ORIGINAL ARTICLE

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Cardiac abnormalities in patients with nonalcoholic fatty liver disease

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SUMMARY

OBJECTIVE: This study aimed to evaluate the correlation between Nonalcoholic fatty liver disease and cardiac abnormalities.

METHODS: Patients with Nonalcoholic fatty liver disease who attended an outpatient clinic in Southern Brazil were prospectively evaluated. Patients should be older than 18 years and have steatosis.

RESULTS: A total of 174 patients were evaluated. The mean age was 63±12 years, 65% were women, 71% white, 82.2% hypertensive, 52.3% diabetic, 56.3% obese, and 30% dyslipidemic. There was no association between Nonalcoholic fatty liver disease and cardiac abnormalities, even after adjusting for age, sex, and metabolic syndrome.

CONCLUSIONS: The present study did not show a direct correlation between Nonalcoholic fatty liver disease and cardiac abnormalities, regardless of metabolic syndrome.

KEYWORDS: Nonalcoholic fatty liver disease. Cardiovascular disease. Cardiac disease. Cardiac arrhythmias.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is one of the most important causes of liver disease worldwide and, in other Western countries, it will be the main cause of indication for liver transplantation until 2030[1]. Its prevalence is around 20–25% of the world population[2,3]. In South America, it affects 30%[4] of the population, reaching 34.4% in Brazil[5].

Clinical evidence supports the hypothesis that NAFLD is a multisystem disease, involving a variety of extrahepatic organs, including the heart. Cardiovascular disease (CVD) is the main cause of death in these patients, even preceding the causes of death related to liver complications. Furthermore, the association of NAFLD with the presence of metabolic syndrome (MetS) reduces survival[6].

The current challenge is to discover the causal factor that directly relates NAFLD and CVD. Evidence suggests that the association of NAFLD and the occurrence of cardiovascular events is independent of traditional risk factors and MetS[7].

Therefore, the early and effective diagnosis of NAFLD in the population of patients at risk of developing this situation becomes increasingly relevant for prevention and effective therapeutic intervention as a public health measure, aimed at preventing or delaying the development of cardiometabolic complications[7].

The main objective of the present study was to evaluate the relationship between NAFLD and cardiac abnormalities through electrocardiographic changes and to evaluate the cardiac structure, function abnormalities, and valvular heart disease.

METHODS

Patients over 18 years of age at the outpatient clinics of Internal Medicine and Gastroenterology of Hospital Nossa Senhora da Conceição (HNSC), a tertiary hospital in southern Brazil, were prospectively evaluated from August 2018 to July 2019. They must have previously undergone electrocardiography (ECG) and abdominal ultrasound in the last 6 months.

The diagnosis of NAFLD was established according to the recommendations of the guidelines of the American Association for the Study of Liver Diseases (AASLD)[1] and the American Heart Association (AHA)[8]. There must be evidence of hepatic steatosis, either by imaging or histology, and a lack of secondary causes of hepatic fat accumulation, such as significant alcohol intake, long-term use of a steatogenic medication, or monogenic hereditary disorders.

Patients with excessive alcohol consumption (daily intake greater than 30 g/day for men and 20 g/day for women for more than 2 years), patients living with human immunodeficiency virus (HIV), hepatitis B or C virus, other causes of

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chronic liver disease, hepatocellular carcinoma, and other secondary causes of NAFLD were excluded.

All patients were evaluated with anamnesis and physical examination, and clinical information was collected about lifestyle habits (e.g., alcohol consumption, smoking, and physical activity), previous diseases, and their respective treatments, in addition to the measurement of weight, height, and waist circumference.

Total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL), triglycerides (TyG), and glucose were evaluated. Total abdominal ultrasound was used in the diagnosis of NAFLD.

The diagnosis of atrial fibrillation (AF), long QT interval, increased PR interval, and left ventricular hypertrophy (LVH) was based on 12-lead ECG. The ejection fraction (EF) value using the Sympson method and the size of the left atrium (LA) and the left ventricle (LV) were obtained by echocardiography.

Obesity[9], systemic arterial hypertension (SAH)[10], type 2 diabetes mellitus (DM2)[11], and dyslipidemia[12] were defined according to international recommendations. MetS was defined by the National Cholesterol Education Program Adult Treatment Panel III[12,13]. Insulin resistance (IR) was assessed by calculating the lipid accumulation product (LAP), which is based on a combination of the abdominal circumference (cm) and TyG (mg/dl) [LAP in man: (waist circumference – 65) × TG; LAP in female: (waist circumference – 58) × TG][14].

To evaluate liver fibrosis, the NAFLD fibrosis score was calculated at the moment of inclusion in the study[15].

Ethical aspects

The research project was carried out in accordance with resolution 466 of 2012, which regulates the performance of research on human beings, and was approved by the local ethics committee. All patients were informed about the research and signed the Free and Informed Consent Form.

Statistical analysis

Data were presented as mean and standard deviation or frequency and percentage. Associations between categorical variables were tested using Pearson's $\chi 2$ test and between groups using McNemar's test. To compare continuous variables between groups, Student's t-test was used for variables with a normal distribution or the Mann-Whitney test for nonparametric distributions. For intragroup comparisons, according to the respective distributions, the paired t-test or Wilcoxon test was used. For the adjusted analysis of electrocardiographic and echocardiographic changes, logistic regression for categorical variables and analysis of covariance for continuous variables were used. The assumed significance level was 5%.

RESULTS

Initially, 184 patients were identified. After the exclusion criteria were applied, 8 (4.3%) patients with excessive alcohol consumption and 2 (1.1%) other patients with hepatitis C virus were excluded, leaving 174 patients. Of these, 94 (54%) presented with NAFLD and 80 (46%) without NAFLD.

The mean age was 63±12.0 years, with a predominance of women (65%), 71.3% white, 74.7% sedentary, 9.2% active smokers, 51.7% previously smoking, and 56.3% obese, with a mean BMI of 31.5±6.5 and mean waist circumference of 107±13.6 cm, with no statistical difference between the groups with and without NAFLD (Table 1).

MetS was present in 74% of patients, being higher in the NAFLD group when compared to patients without NAFLD [78 (83%) vs. 51 (64%); p=0.005]. The mean LAP index was 47±14.0, being higher in NAFLD patients when compared to the group without NAFLD (49.4±12.2 vs. 44.0±15.2; p=0.009).

In NAFLD patients, 30% did not have significant liver fibrosis and 16% met the criteria for advanced liver fibrosis based on the NAFLD score.

Regarding the alteration in the lipid profile, 30.0% of patients presented with dyslipidemia, 43.1% with altered HDL cholesterol, 42% with altered LDL cholesterol, and 40.8% with hypertriglyceridemia (Table 1).

In the assessment of cardiovascular risk using the Framingham score, most had an intermediate classification (38.5%), with no difference between groups (Table 1).

In the electrocardiographic findings, AF was present in 5.3% of patients with NAFLD and 11.3% without NAFLD (p=0.107). A long QT interval was identified in one patient without NAFLD. Prolongation of the PR interval was identified in two patients, one from each group. LVH was evidenced in 11 (11.7%) patients with NAFLD and 12 (15.0%) without NAFLD, with no statistical difference. When making the analysis adjusted for age, sex, and MetS, there was no change in the results between groups with and without NAFLD (Table 2).

In the echocardiographic findings, diastolic dysfunction was identified in 34 (65.4%) patients with NAFLD and aortic valve sclerosis in 26 (50%). In the evaluation of the combined analysis of the two parameters, there was no difference between the groups with and without NAFLD. NAFLD patients presented a mean ejection fraction of 61.1±11.5%, a mean LV size of 50.1±14.6 mm, and a LA size of 42.2±7.3 mm. Adjusted analyses by logistic regression or by the difference of means for age, sex, and MetS did not demonstrate statistical significance between groups with and without NAFLD (Table 3).

Obesity was equally prevalent in patients with and without NAFLD (32.2% vs. 24.1%, p=0.433). The LAP index

in nonobese with NAFLD reaches 47.5±12.0, a similar level observed in obese patients without NAFLD (46.0±15.2).

DISCUSSION

NAFLD is a growing public health problem due to its prevalence and its association with increased cardiovascular risk and metabolic changes[2,3]. It has been related to CVD[7], and patients with NAFLD have a 2 times higher risk of CVD[3]. However, the pathophysiological mechanisms that establish the relationship between these diseases are not fully understood[16].

Recently, an international consensus panel proposed a change in the nomenclature of NAFLD to metabolic-associated fatty liver disease (MAFLD), suggesting that positive criteria should be used for the diagnosis of MAFLD[17]. These criteria require the presence of hepatic steatosis in addition to one of the following: overweight/obesity, type 2 diabetes, or evidence of metabolic dysregulation. Because the change in nomenclature is new and has not yet been universally

Table 1. Basic characteristics (n=174).

	Total n=174	Without NAFLD n=80	With NAFLD n=94	p
Age (years), mean±SD	63±12.0	63.3±11.2	62.9±12.4	0.859
Sex, n (%)				
Female	113 (65.0)	56 (70.0)	57 (60.6)	0.258
Male	61 (35.1)	24 (30.0)	37 (39.4)	
White race, n (%)	124 (71.3)	52 (65.0)	72 (76.6)	0.129
Sedentarism, n (%)	130 (74.7)	57 (71.3)	73 (77.7)	0.540
Tabagism, n (%)				
Active	16 (9.2)	6 (7.5)	10 (10.6)	0.400
Not active	90 (51.7)	31 (38.8)	43 (45.7)	
Not tabagista	84 (48.3)	43 (53.8)	41 (13.6)	
Obesity, n (%)	98 (56.3)	42 (52.5)	56 (59.6)	0.433
BMI, mean±SD	31.5±6.5	31.2±7.2	31.6±5.9	0.701
WC, mean±SD	107±13.6	105±14.0	109±13.1	0.053
SAH, n (%)	143 (82.2)	66 (82.5)	77 (82.0)	> 0.99
DM2, n (%)	91 (52.3)	43 (53.8)	48 (51.1)	0.840
MetS, n (%)	129 (74.0)	51 (64.0)	78 (83.0)	0.005
LAP, mean±SD	47 ± 14.0	44 ± 15.2	49.4 ± 12.2	0.009
TC (mg/dL), mean±SD TC ≥200 mg/dL, n (%)	176±45.4 52 (30.0)	176±42.5 21 (26.3)	177±47.9 31 (33.0)	0.864 0.424
Cholesterol HDL (mg/dL), mean±SD *HDL^M<40/HDL^F<50 mg/dL, n (%)	49±13.7 75 (43.1)	51±15.2 29 (36.3)	47 ± 12.1 46 (48.9)	0.064 0.126
Cholesterol LDL (mg/dL), mean±SD LDL >100 mg/dL, n (%)	98±39.3 73 (42.0)	98±35.2 31 (38.8)	98±42.6 42 (44.7)	0.926 0.525
Tyg (mg/dL), median (95%CI) Tyg >150 mg/dL, n (%)	140 (151–186) 71 (40.8)	124 (91–166) 27 (33.8)	148 (109–234) 44 (46.8)	0.111
IC, n (%)	39 (22.4)	20 (25.0)	19 (20.2)	0.471
Heart failure, n (%)	44 (25.3)	22 (27.5)	22 (23.4)	0.657
Framingham, mean±SD Low risk (<7.4%), n (%) Intermediate (7.5 and 19.9%) High risk (≥20%), n (%)	13.55±1.2 62 (35.6) 67 (38.5) 45 (25.9)	13.5±10.7 30 (37.5) 32 (40.0) 18 (22.5)	14.3±11.4 32 (34.0) 35 (37.2) 27 (28.7)	0.646 0.645

NAFLD: nonalcoholic fatty liver disease; BMI: body mass index; WC: waist circumference; SAH: systemic arterial hypertension; DM: diabetes mellitus; LAP: lipid accumulation product; MetS: metabolic syndrome; Tyg: triglycerides; IC: ischemic cardiomyopathy. *HDL^M: High-density lipoprotein cholesterol in men; HDL^F: High-density lipoprotein cholesterol in women.

adopted[17-20], we decided to continue to use the term NAFLD for the present study.

In the present study, as in two other large cohort studies with long-term follow-up[21,22], there was no association between NAFLD and CVD. Lazo et al. evaluated prospectively 11,371 adults participating in the Third National Health and Nutrition Examination Survey (NHANES III), assessing liver steatosis and evaluating mortality from all causes. They concluded that NAFLD was not associated with an increased risk of death from all causes, CVD, cancer, or liver disease[21]. In the same way, Stepanova et al. evaluated patients from the same cohort, suggesting that NAFLD did not increase cardiovascular mortality over a 14-year period[22].

However, it is necessary to emphasize that CVD is claimed to be the major determinant of the prognosis of NAFLD patients[7]. It is estimated that 5–10% of NAFLD patients die from CVD. Abnormalities in cardiac structure and function, such as LV dysfunction and hypertrophy[23], LA enlargement[24], and heart failure[25], in addition to valvular heart disease such as aortic valve sclerosis[26] and arrhythmias, mainly AF[27], have been reported.

The patients evaluated in the present study presented a high number of classic cardiovascular risk factors, with 82.2% having SAH, 52.3% DM2, 56.3% obesity, 30% dyslipidemia, 74.7% sedentarism, and 60.9% active smokers or ex-smokers. According to the Brazilian Public Health System, the prevalence of SAH is 24.7%, DM2 is 7.7%, and obesity is 19.8% in the general population[28]. This difference can be explained by the fact that these are patients being attended at a tertiary hospital, proving to be a very comorbid population.

Among the 94 patients with NAFLD, obesity was present in 59.6%, DM2 in 51.1%, dyslipidemia in 33%, and SAH in 82%, with no statistical difference compared to patients without NAFLD. This can be considered quite high when compared to the findings of the meta-analysis of Younossi et al.[4], which included 86 studies evaluating patients with NAFLD. The authors observed the presence of obesity in 51%, DM2 in 22.5%, SAH in 39%, and MetS in 42.5% of cases. This finding further reinforces the morbid characteristics of the study population.

In the present study, most NAFLD patients (74%) met the diagnostic criteria for MetS, a prevalence considerably higher when compared to the literature[7].

Insulin resistance (IR) is present in both NAFLD and MetS and is the linking factor of disease to CVD through atherogenic dyslipidemia[7]. When assessing IR in the study population, the mean LAP index was higher in patients with NAFLD when compared to the group without NAFLD (p=0.009).

Table 2. Electrocardiographic findings (n=174).

	Without NAFLD n=80	With NAFLD n=94	Nonadjusted analysis		Adjusted analysis[a]	
			OR (95%CI)	p	OR (95%CI)	p
AF, n (%)	9 (11.3)	5 (5.3)	0.44 (0.14–1.38)	0.172	0.38 (0.11–1.24)	0.107
QT, n (%)	1 (1.3)	0 (0.0)	–	0.460	–	–
PR, n (%)	1 (1.3)	1 (1.1)	–	0.909	–	–
LVH, n (%)	12 (15.0)	11 (11.7)	0.75 (0.31–1.80)	0.654	0.70 (0.28–1.75)	0.451

NAFLD: nonalcoholic fatty liver disease; AF: atrial fibrillation; LVH: left ventricular hypertrophy. [a]Adjusted analysis for age, sex, and MetS.

Table 3. Echocardiographic findings (n=109).

	Without NAFLD n=57	With NAFLD n=52	Nonadjusted analysis		Adjusted analysis[a]	
			OR (95%CI)	p	OR (95%CI)	p
Diastolic dysfunction, n (%)	32 (56.2)	34 (65,4)	1.48 (0.68–3.20)	0.336	1.59 (0.70–3.64)	0.270
AoV sclerosis, n (%)	27 (47.4)	26 (50.0)	1.11 (0.52–2.35)	0.849	1.09 (0.50–2.37)	0.833
Combined analysis[b]	44 (77.2)	39 (75.0)	0.89 (0.37–2.14)	0.825	0.85 (0.34–2.14)	0.732
			Difference of means (95%CI)	p	Difference of means (95%CI)	p
EF, mean±SD	57.4±15.5	61.1±11.5	3.7 (-1.4–8.9)	0.154	3.4 (-1.9–8.6)	0.204
LV size, mean±SD	52.9±11.7	50.1±14.6	-2.8 (-7.9–2.2)	0.267	-2.4 (-7.5–2.7)	0.351
LA size, mean±SD	41.9±8.3	42.2±7.3	0.35 (-2.6–3.3)	0.815	0.1 (-02.9–3.2)	0.934

NAFLD: nonalcoholic fatty liver disease; AoV: aortic valve; EF: ejection fraction; LV: left ventricle; LA: left atrium. [a]Adjusted analysis by age, sex, and MetS. [b]Adjusted combined of diastolic dysfunction and AoV sclerosis.

NAFLD was stratified according to the presence of obesity. Nonobese NAFLD patients presented more criteria for MetS when compared to nonobese patients without NAFLD, and similar to obese NAFLD patients in general, suggesting that NAFLD is an obesity-independent IR marker.

The LAP index in nonobese patients with NAFLD reaches similar values to those observed in obese patients without NAFLD, denoting that NAFLD in nonobese patients can be a sensitive and early marker of metabolic dysfunction, as already described in the literature[29] and an independent factor for obesity.

Even though this is a population of patients with many comorbidities, it is possible to identify NAFLD as an important metabolic factor independent of obesity, demonstrating that it may be important to identify and monitor nonobese NAFLD patients to manage their metabolic profile in advance, thus avoiding future cardiovascular complications[29].

As possible limitations, we could highlight that the number of patients evaluated was smaller than expected, and this fact may have reduced the power of the study. Also, the duration of the disease may have been too short to observe a significant association between NAFLD and structural cardiac alterations.

We should emphasize that this is still an area of debate, and if NAFLD is really an independent factor for CVD or if the CVD is in fact a consequence of the NAFLD or the metabolic syndrome should be better investigated, as suggested by other authors[30,31].

CONCLUSIONS

This study did not show a direct correlation between NAFLD and cardiac abnormalities, regardless of MetS.

AUTHORS' CONTRIBUTIONS

AHM: Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **DW:** Conceptualization, Formal Analysis, Project administration, Writing – original draft, Writing – review & editing. **LEG:** Data curation, Writing – original draft, Writing – review & editing. **VJDAR:** Data curation, Writing – original draft, Writing – review & editing. **YCM:** Data curation, Writing – original draft, Writing – review & editing. **AAM:** Conceptualization, Project administration, Writing – original draft, Writing – review & editing. **CVT:** Conceptualization, Formal Analysis, Project administration, Writing – original draft, Writing – review & editing.

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