

Original Article

Preclinical cardiac disease in nonalcoholic fatty liver disease with and without metabolic syndrome

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Abstract: Background: Metabolic syndrome is associated with preclinical cardiac disease and nonalcoholic fatty liver disease (NAFLD). It is uncertain whether preclinical cardiac disease is present in patients with NAFLD without metabolic syndrome (MetS). Objective: To explore preclinical cardiac disease in patients with NAFLD. Methods: A total of 64 patients with NAFLD, based on computed tomography scans liver attenuation, were identified. A control group, matched to age and gender, comprising of 94 patients was also drafted. Finally, two additional groups of patients with metabolic syndrome, with (n = 40) and without (n = 74) NAFLD, were also identified. Patients with hypertension, diabetes mellitus, and other concomitant liver diseases were excluded from the NAFLD group. Echocardiograms of all groups were reviewed. Results: Severe NAFLD compared to control was associated with a higher left ventricular mass after normalization for height^{2.7} (LVMHt^{2.7}) (95% CI = 0.39, 12.92) and lower ratio of peak “E” (early) and “A” (late) diastolic ventricular filling velocities (E/A) - 0.39 (95% CI = -0.58, -0.19). Patients with metabolic syndrome (95% CI = 0.02, 0.09), metabolic syndrome with NAFLD (95% CI = 0.02, 0.08), or severe NAFLD (95% CI = 0.02, 0.09) compared to control was associated with a higher relative wall thickness (RWT). Conclusion: Healthy adults with NAFLD without metabolic syndrome, after adjusting for body mass index, demonstrated significant echocardiographic changes. Our results show that NAFLD is associated with preclinical cardiac disease, and this association is independent of traditional risk factors like systemic hypertension and diabetes mellitus.

Keywords: Nonalcoholic fatty liver disease, preclinical cardiac disease, diastolic dysfunction, metabolic syndrome, echocardiogram

Introduction

Nonalcoholic fatty liver disease (NAFLD) is characterized by an accumulation of fat in the liver, in the absence of secondary causes like alcohol, drugs and hereditary disorders. NAFLD has been increasingly identified as a leading cause of cryptogenic cirrhosis [1, 2]. It comprises of a spectrum of clinicopathological conditions, ranging from simple fatty liver to nonalcoholic steatohepatitis, which can progress to cirrhosis and eventually hepatocellular cancer.

NAFLD is frequently associated with metabolic syndrome (MetS). Its association with metabolic syndrome is bidirectional [3]. Historically, NAFLD has been considered a hepatic manifestation of metabolic syndrome and its severity

increases with increasing components of metabolic syndrome [4]. On the other hand, studies have also shown NAFLD as being a precursor and a risk factor for the future development of MetS [5].

There is evidence to suggest an association between NAFLD and cardiovascular events. Studies have demonstrated both increased cardiac events and diastolic dysfunction among NAFLD patients with one or more components of metabolic syndrome [6-8]. Few studies have shown an association between NAFLD and diastolic dysfunction [8-12]. However, it is unclear whether these cardiac abnormalities result from a direct effect of NAFLD or due to shared risk factors with metabolic syndrome. We aim to study this association and explore the rela-

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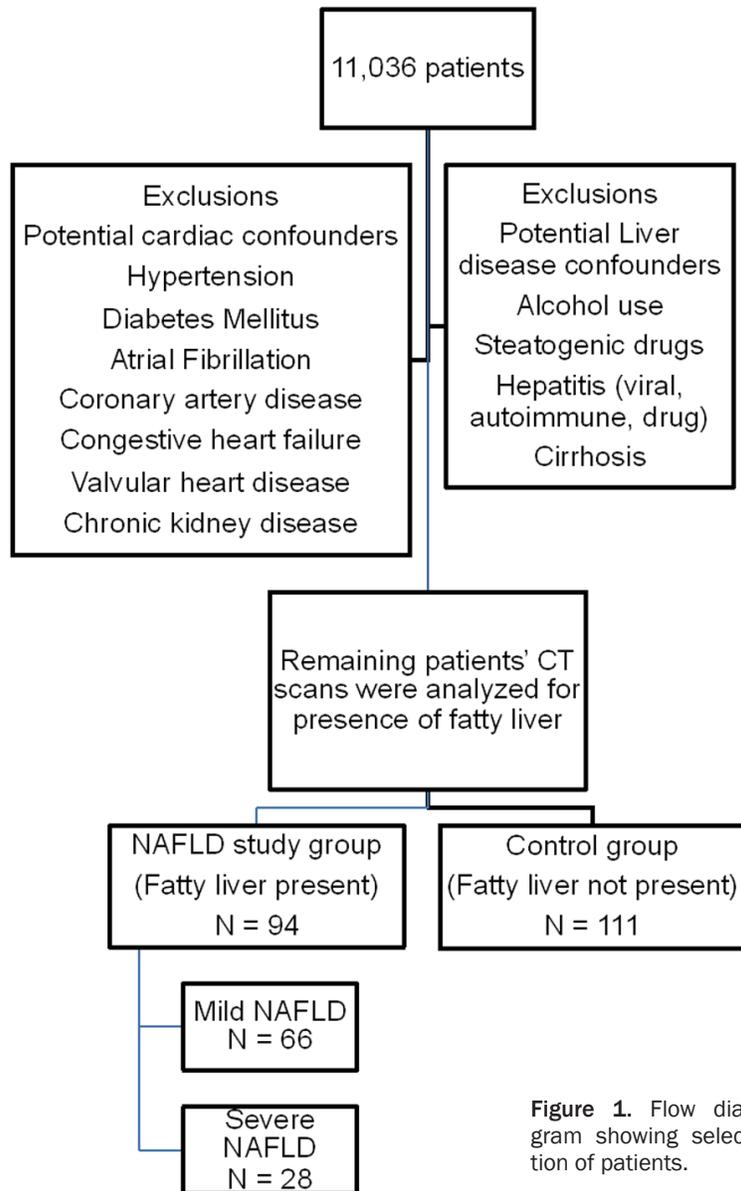


Figure 1. Flow diagram showing selection of patients.

Declaration of Helsinki, as reflected in the Bronx Care Health System Institutional Review Board's approval. Patients with atrial fibrillation, coronary artery disease, congestive heart failure, valvular heart disease and chronic kidney disease were excluded from the study. Further, patients with hypertension and diabetes mellitus were excluded from the NAFLD group but were included in the groups with metabolic syndrome. Patients with significant alcohol use (defined as more than 21 drinks per week in men and more than 14 drinks per week in women, over a 2-year period) and the use of steatogenic medications, such as methotrexate, valproate, tamoxifen, amiodarone and corticosteroids, were excluded. We also excluded patients with known liver diseases like cirrhosis, hepatitis B or C, autoimmune hepatitis and drug-induced hepatitis (**Figure 1**).

We extracted information regarding patient's age, gender, race and ethnicity in all study groups, as well as the control group. We also collected information about body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and routine laboratory blood tests, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.

Diagnosis of nonalcoholic fatty liver disease

Diagnosis of NAFLD required concurrence of i) a positive criterion for hepatic steatosis (as seen on CT scan and explained below) and b) the absence of competing causes of liver disease. Among patients remaining after exclusions, attenuations of the right liver lobe, left liver lobe and spleen, as assessed on non-contrast computed tomography (CT) scans, were recorded. Liver to spleen (L:S) attenuation ratio

tionship of these cardiac abnormalities with an increasing severity of NAFLD. Additionally, we also intend to evaluate the combined effect of MetS and NAFLD on cardiac abnormalities.

Materials and methods

Study population

We conducted a retrospective review of medical records of 11,036 patients who underwent computed tomography scans at Bronx Care Hospital, between a study period of January 2012 to July 2013. The study protocol conformed to the ethical guidelines of the 1975

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was calculated by dividing mean attenuation of the right and left liver lobe by the attenuation of the spleen. It has been shown previously that an L:S attenuation ratio of less than 1.0 on CT scan can be effectively used to diagnose fatty liver [13]. Studies have also shown that a liver attenuation of less than 40 can reliably predict the presence of more than 30 percent fat in the liver [14]. In our study, patients with a liver attenuation of less than 40 were defined as severe NAFLD and patients with a liver attenuation ratio of more than 40 were defined as mild NAFLD.

An age and gender matched control group without NAFLD (L:S ratio > 1) was also identified. Additionally, two more groups - MetS only and MetS combined with NAFLD, were identified. MetS was defined by the National Cholesterol Education Program's Adult Treatment Panel III criteria. It defined it as the presence of three or more of the following five: central adiposity, impaired fasting glucose, hypertension, elevated triglyceride (TG), and low high-density lipoprotein (HDL) [15].

Echocardiographic measurements

As per the standard practice of our institute, echocardiographic parameters of all patients were recorded as per the American Society of Echocardiography (ASE) recommendations [16, 17]. The parasternal acoustic window was used to record 3-5 consecutive beats of 2-dimensional and M-mode recordings of the left ventricle (LV) internal diameter and wall thicknesses, at or just below the tips of the mitral valve leaflets, in long and short-axis views. Correct orientation of planes for imaging and doppler recordings were verified using standard procedures [18]. LV internal dimension and interventricular (septal and posterior wall) thickness were measured at end-diastole and end-systole, for 3 cycles [18]. Where the optimal orientation of the LV could not be obtained by M-mode, correctly oriented 2-D linear dimensions were made by utilizing the leading-edge convention [19, 20]. A close correlation between these two methods has been previously reported [21]. End-diastolic LV dimensions were used to calculate left ventricular mass (LVM) by a formula that yields values closely related ($r = 0.90$, $P < 0.001$) to necropsy LV weight [22] and which showed excellent reproducibility (intra-class cor-

relation coefficient = 0.93, $P < 0.001$) between two separate echocardiograms in 183 hypertensive patients [20].

LV hypertrophy was defined using ex-specific partition values in men and women for LV mass adjusted to its allometric relation to height ($\text{height}^{2.7}$) [23-25]. Left ventricular mass after normalization for height^{2.7} (LVMHt^{2.7}) prognostically validated partition values of > 46 g/m^{2.7} in men and > 44 g/m^{2.7} in women. These values were used to diagnose LV hypertrophy [26].

Relative wall thickness (RWT) was calculated as a ratio of twice the posterior wall thickness (PWT) to the left ventricular internal dimension in diastole (LVEDD). It was considered elevated if it was > 0.42, in both men and women [27]. Normal geometry was considered when both LV mass index and relative wall thickness were normal. A normal LV mass index with an increased relative wall thickness was classified as concentric remodeling, whereas, an increased LV mass index with a normal relative wall thickness was identified as eccentric LV hypertrophy. An increase in both variables was identified as concentric LV hypertrophy [19, 28].

Transmitral flow velocities measured by pulsed doppler recordings at the mitral annulus and leaflet tips were traced along the black-white interface to record peak "E" (early) and "A" (late) diastolic ventricular filling velocities. The E/A ratio was then calculated [29].

Tissue doppler imaging (TDI) was used to calculate the early (e) and late (a) diastolic velocities from the mitral annular margins [30]. The ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e') was calculated among the study population [31].

Statistical analysis

Five study groups were formed based on liver disease status: Control, mild NAFLD, severe NAFLD, MetS only, NAFLD and MetS combined. Demographic information and clinical measurements were stratified across the study groups. Frequencies and percentages were reported for categorical variables. Mean and standard deviations were reported for numerical variables. Pearson's chi-squared tests were used to assess the association between categorical

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variables and liver disease status. ANOVA tests were used to assess the association between continuous variables and liver disease status. Five echocardiogram measures, namely LVM, LVMHt^{2.7}, RWT, E/A, E/e', were stratified across liver disease status. Mean and standard deviations were reported. Post-hoc comparison using the Tukey honest significant difference (HSD) test was used to assess the inter group differences of the five echocardiogram measures, for our study groups. Four separate multivariable linear regressions were used to assess the association between liver disease status and echo variables (LVM, LVMHt^{2.7}, RWT, E/A), controlling for age, gender, BMI, SBP and HR. Because E/e' was not normally distributed, bootstrap multivariable linear regressions with 5000 times resampling was used to assess the association between liver disease status and E/e', controlling for age, gender, BMI, SBP and HR.

Results

Table 1 compares confounders of the different liver disease status. Age, BMI, imputed waist circumference, hypertension status, diabetes mellitus status, intake of anti-hypertensive and anti-diabetic medications, SBP, DBP, pulse pressure, HR, TG level, ALT and AST levels were all significantly associated with liver disease status.

A total of 94 patients were in the control group (mean age 48.7, 27% male). The NAFLD group had 64 patients, who were further divided into mild NAFLD (N: 45, Mean age 44.6, 42% males) and severe NAFLD (N: 19, Mean age 48.4, 42% males), after exclusions. The group of patients with metabolic syndrome included 74 patients (mean age 65.6, 32% males), while the group with NAFLD and metabolic syndrome combined (mean age 56.4, 52% males) had 40 patients (**Table 1**).

Waist circumference and transaminases levels were highest in patients with severe NAFLD and NAFLD with MetS combined. Patients with NAFLD and MetS combined had a significantly higher triglyceride level as compared to other groups (**Table 1**).

The most common indications for echocardiography in the control group were chest pain, shortness of breath and palpitations. Patients with a suspicion of cardiac disease underwent

a cardiac stress test and troponin levels in order to rule out cardiac disease. The average time period between CT liver attenuation score and echocardiographic variables was less than 1 year.

Figure 2 compares echocardiographic variables across liver disease status. The mean LV mass was higher for the NAFLD and MetS combined group compared to both, the control group (195.24 vs. 154.84, $P < 0.001$) and the mild NAFLD group (195.24 vs. 155.80, $P < 0.001$). The LVMHt^{2.7} was also higher for the NAFLD and MetS combined group compared to both, the control group (49.90 vs. 40.77, $P < 0.001$) and the mild NAFLD group (49.9 vs. 39.71, $P < 0.001$). The LVMHt^{2.7} was higher in the severe NAFLD group compared to both, the control group (49.70 vs. 40.77, $P = 0.05$) and the mild NAFLD group (49.70 vs. 39.71, $P = 0.04$). The RWT was higher in the MetS only group, NAFLD and MetS combined group and the severe NAFLD group compared to the control group (MetS only vs. control: 0.47 vs. 0.42, $P < 0.001$; NAFLD and MetS combined vs. control: 0.46 vs. 0.42, $P < 0.001$; severe NAFLD vs. control: 0.47 vs. 0.42, $P = 0.04$). The E/A was lower for the MetS only group, NAFLD and MetS combined group and the severe NAFLD group compared to the control group (MetS only vs. control: 1.00 vs. 1.32, $P < 0.001$; NAFLD and MetS combined vs. control: 1.08 vs. 1.32, $P = 0.01$; severe NAFLD vs. control: 0.92 vs. 1.32, $P < 0.001$). The E/A for the mild NAFLD group was lower compared to the control group (1.28 vs. 1.32, $P < 0.001$). The E/A for the severe NAFLD group was lower compared to the mild NAFLD group (0.92 vs. 1.28, $P = 0.01$). The E/e' was higher for the mild NAFLD group compared to the MetS only group (1.64 vs. 0.87, $P = 0.03$).

Table 2 displays results of regression analysis. Severe NAFLD compared to control group was associated with a higher LVMHt^{2.7} (CI = 0.39, 12.92). Patients with MetS only (CI = 0.02, 0.09), NAFLD and MetS combined (CI = 0.02, 0.08), or severe NAFLD (CI = 0.02, 0.09) had a higher RWT compared to control group. Severe NAFLD was associated with a lower E/A (-0.39) (CI = -0.58, -0.19) compared to control group.

Discussion

Our study demonstrates the presence of pre-clinical cardiac manifestations, as detected by

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Table 1. Clinical and biochemical parameters compared between various study groups

Variable	Control (N = 94)	Mild NAFLD (N = 45)	Severe NAFLD (N = 19)	MetS only (N = 74)	NAFLD and MetS combined (N = 40)	Total (N = 272)	p-value
Age (years) (Mean ± SD)	48.7 ± 12.6	44.6 ± 14.4	48.4 ± 14.5	65.6 ± 12.1	56.4 ± 12.4	53.7 ± 15.1	< 0.001
Gender M:F	27:73	42:58	42:58	32:68	52:48	36:64	0.060
BMI (kg/m ²) (Mean ± SD)	27.6 ± 5.9	29.9 ± 7.8	30.7 ± 5.9	28.9 ± 6.4	33.9 ± 8.6	29.6 ± 7.1	< 0.001
Waist Circumference (cm) (Mean ± SD)	93.7 ± 13.1	99.4 ± 17.8	101.5 ± 11.9	99 ± 14.1	111.5 ± 20.3	99.3 ± 16.3	< 0.001
Smoker	28	9	1	18	8	64	0.186
Hypertension	0	0	0	64	37	101	< 0.001
Anti-hypertensive medications	0	0	0	62	37	99	< 0.001
Diabetes mellitus	0	0	0	53	33	87	< 0.001
Anti-Diabetic medications	0	0	0	49	33	82	< 0.001
Systolic blood pressure (mm of Hg) (Mean ± SD)	118.1 ± 11.2	123.9 ± 10.7	121.9 ± 33.8	141.2 ± 22.8	131.4 ± 17.2	127.5 ± 20.2	< 0.001
Diastolic blood pressure (mm of Hg) (Mean ± SD)	74.1 ± 8.10	73.5 ± 10.20	76.5 ± 22.1	80.5 ± 14.9	76.9 ± 7.3	76.3 ± 12.1	0.006
Pulse pressure (mm of Hg) (Mean ± SD)	43.9 ± 10.40	50.5 ± 9.0	45.4 ± 17.7	59.9 ± 20.4	54.5 ± 15.3	51.1 ± 16.1	< 0.001
Heart Rate (beats per minute) (Mean ± SD)	75.9 ± 10.1	75.3 ± 10.5	80.9 ± 23.6	84.5 ± 15.9	85.0 ± 12.3	79.8 ± 14.1	< 0.001
Triglyceride level (mg/dL) (Mean ± SD)	91.4 ± 51.3	115.7 ± 79.9	129.2 ± 150.7	165.8 ± 179.3	216.9 ± 122.9	135.9 ± 126.1	< 0.001
ALT (U/L) (Mean ± SD)	16.6 ± 6.1	29.6 ± 27.2	41.4 ± 28.9	23.9 ± 27.0	41.2 ± 27.5	26.1 ± 24.1	< 0.001
AST (U/L) (Mean ± SD)	19.3 ± 5.6	24.8 ± 14.9	48.7 ± 62.2	27.7 ± 25.7	36.4 ± 25.2	27.01 ± 25.3	< 0.001

Abbreviations: BMI: body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

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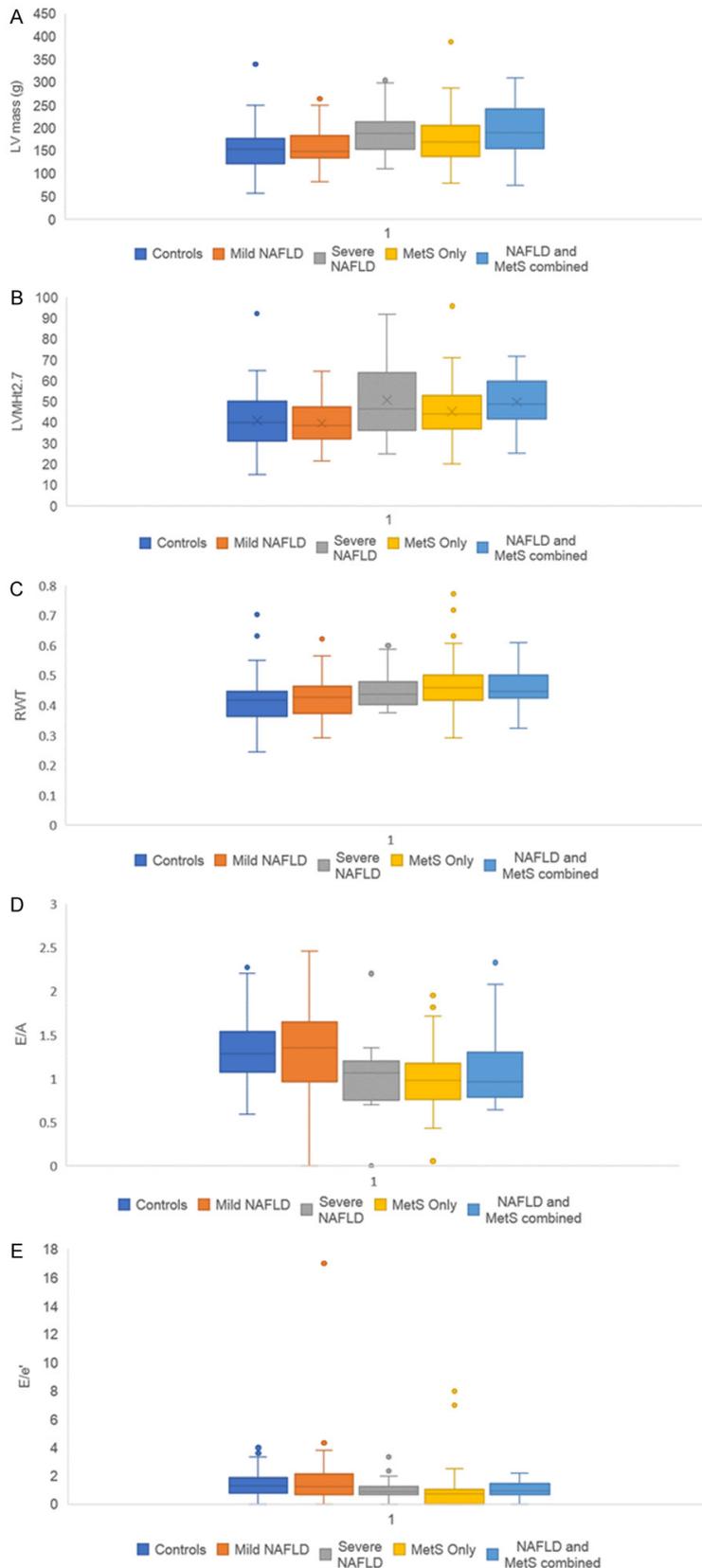


Figure 2. A. Box and whisker plots of mean left ventricular (LV) mass comparison across liver disease status for mild and severe NAFLD, MetS,

NAFLD and MetS combined in comparison with control group. B. Box and whisker plots of left ventricular mass after normalization for height^{2.7} (LVMHt^{2.7}) comparison across liver disease status for mild and severe NAFLD, MetS, NAFLD and MetS combined in comparison with control group. C. Box and whisker plots of relative wall thickness (RWT) comparison across liver disease status for mild and severe NAFLD, MetS, NAFLD and MetS combined in comparison with control group. D. Box and whisker plots of ratio between peak early (E) and late (A) diastolic ventricular filling velocities (E/A) comparison across liver disease status for mild and severe NAFLD, MetS, NAFLD and MetS combined in comparison with control group. E. Box and whisker plots of ratio between early mitral inflow velocity (E) and mitral annular early diastolic velocity (e') (E/e') comparison across liver disease status for mild and severe NAFLD, MetS, NAFLD and MetS combined in comparison with control group.

echocardiographic diastolic abnormalities, in healthy normotensive, non-diabetic individuals with NAFLD. We also compared this group of patients to those with metabolic syndrome, with and without NAFLD. To our knowledge, this is the first study of its kind that illustrates the gradual decline in diastolic cardiac function and worsening of LV geometry with progressively increasing amounts of fat accumulation in the liver.

NAFLD is the leading cause of liver disease in the west [32] and its prevalence is increasing, with worldwide estimates ranging from 6% to 35% (median prevalence of 20%), depending on the method used for diagnosis [33]. NAFLD is commonly associated with metabolic syndrome and this association not only predicts more severe necroinflammatory acti-

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Table 2. Regression results

Control	LVM	LVMHt ^{2.7}	RWT	E/A	E/e'
	ref	ref	ref	ref	ref
Mild NAFLD	-9.09 (-26.68, 8.50)	-2.09 (-6.69, 2.51)	0.01 (-0.02, 0.04)	-0.08 (-0.22, 0.06)	0.22 (-0.36, 1.08)
Severe NAFLD	12.53 (-11.42, 36.47)	6.66 (0.39, 12.92)*	0.05 (0.02, 0.09)**	-0.39 (-0.58, -0.19)***	-0.28 (-0.67, 0.12)
MetS only	12.78 (-5.69, 31.25)	0.99 (-3.84, 5.80)	0.05 (0.02, 0.09)***	-0.13 (-0.28, 0.01)	-0.16 (-0.52, 0.26)
NAFLD and MetS combined	16.42 (-3.85, 36.68)	3.98 (-1.32, 9.28)	0.05 (0.02, 0.08)**	-0.14 (-0.30, 0.02)	-0.21 (-0.54, 0.12)

Significance codes: ***P < 0.001; **P < 0.01, *P < 0.05. Abbreviations: NAFLD: Nonalcoholic fatty liver disease; MetS: Metabolic syndrome; LVM: Left ventricular mass; LVMHt^{2.7}: Left ventricular mass after normalization for height^{2.7}; RWT: Relative wall thickness; E/A: Ratio between peak early (E) and late (A) diastolic ventricular filling velocities; E/e': Ratio between early mitral inflow velocity (E) and mitral annular early diastolic velocity (e').

vity and fibrosis [4], but also has serious implications on overall cardiovascular health. It is not surprising that patients with NAFLD and metabolic syndrome have a greater carotid artery intimal medial wall thickness, which is a measure of subclinical atherosclerosis [34-37]. Metabolic syndrome when combined with NAFLD is also associated with a higher prevalence of both overt and covert cardiovascular disease. Targher et al. have shown a higher prevalence of cardiovascular, cerebrovascular and peripheral vascular diseases in NAFLD patients with type-1 [38] and type-2 [39] diabetes mellitus. Several studies have shown an increasing association between NAFLD and cardiovascular events, especially as the disease progresses, thereby leading to increased morbidity and mortality [40-46]. However, all these studies included patients with one or more components of metabolic syndrome. Due to the presence of these shared risk factors in such studies, it is unclear if NAFLD can directly lead to cardiovascular problems.

Studies exploring the relationship between NAFLD and echocardiographic changes are not new. However, it remains unclear if these echocardiographic abnormalities can occur independently of metabolic syndrome. The pro-atherothrombotic state of metabolic syndrome causes cardiac remodeling resulting in subclinical cardiovascular abnormalities, such as increased left ventricular mass and subsequent systolic and diastolic dysfunction [19, 47-49]. Endothelial dysfunction and eventual atherosclerosis is the main triggering event responsible for these effects and association between NAFLD and cardiac disease. It is well established in previous studies that an abnormal left ventricular geometry and function is present in patients with metabolic syndrome [24, 47, 49]. The progressive addition of metabolic risk factors is associated with a higher LV mass [50]. A

higher prevalence of left ventricular diastolic dysfunction among patients with NAFLD and type-2 diabetes mellitus was demonstrated by Bonapace et al. [51]. In another study, de Simone et al. found that addition of multiple metabolic risk factors was associated with a higher LV mass normalized by height^{2.7} [50, 52]. A small study by Goland et al. [53] showed echocardiographic abnormalities in 38 NAFLD patients, after excluding those with diabetes mellitus, hypertension and morbid obesity. Although, the study demonstrated an increased thickness of the intraventricular septum and posterior wall, as well as a larger LV mass and LV mass/height in NAFLD patients, it did not exclude patients with impaired fasting glucose, which has been shown to independently influence cardiac function [54]. Another small study by Fotbolcu et al. [11] involving 35 NAFLD patients, demonstrated significant differences in the diastolic interventricular septal thickness. They also showed that NAFLD patients have a higher LV mass and LV mass index to body surface area. Since obesity has been independently shown to be associated with left ventricular hypertrophy [55], LV mass indexing has been used to eliminate the effect of obesity on left ventricular mass and therefore avoid any misleading estimates. Among the various methods of indexing the LV mass, LV mass calculated using the Devereux formula [56] and indexed for height powered to 2.7, has shown to be superior to body surface area in predicting cardiovascular events [57]. However, in the study by Fotbolcu et al., indexing with body surface area was used which could have affected the results. Hence, in our study we chose to eliminate the effect of obesity by indexing for height powered to 2.7. Lin et al. found a higher prevalence of ischemic electrocardiographic changes in patients with NAFLD, but they also included patients with impaired fasting glucose and hypertension in their

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NAFLD cohort [58]. A few others have also studied the association between NAFLD and cardiac dysfunction, however they all either included patients with metabolic syndrome [10, 59, 60] or included patients with other confounding components of metabolic syndrome, such as hypertension, diabetes mellitus and dyslipidemia, alone or in combination [9, 11, 12, 61-64]. Similarly, there have been other studies which have shown a relationship between NAFLD and coronary artery disease severity as seen on angiography, however these included patients with metabolic syndrome [65-67].

In our study, we precluded patients with hypertension and/or diabetes mellitus in the NAFLD groups - mild and severe, to see the true effect of NAFLD on echocardiographic variables. Findings of our study highlight, not only the existence of subclinical diastolic dysfunction among patients with NAFLD, but also the declining diastolic dysfunction with a worsening severity of NAFLD. An increasing severity of NAFLD correlated with worsening cardiac structural disease, as measured by RWT. A gradual decline in the cardiac diastolic function, as measured by LV mass indexed for height^{2.7} and E/A ratio, was also observed with an increasing severity of NAFLD.

LV hypertrophy has been found to be associated with endothelial dysfunction which in turn leads to arterial stiffness [68]. Prior studies have shown that this effect is seen in long standing hypertension. In our study, we noted LV hypertrophy in patients with NAFLD and metabolic syndrome combined, yet interestingly LV hypertrophy was also present in the severe NAFLD group.

In our study, a higher degree of hepatic steatosis was associated with a higher RWT, which in itself is an indicator of concentric LV geometry occurring without LV hypertrophy. Concentric LV geometry has been shown to be associated with an increase in all-cause mortality in cardiovascular disease patients [69].

Ratio of transmitral “E” (early) and “A” (late) diastolic ventricular filling velocities (E/A) is a measure of LV filling pressures. As the ventricle gets stiff, E/A ratio declines suggesting a decline in LV diastolic function. We noticed a decline in E/A with an increasing severity of hepatic steatosis. A study from our institution by Bella et

al. explains the effect of low or high E/A. In a sample of 3008 American Indian individuals, it was observed that mitral E/A > 1.5 at baseline doppler echocardiography was associated with a 2-fold increase in all-cause, and a 3-fold increase in cardiac related mortality. Whereas, mitral E/A < 0.6 was also associated with 2-fold increase in all-cause and cardiac mortality [29]. Decline in E/A ratio has also been shown to increase the risk of major cardiovascular events, as established in the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study [70].

In our patient population, a widened pulse pressure was observed in the NAFLD and NAFLD with MetS combined group. Widened pulse pressure increases the arterial stiffness resulting in concentric left ventricular geometry and diastolic abnormalities [71]. It has also been reported by Palmieri et. al. that a greater pulse pressure/stroke volume index was associated with a higher mitral E-wave/A-wave ratio and a shorter isovolumetric relaxation time [72].

It is known that chronic hypertension results in a parallel adaptation of the cardiac and arterial system [73], and our study suggests a similar mechanism of cardiac and arterial remodeling in patients with NAFLD. Increased arterial stiffness and wave reflection have been found in individuals with asymptomatic left ventricular (LV) diastolic dysfunction, which in turn can progress to heart failure with reduce ejection fraction [74]. In our analysis, this phenomenon is also seen in patients with NAFLD. Wang et al. have studied and reported cardiovascular morbidities occurring as a result of the aforementioned process [75]. Based on our study results, we suggest that NAFLD leads to the development of subtle but significant changes in the LV structure and diastolic function, in these otherwise apparently healthy individuals without concomitant diabetes mellitus and/or hypertension.

Implications of the association between NAFLD and preclinical disease

We conclude that it is reasonable to screen for preclinical cardiac disease with echocardiography in patients with severe NAFLD given the sufficient evidence of association between the two. Screening would not only help to intervene at an earlier stage of the disease but would

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also reduce the long-term morbidity and mortality associated with cardiac diseases. Its clinical significance needs to be proven in prospective trials with long term follow up of patients. Further studies are needed to determine the prognostic significance of preclinical cardiac disease, and whether or not actual screening and interventions can reduce the risk of cardiovascular events in patients with NAFLD.

Study limitations

Our study did have a few limitations. The study design is retrospective and has its inherent limitations due to reliance on previously recorded medical information. This study does not represent ethnic groups other than Hispanics and African Americans. However, these two underserved ethnic groups have not been studied in the past. Diagnosis of NAFLD was made based on imaging study and not by liver biopsy, which remains the gold standard diagnostic technique. We included patients with prehypertension (mean systolic blood pressure in mild NAFLD and severe NAFLD was 124 and 122 mmHg, respectively), which may have had an influence on our results. American and International Society of Hypertension define the preceding values of minimally elevated systolic blood pressure as prehypertension; however, recommend no pharmacologic therapy for this group of people. Population-based studies are required to confirm our findings in this clinical cohort.

Conclusion

In conclusion, our results indicate that NAFLD is associated with preclinical cardiac disease and this association is independent of traditional risk factors like systemic hypertension and diabetes mellitus. The differences in relative wall thickness and E/A ratio were independent of age, sex and body size. Further prospective studies are necessary to validate these results and to determine whether detection of NAFLD predicts future cardiovascular disease.

Disclosure of conflict of interest

None.

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