Prevalences of Hypertension, Type 2 Diabetes Mellitus, and Cardiovascular Disease in a Cohort of Puerto Ricans with Non-alcoholic Fatty Liver Disease*

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Background & Objectives: Patients with non-alcoholic fatty liver disease (NAFLD) have high prevalences of hypertension (HTN), type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD), and vice versa. The mechanism of this development is unknown but appears to be related to an underlying metabolic derangement that affects multiple organs. This study aimed to determine the prevalences of these conditions in patients with diagnosed NAFLD.

Methods: Our cohort study aimed to determine the prevalences of HTN, T2DM, and CVD in NAFLD patients registered in the liver database of the University of Puerto Rico School of Medicine; this information is recorded in their medical records. Patients whose liver disease had a different etiology were excluded. The study was approved by the UPR Medical Sciences Campus Institutional Review Board.

Results: Our final sample consisted of 141 NAFLD patients; 64.5% (n = 91) of them were females. The average age was 69 (±10.2 years). The prevalences of HTN, T2DM, and CVD were 53.9%, 57.5%, and 7.8%, respectively. In patients with NAFLD, there was a significant association between T2DM and being 65 years old or older (P < 0.001).

Conclusion: Our data indicate that HTN and T2DM are highly prevalent in NAFLD patients in PR; however, CVD prevalence was lower than expected. Additional, studies are required to further define the associations. We recommend metabolic condition screening for all NAFLD patients.

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Key words: NAFLD, Prevalence, Screening

Non-alcoholic fatty liver disease (NAFLD) is a liver disorder characterized by the fatty infiltration of hepatocytes (equaling 5% or more of total liver weight) when no other causes of secondary fat accumulation, such as alcohol use, medications, infection, or others, are present (1). Non-alcoholic fatty liver disease can be further categorized into NAFL and nonalcoholic steatohepatitis (NASH); the difference being that in NAFL there is a 5% or greater accumulation of fat without any sign of inflammation. In contrast, in NASH there is steatosis with inflammation and hepatocyte injury with or without any fibrosis (2, 3). Around 20% of the patients with NAFLD develop NASH, which is known to be a leading cause of progression to cirrhosis and hepatocellular carcinoma (HCC) (4). Currently, NAFLD currently affects 25% to 30% of the world's population, with the variations in its prevalence depending on the country and how the disease is diagnosed there (3). Whatever the circumstances, NAFLD prevalence is projected to keep increasing in the following years, making

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**After this article was submitted, the nomenclature for non alcoholic fatty liver disease (NAFLD) and non alcoholic steatohepatitis (NASH) was changed to metabolic dysfunction associated liver disease (MAFLD) and metabolic dysfunction associated steatohepatitis (MASH), to better characterize the pathophysiology and implications of the disease.*

NAFLD/NASH the leading cause of progression to cirrhosis and HCC (5).

Non-alcoholic fatty liver disease has been described as the hepatic manifestation of the metabolic syndrome (MetS) (6). The most accepted definition of the MetS was established by the National Cholesterol Education Program Adult Treatment Panel III guidelines, which state that a patient with 3 of the following 5 traits has the MetS: (1) abdominal obesity (waist circumference ≥102 cm [40 in] in men and ≥88 cm [35 in] in women), (2) elevated triglycerides (≥150 mg/dL), (3) low high-density lipoprotein (HDL) cholesterol (<40 mg/dL (1 mmol/L) in males and <50 mg/dL (1.3 mmol/L) in females), (4) elevated blood pressure (≥130/85 mmHg), and (5) high fasting plasma glucose (≥100 mg/dL) (7). Given this definition of the MetS, it is not a coincidence that patients with NAFLD are at risk of developing or having cardiovascular diseases (CVD) or such metabolic disorders as hypertension (HTN), type 2 diabetes mellitus (T2DM), coronary artery disease (CAD), and peripheral artery disease (PAD), among others.

There is plenty of evidence that supports the strong association between NAFLD and T2DM, which association is sometimes described as a bi-directional relationship, in which NAFLD can precede and promote T2DM. A meta-analysis found that patients with imaging-diagnosed NAFLD were at increased risk of having incident T2DM, which risk appeared to increase further with a greater severity of NAFLD (8). Of all the risk factors, T2DM seems to be the most important in terms of the development of NAFLD and as a clinical predictor of adverse clinical outcomes such as advanced hepatic fibrosis and mortality (9). It has also been shown that the presence and severity of NAFLD are highly associated with HTN (10, 11). Recent cohort studies have shown that HTN and NAFLD can have a bi-directional relationship as well, in that the presence of HTN has predicted the development of NAFLD, and NAFLD has been associated with an increased risk of incident HTN (12, 13).

The American College of Cardiology and American Heart Association (ACC/AHA) define CVD as a number of conditions that affect the heart and/or blood vessels, including atherosclerotic cardiovascular disease (ASCVD)-related events, diseases, and syndromes (myocardial infarction, stable or unstable angina, stroke, transient ischemic attack, or PAD), as well as heart failure, arrhythmias and valvular diseases. As described above, multiple components of the MetS are risk factors to develop some of the conditions described by ACC/AHA, specially ASCVD. In view of the relationship between NAFLD and the MetS it is not surprising that these patients are at risk of CVD as well. A meta-analysis of 16 cohort studies found that NAFLD is predictive of CVD and that the risk of CVD events increased with NAFLD severity (14). Also, it has been shown that patients with NAFLD have a higher risk of all-cause mortality and that mortality by CVD is higher than hepatic-related death (2, 15). However, 1 meta-analysis pointed out that NAFLD was not associated with overall mortality or CVD mortality, emphasizing the importance of continuing to investigate this relationship (16). Finally, according to a meta-analysis performed to determine the global prevalence of NAFLD, 69.16% (95% CI: 49.91-83.46%) of the patients included in the studies analyzed who had this condition had hyperlipidemia (HLD), 51.34% (95% CI: 41.38-61.20) were obese, 42.5% (95% CI: 30.06-56.05) had the MetS, and 39.34% (95% CI: 33.15-45.88) had HTN, which are all risk factors for CVD (13).

Although multiple global studies, have been conducted to determine the prevalence of HTN, T2DM, and CVD in patients with NAFLD, but there are no data on these prevalences for Puerto Rico (PR). According to a study conducted by Pérez and colleagues, the prevalence of the MetS in the Puerto Rican population was 43.3%, pointing to the importance of NAFLD surveillance on the island (17). Hence, this study aimed to determine the prevalences of these comorbidities in Puerto Ricans with NAFLD attending the University of PR liver clinic.

Materials and methods

This was a cross-sectional study that consisted of a review of medical records of patients in the Liver Database (IRB # 7180102), a database created by the Gastroenterology Research Unit of the UPR School of Medicine that collected the demographic and medical data of all the patients seen at the special liver and transplant clinics from 2003 to 2018. Since the liver clinic receives patients from all over PR who have with commercial and/or government insurance, the population studied is believed to represent that of the entire island.

All the patients in the liver database with an established diagnosis of NAFLD, NASH, fatty liver, and/or cirrhosis caused by NAFLD were included in our study. Patients with other causes of liver disease were excluded. Patients under 18 years old and with more than half of their data/information missing were also excluded. The variables included in the study were each patient's demographic information (age, sex), weight, height, body mass index (BMI), smoking status, medical insurance, a specific diagnosis stage of NAFLD (NASH, cirrhosis, HCC), date of diagnosis of NAFLD, mortality (alive or deceased), and diagnosis (when present) of HTN, T2DM, and/or CVD. For our study, patients were said to have CVD if they had any of the following diagnoses or risk factors: hypercholesterolemia, dyslipidemia, ischemic heart disease (IHD), or PAD. The diagnosis of T2DM, HTN or CVD had to be listed in a patient's medical record.

Table 1. Demography and clinical profile of patients with NAFLD diagnosis in our study

Demography and clinical profile	Total (n=141)	Percentage % (or mean)
Sex		
Female	91	64.5
Male	50	35.5
Age	133*	69 years ± 10
BMI	110*	31.6 ± 6
Obesity (BMI ≥ 30)	110*	62
Hypertension	76	53.9
Type 2 diabetes mellitus	81	57.5
CVD	11	7.8
Ischemic heart disease	8	5.7
Hypercholesterolemia	1	0.71
Dyslipidemia	8	5.7
PAD	5	3.6
Cirrhosis caused by NAFLD	2	1.42
HCC	3	2.13

BMI, body mass index; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; PAD, peripheral artery disease
Lean: BMI ≤ 25; overweight: 25 < BMI < 29.9; and obese: BMI ≥ 30.
*Of our final sample of participants, not all had their ages and BMIs reported in their medical records.

The prevalences of the chronic conditions of interest in our patients with NAFLD were compared with those prevalences reported by other studies. The prevalences of these comorbidities were also compared with those of the general population of PR.

Descriptive statistics were first used to present a profile of the patients' demographic and clinical data. The unadjusted relationship of these variables with chronic conditions of interest was assessed through the chi-square and Fisher's exact tests for categorical variables. Significance was defined as having a P value of 0.05 or less. The Cramér's V strength of association measure was used for crossed tabulations with significant results. A given association was considered weak (0.05 < x < 0.10), moderate (0.10 x < 0.15) or strong (0.15 < 15 x < 0.25). Statistical analysis was performed using Stata 14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX; StataCorp LP). The study was approved by the UPR Medical Sciences Campus Institutional Review Board (# 1250218).

Results

The sample consisted of 141 participants, 91 women and 50 men. Table 1 shows the demographic and clinical characteristics of the participants. The mean age was 69 (± 10.2) years. The mean BMI entered (n = 110) was 31 (± 6); 56.4 % of the patients were obese (BMI ≥ 30) (Table 1). Table 1 also details the clinical profile of our subjects. The prevalences of HTN and T2DM were 53.9% (76 patients) and 57.5% (81 patients), respectively. However, CVD was less prevalent, at only 7.8 % (11 patients), of which 5.7% (8 patients) had a diagnosis of IHD, 0.71% (1 patient), hypercholesterolemia, 5.7% (8 patients) dyslipidemia, and 3.6% (5 patients) PAD (Table 1).

The unadjusted bivariate relationship between key clinical variables and chronic comorbidities is shown in Tables 2, 3, and 4. In patients with NAFLD and T2DM, the chi-square test (with 1 degree of freedom) showed a very strong association between being 65 years of age or older and having T2DM (Table 2). Also, a strong association was seen between being obese (BMI ≥ 30) and having T2DM (Table 2). However, no association was seen between sex and having T2DM. In patients with HTN, no associations were seen between having said diagnosis and age, sex, or obesity (Table 3). Similarly, no association was seen between having CVD and any variables (Table 4).

Table 2. Unadjusted bivariate analysis between T2DM and key clinical variables.

	T2DM		X^2	*P* value*	Cramér's V^
	Yes	No			
Sex					
Female	48 (59.3%)	43 (71.7%)	2.32	.128	-
Male	33 (40.7%)	17 (28.3%)			
Age					
≥65 years	65 (80.3%)	31 (51.7%)	12.96	> .001	.303
<65 years	16 (19.8%)	29 (48.3%)			
Obesity					
BMI ≥ 30	31 (47.7 %)	31 (68.9 %)	4.86	0.028	0.210
BMI < 30	34 (52.3 %)	14 (31.1%)			

BMI, body mass index; T2DM, type 2 diabetes mellitus
Lean: BMI ≤ 25, overweight: 25 < BMI < 29.9, and obese: BMI ≥ 30.
*A *P* value of 0.05 or less was considered an indicator of significant difference.
^The Cramér's V strength of association measure is provided for crossed tabulations with significant results. These are considered either weak (.05 < x < .10), moderate (.10 < x < .15), strong (.15 < x < .25) or very strong (x > 0.25).

Table 3. Unadjusted bivariate analysis between hypertension and key clinical variables.

	Hypertension		X^2	*P* value	Cramér's V
	Yes	No			
Sex					
Female	50 (65.8%)	41 (63.1%)	.113	.737	-
Male	26 (34.2%)	24 (36.9%)			
Age					
≥65 years	55 (72.4%)	41 (63.1%)	1.39	.238	-
<65 years	21 (27.6%)	24 (36.9%)			
Obesity					
BMI ≥ 30	35 (53.85%)	27 (60.0 %)	.409	.522	-
BMI < 30	30 (46.15 %)	18 (40.0%)			

BMI, body mass index
Lean: BMI ≤ 25, overweight: 25 < BMI < 29.9, and obese: BMI ≥ 30.
*A *P* value of 0.05 or less was considered an indicator of significant difference.
^The Cramér's V strength of association measure is provided for crossed tabulations with significant results. These are considered either weak (.05 < x < .10), moderate (.10 < x < .15), strong (.15 < x < .25), or very strong (x > 0.25)

Discussion

As expected, based on other published studies, our Puerto Rican cohort also had a high prevalences of HTN and T2DM. However, unexpectedly, CVD was not frequent. The associations between obesity and having T2DM found in our patients of advancing age were not surprising since obesity is a well-documented risk factor for the disease (18, 19). However, these associations were not seen with HTN or CVD, in our patients.

The prevalence of T2DM in patients with NAFLD in our study was 57.5 % (Table 1), which is similar to what has been found in other studies. A meta-analysis performed to determine the global prevalence of NAFLD showed that the prevalence of NAFLD in patients with T2DM was 55.5% (9). Similarly, a 2017 meta-analysis found a prevalence of NAFLD of 59.7% in patients diagnosed with T2DM (20). Our study confirms that T2DM is strongly associated with NAFLD in our population, mirroring the findings of the previously mentioned studies that demonstrate that T2DM is a significant risk factor for developing NAFLD.

Additionally, the prevalences of HTN and CVD in the patients with NAFLD in our study were 53.9% and 7.8%, respectively (Table 1). A meta-analysis performed in 2016 found that the prevalences of HTN and HLD in patients with NAFLD were 39.34% and 69.16% respectively (2). Another study found (Younossi et al., 2019) that of the patients with NAFLD and T2DM, 60% had HTN, 50% had HLD, 24.3% had CVD, and 9.1% had PAD (9). Although this study did not specify the inclusion criteria for CVD, these results are different from the ones in our study, especially the prevalences of CVD and HLD, which were much lower in our cohort. Possible reasons for this difference might be that manifestations of CVD such as arrhythmia, stroke, heart failure, or valvular diseases were not considered by the treating physician. Also, the failure to test for lipid abnormalities could have led to underdiagnosis. We depended on the presence of a registered diagnosis in the liver database. A detailed record review including laboratory results may have yielded different results. It could also be explained by incomplete information in the medical records, the small sample of the study, or a bias introduced by selecting said sample from a subspecialty clinic.

However, we compared the prevalences of the chronic illnesses of interest in patients with NAFLD with those in the Puerto Rican general population, and found some notable differences. According to the last *Chronic diseases*

Table 4. Unadjusted bivariate analysis between CVD and key clinical variables.

	CVD		X^2	*P* value*	Cramér's V^
	Yes	No			
Sex					
Female	6 (54.55%)	85 (65.4%)	-	.520§	-
Male	5 (40.45%)	45 (34.6%)			
Age					
≥65 years	9 (81.8%)	87 (66.9%)	1.036	.309	-
<65 years	2 (18.2%)	43 (33.1%)			
Obesity					
BMI ≥ 30	8 (88.9%)	54 (53.5 %)	-	.075§	-
BMI < 30	1 (11.1%)	47 (46.5%)			

BMI, body mass index; CVD, cardiovascular diseases
Lean: BMI ≤ 25, overweight: 25 < BMI < 29.9, and obese: BMI ≥ 30.
*A *P* value of 0.05 or less was considered an indicator of significant difference.
^The Cramér's V strength of association measure is provided for crossed tabulations with significant results. These are considered either weak (.05 < x < .10), moderate (.10 < x < .15), strong (.15 < x < .25), or very strong (x > 0.25)
§Because the sample was small, Fischer's exact test performed instead of chi-square test.

report of Puerto Rico, 2016-2017 (compiled by the Division for the Prevention and Control of Chronic Diseases), in 2016, the prevalences of HTN and T2DM, adjusted by age, were 41 % and 15.3%, respectively (21). The prevalences of CVD (defined as any person with angina, coronary disease, and/or heart attack) and hypercholesterolemia, adjusted by age, were 9.0 % and 31.2 %, respectively. These findings suggest differences between the prevalence of comorbidities in a cohort of Puerto Ricans with NAFLD and such a prevalence in the general population, notably that T2DM and HTN are less prevalent in the general population, supporting the hypothesis that NAFLD is a risk factor for both T2DM and HTN. However, according to these data, hypercholesterolemia was higher in the general Puerto Rican population.

There were important limitations in our study. One of them was that we accepted a given patient's diagnosis of NAFLD regardless of the method used to establish it; another was that stage of disease was not stratified for analysis. The advancement of an indivual's liver disease may impact the biochemical manifestations of his or her MetS. Another limitation was the small size of our sample (141), which could have affected the statistical power our study. This study was not exempt from bias, either, as our cohort was part of the patient population of a tertiary academic specialized clinic with patients with a mean age of 60 years, which could have affected the external validity of our study in term of comparing the patients of our study with the general population. Since this study was in the form of a record review, we were limited by the data available; for example, there is no way to discern whether the patients were or were not adequately screened for the comorbidities explored in this study. Finally, we collected information from the records, a source prone to missing or having erroneous data, as well. Despite these limitations, our study supports findings reported in other populations and points to the need for more investigations in this area in our population.

The high prevalences of T2DM and HTN in patients with NAFLD in PR emphasizes the need to increase surveillance for these comorbidities in patients with NAFLD, as these conditions are known for being risk factors for several health complications. Increased surveillance will not only provide the opportunity to detect these comorbidities but will also aid in improving the management of these patients. A recent study collected data on the presence of NAFLD-relevant policies from 102 countries and regions, including PR, and found that NAFLD was receiving far too little attention in national or regional health agendas, with a third of the locations scoring 0 on the preparedness index (4). The investigative group discovered, as well, that no written strategies or action plans aimed at addressing NAFLD existed in any other participating nations or territories (4). In view of this lack of guidance, national and regional associations play a pivotal role in the preparation for and management of NAFLD and the patients who have it. For example, the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD), and the European Association for the Study of Obesity (EASO) all recommend screening for NAFLD (elevated liver enzymes) and/or performing ultrasound on subjects with obesity or the MetS (23). They also advise additional screening for findings of advanced disease (i.e., NASH with fibrosis) in high-risk individuals (aged > 50 years old with T2DM and/or the MetS) (23). Additionally, the American Diabetes Association (ADA) recommends screening for NASH and advanced fibrosis in patients with elevated liver function tests or hepatic steatosis on ultrasound (4). Moreover, the European and American societies guidelines have strongly recommended that all patients with NAFLD should undergo careful cardiovascular surveillance (3, 22). In contrast, because of the uncertainties surrounding diagnostic test, lack of knowledge related to long term-benefits, and cost-effectiveness of screening, the American Association for the Study of Liver Disease (AASLD) does not advise NAFLD screening in high-risk groups attending primary care, diabetes, or obesity clinics (3).

More studies are required to further define the associations between T2DM, HTN, CVD, and NAFLD and to develop more specific guidelines and policies to address this public health challenge, adequately. Meanwhile, we recommend more careful surveillance and treatment of these comorbidities, especially CVD, as it consists of a wide spectrum of disorders that can be underdiagnosed or not screened appropriately, either or both of which may have happened in our study. We also recommend that all patients with a diagnosis of NAFLD be screened for other metabolic conditions and other pathologic correlations not strictly linked to any metabolic diseases.

Resumen

Introducción y objetivos: Pacientes con enfermedad de hígado graso no alcohólica (EHGNA) tiene una alta prevalencia de hipertensión, diabetes mellitus tipo 2 (DMT2) y enfermedades cardiovasculares y viceversa. El mecanismo de esta relación no se conoce del todo, pero parece estar relacionado a un disturbio metabólico que afecta diferentes órganos. El objetivo de nuestro estudio era determinar las prevalencias de dichas condiciones en pacientes con diagnóstico de EHGNA vistos en la cínica de enfermedades de hígado. Métodos: Llevamos a cabo un estudio de cohorte para determinar la prevalencia de hipertensión, DMT2 y enfermedades cardiovasculares según registrado en el récord médico en pacientes con EHGNA incluidos en la base de datos de la clínica de hígado de la Escuela de Medicina de la Universidad de

Puerto Rico (UPR). Las enfermedades cardiovasculares se definieron como hipercolesterolemia, dislipidemia, enfermedad isquémica de corazón y enfermedad vascular periférica. Pacientes con otras causas de enfermedad de hígado fueron excluidos. El estudio fue aprobado por la Junta de Revisión Institucional del Recinto de Ciencias Médicas. Resultados: Nuestra muestra final consistió en 141 participantes con diagnóstico de EHGNA, de los cuales 64.5% (n = 91) eran mujeres. La edad promedio fue 69 ±10.2 años (rango 36-114). La prevalencia de hipertensión, DMT2 y enfermedades cardiovasculares fue de 53.9%, 57.5% y 7.8% respectivamente. Se encontró una asociación estadísticamente significativa entre tener DMT2 en dichos pacientes y tener 65 años o más (P < 0.001). Conclusión: Nuestros datos indican que hipertensión y DMT2 son altamente prevalentes en pacientes con EHGNA en Puerto Rico, sin embargo, mientras que enfermedades cardiovasculares no fueron menos prevalentes que lo esperado. Más estudios son requeridos para definir mejor dichas asociaciones. Recomendamos que todos los pacientes con diagnóstico de EHGNA sean examinados para otras condiciones metabólicas.

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