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Interaction of Clinicals Values in Metabolic Syndrome and Nonalcoholic Fatty Liver Disease in Adults

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ABSTRACT

Background: High-risk cases for NAFLD are currently underreported or not identified in a timely manner. It is important to elucidate the clinical behavior of the interaction of clinical values in metabolic syndrome (MetS) and non-alcoholic fatty liver disease (NAFLD), considering the complications that may occur in the group of patients with this comorbidity.
Methods: A total of 1,604 adults diagnosed with metabolic syndrome (MetS) and non-alcoholic fatty liver disease (NAFLD) were randomly selected for a cross-sectional study. Metabolic status and non-alcoholic fatty liver disease were measured using the MetS Metabolic Syndrome Diagnostic Criteria (NCEP/ATP-III), laboratory tests, and diagnostic imaging, respectively.
Results: In the study no significant differences were found between the two groups in age ($p=0.379$) and sex ($p=0.146$), although a higher prevalence was found in women after menopause. BMI (Body mass index) was significantly higher in the NAFLD group than in the comparison group ($p=0.827$). According to the NCEP/ATPIII criteria (0.941), there was a significant association between MetS and NAFLD. Mean MetS components were higher in the NAFLD group than in the comparison group. MetS values and the presence of NAFLD are compared at each clinical value. It is shown that the evaluated clinical values of MetS presented a significant association with NAFLD ($p=0.841$). The clinical values corresponding to blood pressure ($p=0.721$/ $p=0.675$), triglycerides ($p=0.740$), fasting blood glucose ($p=0.697$) and lipoproteins ($p=0.713$) presented a significant association.
Conclusion: Considering the clinical values analyzed, a significant association was observed between clinical values of metabolic syndrome (MetS) and non-alcoholic fatty liver disease (NAFLD).
Key words: metabolic syndrome, non-alcoholic fatty liver disease, blood pressure, triglycerides, cholesterol, HDL

INTRODUCTION

Metabolic syndrome includes metabolic abnormalities that would lead to an increased risk of cardiovascular disease (CVD) and diabetes mellitus (DM). The main features of the metabolic syndrome include obesity, hypertriglyceridemia,

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high-density lipoprotein (HDL), hyperglycemia, and hypertension. Fatty liver is common. However, in non-alcoholic fatty liver disease (NAFLD), triglyceride accumulation and inflammation coexist. The increasing prevalence of overweight/obesity and the metabolic syndrome make it possible for NAFLD to become one of the most common causes of end-stage liver disease and hepatocellular carcinoma. Currently, non-alcoholic fatty liver disease (NAFLD) is considered the most common liver problem, affecting between 15% and 40% of the world's general population. A more serious form of the disease is known as non-alcoholic steatohepatitis (NASH). NASH can cause liver failure and can also cause liver cancer (1,2). NAFLD ranges from simple steatosis to steatohepatitis, advanced fibrosis, and cirrhosis. It resembles alcohol-induced liver disease, but also occurs in patients who do not abuse alcohol. Non-alcoholic steatohepatitis characterized by hepatic steatosis, liver cell injury, liver inflammation, fibrosis, and necrosis are believed to be an intermediate stage of NAFLD. The prevalence of NAFLD in Europeans is 26%, in Asians between 11.8% and 30%, while in North Americans the prevalence is 39%. In India, there is evidence of a prevalence of 32% in men and 29.1% in women, and a prevalence of 54.5% in diabetics (3). In Peru and Latin America there are no reports for MetS and NAFLD. Due to these conditions, in our study it is important to elucidate the clinical behavior of the association between metabolic syndrome (MetS) and non-alcoholic fatty liver disease (NAFLD) in adults, considering the complications that may occur in the group of patients with this comorbidity.

METHODS

Participants

Patients were randomly selected from a population diagnosed with metabolic syndrome (MetS) and non-alcoholic fatty liver disease (NAFLD). The cross-sectional study was conducted at the Military Hospital of Lima, Peru and was conducted for a period of five years in accordance with the principles of the Declaration of Helsinki for medical research according to the STROBE guidelines. The study protocol was approved by the Institutional Review Board of the institution to which the researchers are affiliated. All patients provided written informed consent.

The selected patients included participants of both sexes, grouped by age, who attended their medical controls, within the study period. The selected patients underwent clinical and laboratory tests for the diagnosis of metabolic syndrome (MetS) and on the other hand ultrasound examinations for the diagnosis of non-alcoholic fatty liver disease (NAFLD). To select the group by age and sex the NAFLD group was compared with a non-NAFLD group. Exclusion criteria were alcoholism, pregnancy, autoimmune hepatitis, viral hepatitis, drug-induced liver injury, cirrhosis, and use of drugs that induce hepatic steatosis Diagnosis of MetS and NAFLD as well as the records in each patient were made by a gastroenterologist. Likewise, the data of the patients was collected, such as: sex, age, height, weight, blood pressure, abdominal perimeter, and laboratory data, which were conducted by two trained interviewers. MetS values with and without NAFLD study participants were measured and compared.

Measurements

Metabolic syndrome (MetS) was diagnosed by reference to the MetS Metabolic Syndrome Diagnostic Criteria (NCEP/ATP-III). MetS is defined as the presence of three or more of the components within the diagnostic criteria (*table 1*).

Non-alcoholic fatty liver disease (NAFLD) was diagnosed through hyper-echogenicity images on ultrasound. According to the severity of the disease, the following was considered: grade 1: mild and diffuse increase in the liver parenchyma with normal visualization of the intrahepatic borders and diaphragm, grade 2: moderate and diffuse increase in the liver parenchyma with the diaphragm and intrahepatic vessels slightly altered, grade 3: hepatic parenchyma with poor or no visualization of the intrahepatic borders, diaphragm, and right posterior lobe of the liver. The patients were examined through longitudinal and transverse - oblique examinations. Waist circumference was measured between the lowest rib and the iliac crest at the level of the umbilicus. Systolic and diastolic blood pressure was recorded in the left arm of each patient using a sphygmomanometer. Laboratory tests were performed under international standards in the institution's clinical

Table 1 - MetS metabolic syndrome diagnostic criteria

Measures	MetS criteria NCEP / ATP-III
Waist circumference	>102 and > 88 cm; men and women
Triglycerides	≥ 150 mg/Dl
High density lipoprotein	< 40 and < 50 mg/Dl; men and women
Blood pressure	SBP/DBP ≥ 130/85 mmHg
Fasting glucose	≥ 110 mg/Dl

SBP, systolic blood pressure; DBP, diastolic blood pressure

laboratory. Plasma glucose was measured by the enzymatic colorimetric glucose-peroxidase method with a sensitivity of 5 mg/ dL. Serum cholesterol and triglycerides of all participants were measured after 12 to 14 hours of fasting with the colorimetric method with a sensitivity of 5 mg/ dL.

Statistical analysis

The data was stored and processed through an information base. All qualitative data were expressed as frequency and percentage. The analysis of the relationship between MetS and NAFLD was performed through the Chi-Square test. The mean and standard deviation (SD) were used to analyze the quantitative data, and the differences between two groups were studied using two independent samples t-tests.

RESULTS

The general population consisted of 1604 selected patients, 1168 patients who did not meet the diagnostic criteria for MetS were excluded; of the 336 that did meet MetS criteria 84 had NAFLD and 252 did not have NAFLD, in a 1:3 ratio (*fig. 1*). Within the diagnostic criteria for MetS metabolic syndrome in the patients evaluated, the NCEP/ATP-III criteria are included (*table 1*).

In the NAFLD group, 32 (38,0%) men and 52 (62,0%) women were evaluated, with a mean age of 56,45 ± 10,1 years. The comparison group consisted of 84 (27.3%) men and 168 (72,7%) women with a mean age of 54,31 ± 10,1 years. No significant differences were found between the two groups in age (p=0,379) and gender (p=0,146), although a higher prevalence was found in women after menopause. BMI was significantly higher in the NAFLD group than in the comparison group (p=0,827). According to the NCEP/ATPIII criteria (0,941), there was a significant association between MetS and NAFLD (*table 2*).

Table 2 - Clinical characteristics of NAFLD (n=84) and non-NAFLD (n=252) participants

Variable	NAFLD N (%)	Non NAFLD N (%)	p-value
Gender*			
Woman	52 (62%)	168 (72.7%)	0.146
Male	32 (38%)	84 (27.3%)	
Age (years)**	56.45 ± 10.1	54.31 ± 10.1	0.379
BMI* (K/M2)	29.79 (4.8%)	25.16 (4.6%)	0.827
NCEP/ATP-III Criteria	32 (38.1%)	84 (33.3%)	0.841

*Chi square test, **mean (standar deviation)

Mean MetS components were higher in the NAFLD group than in the comparison group. MetS values and the presence of NAFLD are compared at each clinical value. It is shown that the evaluated clinical values of MetS presented a significant association with NAFLD (p=0,841). The clinical values corresponding to blood pressure (p=0,721/ p=0,675), triglycerides (p=0,740), fasting glucose (p=0,697) and high-density lipoproteins

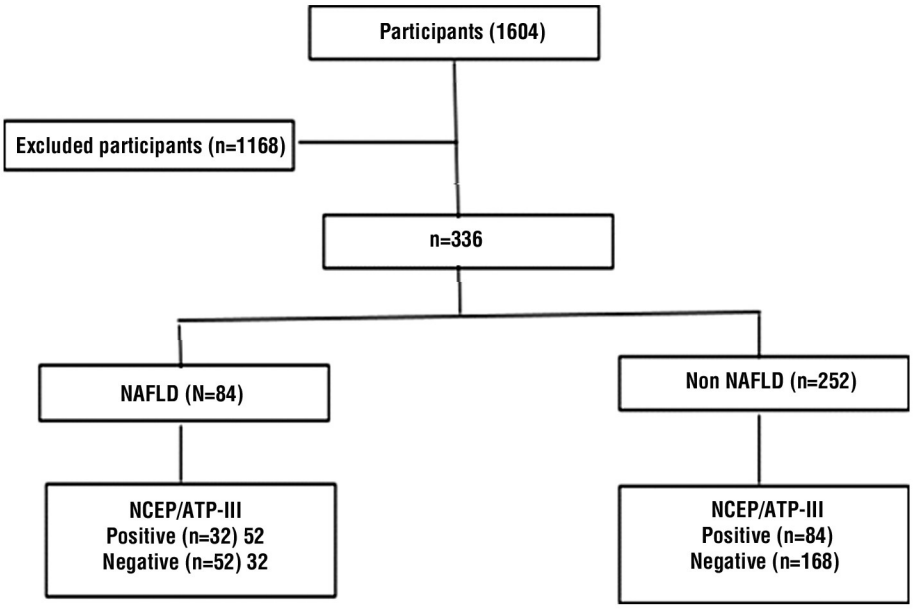

Figure 1 - Participant selection diagram

Table 3 - Metabolic syndrome (MetS) and nonalcoholic fatty liver disease (NAFLD)

MetS	Groups	Mean ± standard deviation	p-value*
Waist circumference	NAFLD	92.13 ± 14.11	0.409
	Not NAFLD	86.22 ± 13.44	0.187
Systolic blood pressure	NAFLD	120.68 ± 19.36	0.721*
	Not NAFLD	115.45 ± 15.13	0.585
Diastolic blood pressure	NAFLD	76.09 ± 11.36	0.675*
	Not NAFLD	73.07 ± 11.05	0.273
Triglycerides	NAFLD	135.44 ± 102.68	0.740*
	Not NAFLD	122.09 ± 105.87	0.203
Fasting glucose (mg/dL)	NAFLD	97.99 ± 25.12	0.697*
	Not NAFLD	92.56 ± 23.75	0.241
HDL-cholesterol (mg/dL)	NAFLD	46.1± 10.3	0.713*
	Not NAFLD	44.9 ± 10.1	0.345

*Significant association

or HDL cholesterol (p=0,713) presented a significant association (*table 3*).

DISCUSSION

We evidenced in the sample analyzed within a period of five years according to the diagnostic criteria of metabolic syndrome (MetS) as an associated factor to develop NAFLD including this syndrome the criteria of: hyperglycemia, blood pressure, dyslipidemia, abdominal perimeter. Our study allows us to elucidate the relationship between Mets and NAFLD values in the patients evaluated. Clinical findings in NAFLD show high serum triglycerides with the same occurring in high-density lipoproteins (HDL-C).

The prevalence of NAFLD worldwide is 25,24%. In South America and the Middle East, prevalence rates are as high as 30,0% (2). In our study, considering gender, the prevalence among patients diagnosed with NAFLD was higher in women with 62,0% compared to men with 38,0%, especially identified in post-menopausal women (56,45 ± 10,1), which is related to that reported by other authors (4,5). In reference to age, the correlation of the age of the patients evaluated with NAFLD and not NAFLD was (p=0,379) without finding a significant difference. The values of the body mass index (BMI) in the evaluated patients of the NAFLD group was 29,79 kg/m^2 (p=0,827), as evidenced in *table 2*. In this regard, some studies suggest that values greater than a BMI >30 kg would be associated with an increased risk of serious liver disease events (6).

Non-alcoholic fatty liver disease is a multisystem disease, and is involved in pathologies such as cardiovascular disease, type 2 diabetes mellitus, liver cirrhosis, hepatocellular carcinoma, chronic kidney disease, and increased risk of thromboembolic events and heart disease (7). We observe in our findings that blood pressure is higher in the NAFLD group (120,68 ± 19,36, p=0.721/76,09 ± 11,36, p=0.675). Although some investigations report a high prevalence of NAFLD in hypertensive patients (8), the pathogenic mechanisms of this association are still unclear. In experimental studies in mice, it has been observed that the absenteeism of the intestinal flora in NAFLD is derived from the altered expression of some relevant hepatic genes such as the constitutive androstane receptors, which leads to the accumulation of high amounts of its ligands such as bilirubin, fatty acids bile ducts and steroid hormones, which would lead to altered hepatic metabolism, which may favor the development of NAFLD, with the consequent changes in the permeability of the intestine and alterations in the genes involved in lipogenesis. The metabolic signaling pathways of choline and bile acids would be involved together with the production of ethanol in the intestine and its interactions with innate immunity. Intestinal dysbiosis would have an important effect on hypertension, through the differentiation and maturation of immune cells produced by short-chain fatty acids, inflammation, and vasodilation (9,10).

Fasting glucose values in NAFLD presented values with significant association (p=0,697). In a study carried out on patients with DM2, it is evident that insulin resistance in patients with increased liver fat is due to a decrease in insulin clearance evaluated through glucose infusion (3-3H) and through the technique of euglycemic insulin clamping, confirming that DM2 had higher liver fat (54,0%) and lower insulin clearance (24,0%) than non-diabetic subjects (11).

In reference to the triglyceride values in the analyzed sample, a significant association was found with high values in NAFLD (p=0,740). Within the context of overnutrition and obesity, hepatic fatty acid metabolism is altered, leading to the accumulation of triglycerides within hepatocytes with the consequent development of non-alcoholic fatty liver disease (12).

Non-alcoholic fatty liver disease, diabetes mellitus 2 and obesity are epidemiologically correlated. From a pathogenic point of view, obesity contributes to the initial fat accumulation in the hepatocyte, but also to the progression of nonalcoholic steatohepatitis, related cirrhosis, and hepatocellular carcinoma (13). It is possible that NAFLD genetically promotes early-onset type 1 diabetes. tardiness and obesity, as well as leading to lower circulating cholesterol. In NAFLD associated with obesity, the balance of adipokines is lost, which triggers a compensatory mechanism that

seeks to preserve insulin sensitivity and limit liver progression to non-alcoholic steatohepatitis (NASH) (14). However, their causal relationships are not clearly defined, which requires more detailed investigations by subtypes of these pathologies. Clinically, obesity increases morbidity and mortality when combined with NAFLD. Specific cardiovascular and hepatic mortality leads us to consider the need for diet and exercise together with pharmacological treatment in affected patients (15). Epidemiologic investigations recommend screening for advanced liver disease among adults with type 2 diabetes mellitus or the metabolic syndrome. Current studies are providing evidence of clinical efficacy in finding NAFLD cases based on risk factors (16).

Our study evidences a significant association between the values of MetS and NAFLD, as presented in *table 3*. The results obtained lead us to agree with what was stated by other author (17), when mentioning that the absence of evaluations of people high- risk and cases are currently under-identified and are found by chance during blood tests or imaging studies for other purposes. In many care settings, this presents a late diagnosis in the natural history of the disease, with limited scope for effective intervention. It is important to include an approach that identifies those most at risk.

CONCLUSION

In our study, a significant association was observed between clinical values of metabolic syndrome (MetS) and non-alcoholic fatty liver disease (NAFLD) for the population evaluated. The clinical values corresponding to blood pressure, triglycerides, fasting blood glucose and lipoproteins. More research is needed to elucidate the pathogenic mechanisms of this association.

Conflicts of interest

There are no conflicts of interest.

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Institutional Review Board Statement

Written informed consent was obtained from all subjects involved in the study to publish this paper.

Author's Contributions

Conceptualization, V.D. and V.CD.; methodology, V.D.; V.CD.; G.R vali-dation, V.D.; V.CD.; G.R., R.J, C.M, V.R, V.DA, J.A.; formal analysis, V.D.; VC.; G.R., R.J, C.M, V.R,V. DA; J.A; investigation, V.D.; V.C.; G.R., R.J, C.M, V.R.; writing—original draft preparation, V.D.; V.C.; G.R., R.J, C.M, V.R, V.D, J.A.; writing—review and editing, V.D.; V.C.; G.R., R.J, C.M, V.R, V.D, J.A. VR acts as the guarantor for the paper. All authors have read and agreed to the published version of the manuscript.

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