOGY: Cross-sectional study with patients with severe obesity (BMI ≥35 kg/m²) diagnosed with NAFLD on liver biopsy during bariatric surgery between Sep/2014 and May/2015. Patients with a history of chronic alcohol consumption and other liver diseases were excluded. MS diagnosis was based on the International Diabetes Federation criteria. Statistical analyses were performed using Chi-square and t tests. P<0.05 were considered significant.

RESULTS: The simple included 170 patients with severe obesity with histological diagnosis of NAFLD. The mean BMI (body mass index) was 43.2±5.3 kg/m²; 60% were female and the mean age was 37.1±10.7 years. Dyslipidemia (81.7%) and arterial hypertension (48.2%) were the most frequent NAFLD risk factor associated with obesity in these patients. A total of 75 of them (44.1%) did not meet the criteria for MS. They were younger than those with MS [33.8 (9.9) vs 39.7 (10.8) years; p<0.001], and 68.0% (51) of them had nonalcoholic steatohepatitis (NASH) and fibrosis.

CONCLUSION: The results reinforce the relevance to evaluate NAFLD in people with severe obesity, even those without MS. Despite not presenting MS, these patients with severe obesity already had NASH with fibrosis and can potentially evolve to cirrhosis.

Keywords: 1 non-alcoholic fatty liver disease, 2 morbid obesity, 3 metabolic syndrome, 4 nonalcoholic steatohepatitis, 5 steatosis.

ABSTRACT

ANTECEDENTES: A doença do fígado gordo não alcoólico (NAFLD) é uma condição geralmente associada à síndrome metabólica (EM). Esta associação é frequentemente encontrada em pessoas com obesidade grave, no entanto, alguns que são diagnosticados com NAFLD não preenchem os critérios para a EM. O nosso objectivo era comparar as características clínicas e histológicas da NAFLD em doentes com obesidade com e sem EM.

METODOLOGIA: Estudo transversal com pacientes com obesidade grave (IMC ≥35kg/m²) diagnosticados com NAFLD em biopsia hepática durante cirurgia bariátrica entre Set/2014 e Maio/2015. Foram excluídos os doentes com antecedentes de consumo crónico de álcool e outras doenças hepáticas. O diagnóstico de EM foi baseado nos critérios da Federação Internacional de Diabetes. Foram realizadas análises estatísticas utilizando testes Qui-quadrado e t. P<0.05 foram considerados significativos.

RESULTADOS: O simples incluiu 170 doentes com obesidade grave com diagnóstico histológico de NAFLD. O IMC médio (índice de massa corporal) foi de 43,25,3 kg/m²; 60% eram do sexo feminino e a idade média foi de 37.110,7 anos. A dislipidemia (81,7%) e a hipertensão arterial (48,2%) foram o factor de risco mais frequente de NAFLD associado à obesidade nestes pacientes. Um total de 75 deles (44,1%) não preenchiam os critérios para a EM. Eram mais jovens do que aqueles com EM [33,8 (9,9) vs 39,7 (10,8) anos; p<0,001], e 68,0% (51) deles tinham esteato-hepatite não alcoólica (NASH) e fibrose.

CONCLUSÃO: Os resultados reforçam a relevância de avaliar a NAFLD em
Introdução

Obesidade, uma condição multifatorial caracterizada pela acumulação excessiva de tecido adiposo no corpo, pode ser altamente prejudicial para a saúde. Devido à prevalência cada vez maior em todo o mundo, a obesidade hoje é considerada uma epidemia de saúde (1). No Brasil, a prevalência é estimada em 19.5% para homens e 21.0% para mulheres acima de 18 anos (2).

Obesidade é um fator de risco para diversas doenças, como doenças cardiovasculares, metabólicas e neoplásicas, entre outras. Fatores socioambientais e genéticos podem grande influência na evolução da obesidade. NAFLD é uma condição clínico-patológica caracterizada pela acumulação de gordura, especialmente triglicérides, nos hepatócitos. NAFLD apresenta-se como uma gama de alterações histológicas no fígado, variando de simples steatose para NASH, e pode ser caracterizada por steatose associada ao balão de hepatócitos, inflamação, e variações de graus de fibrose. Pacientes com NASH podem evoluir para cirrose e desenvolver hepatocarcinoma (3,4).

Insulina resistência, obesidade, diabetes mellitus, dislipidemia, e síndrome metabólica (MS) são todos considerados como fatores de risco para o desenvolvimento de NAFLD.

A relação entre NAFLD e Metabolic Syndrome (MS) parece estar bem estabelecida, mas os pesquisadores recentemente têm se interessado em comparar os aspectos clínicos e patológicos de pacientes com NAFLD com e sem MS.

O nosso grupo tem estudo NAFLD em pacientes com obesidade grave submetida a cirurgia bariátrica por muitos anos (5-8), e o objetivo do presente estudo era comparar as características histológicas de NAFLD em esses indivíduos, com e sem MS.

2 Material e Métodos

2.1 Design do Estudo e População

O presente estudo transversal utilizou dados secundários de um projeto anterior que avaliou NAFLD em pessoas com obesidade grave de um centro especializado no tratamento da obesidade.
Written informed consent was obtained from all included patients and the present research protocol (CAAE: 14354313.4.0000.5577) was approved by the Institutional Review Board of the Federal University of Bahia Medical School (Bahia, Brazil).

2.2 INCLUSION CRITERIA

Patients with BMI ≥35 kg/m² who underwent bariatric surgery (BS) with histological diagnosis of NAFLD.

2.3 EXCLUSION CRITERIA

Patients under 18 years of age, those with a known history of liver disease or alcohol intake > 140g / week (men) or > 70g / week (women).

2.4 CLINICAL EVALUATION

Data collected from clinical records and interviews with patients included: age, gender, history of chronic disease, alcohol intake, medication use, exposure to environmental toxins and BMI. Biochemical testing involved a liver panel, including serum levels of ALT, AST, GGT, FA, TP, bilirubin, total proteins and fractions; total cholesterol and fractions; triglycerides; fasting blood glucose; serum insulin; viral markers for hepatitis B and C viruses; ferritin; transferrin saturation. Dysglycemia was defined as any type of abnormal glucose tolerance, including fasting glucose alterations, glucose intolerance or diabetes mellitus. The diagnosis of MS was based on International Diabetes Federation guidelines (9). Any patient with at least one of the following factors was considered to have dyslipidemia: low HDL-cholesterol (<40 mg/dL for men and <50 mg/dL for women); triglycerides ≥ 150 mg/dL or the use of statins or fibrates, regardless of serum lipid levels. Insulin resistance was assessed using the Homeostasis Model Assessment for Insulin Resistance (HOMAR IR). Insulin resistance was considered when index values were ≥ 3 (10).

2.5 LIVER BIOPSY AND HISTOLOGY

During bariatric surgery, liver biopsy was the first procedure performed and samples were submitted to histological examination by the same pathologist with experience in liver disease. Liver alterations were classified according to Brunt et al. (1999) (3). Thus, the histological diagnosis of NASH was based on a finding of macrovacuolar hepatocellular steatosis associated with hepatocyte ballooning and parenchymal inflammation, whereas staging refers to the degree of hepatic fibrosis: F0 (without fibrosis); F1 (with perisinusoidal
fibrosis, mainly in zone 3 of the hepatic acini), F2 (perisinusoidal and portal/periportal fibrosis), F3 (septal fibrosis), or F4 (cirrhosis).

2.6 STATISTICAL ANALYSES

The Statistical Package for the Social Sciences (SPSS Chicago - IL, version 23.0, 2016) was used for data analysis. Quantitative variables were expressed as means and standard deviation, or as medians and interquartile range, while categorical variables were described as absolute and relative frequency. Student's t test, Mann-Whitney and Pearson's chi-square tests were used to compare the groups. After bivariate analysis of the groups with and without perisinusoidal and/or periportal fibrosis, the variables with a p-value <0.20 (BMI, MS, and insulin resistance) were adjusted in a logistic regression model. The components of metabolic syndrome were excluded for logistic regression because of collinearity. P values <0.05 were considered statistically significant.

3 RESULTS

A total of 170 patients with severe obesity and NAFLD were included and most of them were female (60.0%). Age ranged from 18 to 64 years (mean 37.1±10.7) and BMI varied from 35.0 to 68.5 kg/m² (mean 43.2 ± 5.3 kg/m²).

Histological analysis showed that 81.8% (139/170) of the patients had NASH. Of these, 15 (10.8%) did not present fibrosis (F0), 93 (66.9%) were classified as F1, 28 (20.1%) as F2, and 3 (2.2%) as F3. Table 1 shows the characteristics of the patients, as well as the main clinical and histological findings according to the presence or absence of MS.

The prevalence of MS was 55.9%, with dyslipidemia being the most frequent component (81.7%), followed by hypertension (48.2%) and dysglycemia (40.6%). Insulin resistance was observed in 93 (72.7%) obese patients.

Although patients with MS have a higher frequency of NASH with fibrosis on liver biopsy, the majority (68.0%) of those without this syndrome (44.1%) also had some type of liver fibrosis (Table 1).

Considering that fibrosis is a risk for cirrhosis, the patients were analyzed according to the presence or absence of perisinusoidal and/or portal fibrosis. MS remained as an independent risk factor for hepatic fibrosis even after adjusted for BMI and insulin resistance (Table 2).
4 DISCUSSION

This large case series demonstrates that people with severe obesity and with histological NAFLD, who underwent bariatric surgery, did not have metabolic syndrome (MS). These patients had a lower mean age and BMI than those with MS, and they also presented elevated frequency of NASH-related liver fibrosis.

The relationship between NAFLD and obesity has been well-established, and NAFLD tends to be more frequent in individuals with a higher BMI. Several studies have demonstrated direct associations between obesity and the prevalence of NAFLD, as well as a higher risk of NASH with fibrosis and evolution to cirrhosis. However, there is a growing interest in investigating clinical and pathological parameters in severely obese without MS, even though NAFLD has been shown to be more common in individuals with metabolic abnormalities (11 - 14).

NAFLD was evaluated in patients with grade 2 or 3 of obesity with and without the criteria for MS. Data in the literature suggests that although obesity often implies harmful effects on health, there are differences between people with obesity with NAFLD with MS, versus those with NAFLD without MS. In addition, as in patients with obesity with NAFLD and MS, non-obese individuals with NAFLD, defined as “metabolically unhealthy normal weight” (MUNW), are also at risk of health damage.

The prevalence of individuals who are considered with obesity and do not have MS varies in the general population depending on the diagnostic criteria used. A recently published review showed that up to 30% of people with obesity do not have MS (15).

The absence of MS in individual with obesity seems to be associated with a lower level of systemic inflammation and liver dysfunction. Recent studies suggest that heterogeneity in metabolic profiles among patients with obesity may be associated with lifestyle and genetic factors (16). A cross-sectional study comparing the clinical characteristics of individuals with and without MS found that most young people who exercised regularly presented a favorable profile (16). Some studies have also suggested that metabolic abnormalities increase with age in individuals with obesity and emphasize that the metabolic state is dynamic, and that metabolic profiles can change throughout life (13, 14, 16, 17).

The present findings reinforce the data in the literature indicating that people with severe obesity without MS present NALFD with less advanced fibrosis. Herein, patients with this profile were younger and had lower BMI, with a small percentage presenting dysglycemia, yet none had diabetes mellitus. The latter finding suggests that dysfunction in carbohydrate metabolism could influence the development of NASH and fibrosis. It also is possible that this
dysfunction may be associated with other known risk factors for NAFLD progression, including age >45 years, type 2 diabetes mellitus (T2DM), obesity, alanine aminotransferase ratio > 1, increases in serum ferritin levels and hypertension (18, 19).

Leite et al. (20) demonstrated a higher frequency of severe forms of NAFLD in patients with T2DM. This finding is consistent with our results, although we observed that patients with obesity and MS presented higher rates of T2DM, systemic arterial hypertension, older age and higher BMI than obese without MS.

Histological analysis revealed a relationship between the number of components of MS and the severity of NAFLD. Patients without MS presented NASH with fibrosis (degrees 2 and 3) less frequently than patients with MS, which is suggestive of a better prognosis. A cross-sectional multicentric study analyzed 1,058 patients with obesity and NAFLD diagnosed by liver biopsy, who presented or not metabolic abnormalities or MS. This study reported more liver alterations in patients with obesity and MS or other metabolic abnormalities (NASH 57.3% vs 42.4%; significant fibrosis 32.4% vs 15.3%, and advanced fibrosis, 17.1% vs 5.9% (12).

Although the pathogenesis of NAFLD in patients without MS remains unclear, the most relevant factors under investigation nowadays are genetic background, exposure to hepatotoxic substances and alterations in the intestinal microbiota (IM) (21). The IM plays an important role in the homeostasis of metabolic and immunological processes, as well as in energy production and protection against exogenous microorganisms. IM composition varies in accordance with an individual’s diet, nutritional status, stress, and the use of medications, such as antibiotics, which can favor the growth of transient microbiota and dysbiosis. It seems that differences in IM can affect intestinal permeability, thereby favoring the absorption of carbohydrates and bacterial translocation. In addition, increases in lipoprotein lipase (LPL) may lead to de novo lipogenesis and triglyceride production, as well as the activation of toll-like inflammatory receptors in hepatocytes, which are key to the development of NAFLD (21,22).

Study limitations: the study suffers from some weaknesses and limitations: its cross-sectional design does not allow for the assessment of causality; since this study was conducted in individuals with severe obesity, the findings may not apply to other degrees of obesity.

On the other hand, we call attention to the study’s strengths: all patients were submitted to liver biopsy (the gold standard for NAFLD diagnosis), which is the only method that allows certainty in the diagnosis of NASH and evaluates disease activity and staging, therefore providing insight into the risk of evolution to cirrhosis. In addition, all biopsies were evaluated by a single pathologist with recognized expertise in liver pathology. Although not the aim of this study, our results reinforce the relevance of performing liver biopsy during bariatric surgery.
to identify patients with NASH who present fibrosis and/or advanced liver disease (cirrhosis). Many patients with severe obesity did not present clinical and/or biochemical liver alterations, yet many already had NASH with fibrosis, a condition with significant risk to evolve to cirrhosis.

5 CONCLUSIONS

The results herein reinforce the relevance of evaluating NAFLD in individual with severe obesity, even in those without MS. Many patients evaluated, despite not presenting clinical and/or biochemical liver alterations, already had steatohepatitis (NASH) with varying degree of fibrosis, a condition that can potentially evolve to cirrhosis.

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ETHICAL STATEMENT

The authors declare that all experiments on human subjects were conducted in accordance with the Declaration of Helsinki, and that all procedures were carried out with the adequate understanding and written consent of the subjects.

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CONFLICT OF INTERESTS

No potential conflict of interest relevant to this article was reported.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Ana Paula Berbert de Castro: Formal analysis, Investigation, Data curation, Writing - original draft, Visualization. Luiz Antonio R de Freitas: Supervision. Carla Daltro: Methodology, Validation, Formal analysis, Writing - review & editing, Visualization, Project administration, Funding acquisition. Kellyane SD Carvalho: Writing - review & editing, Visualization. Claudia Daltro: Data Curation, Investigation. Raquel Rocha: Resources, Investigation. Helma P Cotrim: Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration.
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Table 1: Clinical and demographic characteristics of the studied patients, in total and according to the presence or absence of Metabolic Syndrome.

| Variables                      | Total (100%) | Metabolic syndrome | P       |
|--------------------------------|--------------|--------------------|---------|
|                                |              | Yes (55.9%) | Not (44.1%) | |
| Women                          | 102 (60.0%)  | 52 (47.4%) | 50 (66.7%)  | 0.115   |
| Age (years) (1)                 | 37.1 (10.7)  | 39.7 (10.8) | 33.8 (9.9)  | <0.001  |
| BMI (kg/m²) (1)                 | 43.2 (5.3)   | 44.4 (5.9)  | 41.6 (4.0)  | <0.001  |
| AST/ALT >1                      | 49 (29.3%)   | 28 (29.8%) | 21 (28.8%)  | 0.886   |
| Arterial Hypertension           | 82 (48.2%)   | 68 (71.6%)  | 14 (18.7%)  | <0.001  |
| Dyslipidemia                    | 138 (81.7%)  | 88 (93.6%)  | 50 (66.7%)  | <0.001  |
| Dysglycemia                     | 69 (40.6%)   | 65 (68.4%)  | 4 (5.3%)    | <0.001  |
| Diabetes mellitus               | 20 (11.8%)   | 20 (21.1%)  | -           | <0.001  |
| Insulin resistance (2)          | 93 (72.7%)   | 55 (84.6%)  | 38 (60.3%)  | 0.002   |
| HOMA-IR (2) (3)                 | 4.4 (2.9 – 6.2) | 5.0 (3.7 – 6.8) | 3.4 (2.1 – 5.2) | <0.001 |

**Histology**

|                      |               |                  |         |
|----------------------|---------------|------------------|---------|
| Steatosis            | 31 (18.2%)    | 10 (10.5%)       | 21 (28.0%) |
| NASH + NASH F1       | 108 (63.5%)   | 63 (66.3%)       | 45 (60.0%) 0.006 |
| NASH F2 + NASH F3    | 31 (18.2%)    | 22 (23.2%)       | 9 (12.0%)  |
| Portal/ perisinoidal fibrosis | 131 (77.1%) | 80 (84.2%) | 51 (68.0%) 0.013 |

BMI: Body Mass Index; AST/ALT: Aspartate aminotransferase/Alanine aminotransferase; HOMA-IR: Homeostatic Model Assessment; NASH: Nonalcoholic steatohepatites; F1: Grade 1 fibrosis; F2: Grade 2 fibrosis; F3: Grade 3 fibrosis.

(1) Mean and standard deviation; (2) Data for 128 patients, 20 diabetic patients were excluded, and 22 patients had no data on serum insulin; (3) Median and interquartile range.

Table 2: Clinical and demographic characteristics of the studied patients according to the presence or absence of perisinoidal and / or portal fibrosis.

| Variables                      | Perisinoidal and / or portal fibrosis | P value | P adjusted |
|--------------------------------|---------------------------------------|---------|------------|
|                                | Sim (75.9%) | Não (24.1%) |         |           |
| Age (years) (1)                 | 37.0 (10.6) | 37.2 (11.4) | 0.942 | -          |
| Women                          | 77 (59.7%)  | 25 (61.0%)  | 0.884 | -          |
| BMI (kg/m²) (1)                 | 43.9 (5.5)  | 40.9 (4.1)  | 0.002 | 0.037      |
| Arterial Hypertension           | 67 (51.9%)  | 15 (36.6%)  | 0.087 | -          |
| Dysglycemia                     | 58 (45.0%)  | 11 (26.8%)  | 0.039 | -          |
| Dyslipidemia                    | 104 (81.3%) | 34 (82.9%)  | 0.809 | -          |
| Metabolic syndrome              | 79 (61.2%)  | 16 (39.0%)  | 0.013 | 0.040      |
| Insulin resistance              | 67 (70.5%)  | 26 (78.8%)  | 0.359 | 0.103      |

BMI: Body Mass Index; HOMA-IR: Homeostatic Model Assessment.

(1) Mean and standard deviation; (2) Diabetic patients were excluded from analysis. Variables included in logistic regression model: BMI, metabolic syndrome, and insulin resistance.