CorSalud 2020 Oct-Dec;12(4):425-431

CorSalud

Cuban Society of Cardiology

Review Article

Cardiocentro Ernesto Che Guevara Santa Clara Cuba

Ventricular structure and function in non-alcoholic fatty liver disease

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Este artículo también está disponible en español

ARTICLE INFORMATION

Received: February 1, 2020
Accepted: March 18, 2020

Competing interests
The authors declare no competing interests.

Abbreviations
MRI: magnetic resonance imaging
NAFLD: non-alcoholic fatty liver disease

ABSTRACT
Non-alcoholic fatty liver disease is associated with metabolic syndrome and cardiovascular disease through multiple pathogenic pathways including insulin resistance, altered lipid metabolism, inflammation and endothelial dysfunction. These mechanisms lead to cardiac remodeling, atherosclerosis, and potentially increased cardiovascular morbidity and mortality. In this short review we address the relationships of non-alcoholic fatty liver disease with metabolic syndrome and their impact on imaging and biochemical markers of ventricular function.
Keywords: Non-alcoholic fatty liver disease, Hepatic steatosis, Cardiac function, Echocardiography

Estructura y función ventriculares en la enfermedad de hígado graso no alcohólica

RESUMEN
La enfermedad del hígado graso no alcohólica se asocia al síndrome metabólico y a la enfermedad cardiovascular a través de múltiples vías patogénicas, que incluyen la resistencia a la insulina, la alteración del metabolismo lipídico, inflamación y disfunción endotelial. Estos mecanismos conducen a remodelación cardíaca, aterosclerosis y un aumento potencial de la morbilidad y la mortalidad cardiovasculares. En esta breve revisión se abordan las relaciones de la enfermedad del hígado graso no alcohólica con el síndrome metabólico y su impacto en las pruebas de imagen y en los marcadores bioquímicos de función ventricular.
Palabras clave: Enfermedad del hígado graso no alcohólica, Esteatosis hepática, Función cardíaca, Ecocardiografía

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) comprises a broad spectrum of liver disorders unrelated to alcohol consumption in quantities that would induce liver damage. Its diagnosis is based on the following criteria[1]:

1. Hepatic steatosis on imaging or histology.
2. Absence of significant alcohol consumption.
3. Absence of other causes for steatosis.
4. Absence of coexisting causes of chronic liver disease.

NAFLD is subdivided into non-alcoholic fatty liver (NAFL) and non-alco-

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holic steatohepatitis (NASH). NAFLD has a reported prevalence of up to 35 percent. The link between non-alcoholic fatty liver disease and metabolic syndrome components has inspired interest in studies on its alleged contribution in the development and progression of cardiovascular disease[2].

Pathogenetic links with metabolic syndrome and cardiac dysfunction

Metabolic syndrome components are obesity, type 2 diabetes and insulin resistance, high blood pressure and dyslipidemia (**Table 1**)[3].

Epidemiological studies have shown that obesity is a predictive factor for the development of metabolic syndrome and non-alcoholic fatty liver disease. Multiple mechanisms contribute to left ventricular dysfunction in obesity, including lipotoxicity associated with cardiac steatosis and lipoapoptosis, alteration of fatty acid metabolism, overproduction of cardioinhibitory cytokines, myocardial fibrosis[4-6]. Obesity increases the resistance to insulin, which in turn stimulates myocyte growth and interstitial fibrosis; also, insulin causes retention of sodium and activates the sympathetic nervous system that can affect cardiac performance[5,6]. Sodium retention increases blood pressure, which in turn causes myocardial tissue damage, myocardial fibrosis and impaired left ventricular function in response to pressure overload. Iacobellis and collaborators have shown that insulin resistance seen in obese patients in the absence of diabetes mellitus was associated with geometric change and increased left ventricular mass[7]. However, not all studies conducted in non-diabetic patients sustained these results. When data was adjusted for body mass index and blood pressure levels, insulin resistance was no longer an independent determinant of left ventricular mass[8].

Nowadays, there is enough evidence to prove that patients with NAFLD have an increased risk of cardiovascular events, with an association between NAFLD and certain markers of subclinical vascular dysfunction such as the intima-media thickness of the carotid artery[9]. In contrast, information on heart function abnormalities among patients with non-alcoholic fatty liver disease is limited and controversial.

Recent studies have shown an increased prevalence of left ventricular remodeling and implicitly of diastolic dysfunction in patients with metabolic syndrome. These studies included patients with obesity and/or high blood pressure who are themselves independent risk factors for diastolic dysfunction of the left ventricle. Therefore, it is not clear whether this impairment of diastolic function is a consequence of high blood pressure and/or obesity or the effect of insulin resistance in the myocardium. There are currently few data on changes concerning the structure and function in left ventricle in normotensive, non-diabetic patients with metabolic syndrome and non-alcoholic fatty liver.

Imaging indices of left ventricular dysfunction in NAFLD

Left ventricular structure and function is currently assessed by echocardiography (conventional, tissue doppler, speckle-tracking) and magnetic resonance imaging (MRI). Given the progressive nature of pathological myocardial remodeling, early detection of myocardial dysfunction in the subclinical stages is of major importance, mandating measures which could prevent further evolution to heart failure.

Tissue Doppler Imaging (TDI) echocardiography is the simplest and most reliable method for assessing subclinical changes in left ventricular func-

Table 1. Definition of the metabolic syndrome according to International Diabetes Federation[3].

Parameter	Metabolic syndrome present if there are ≥ 3 criteria of:
Glucose	Fasting glucose ≥100 mg/dL (5.6 mmol/L) or diagnosed diabetes
HDL cholesterol	< 40 mg/dL (1.0 mmol/L) (men); < 50 mg/dL (1.3 mmol/L) (women) or drug treatment for low HDL cholesterol
Triglycerides	≥ 150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides
Obesity	Waist circumference ≥ 94 cm (men) or ≥ 80 cm (women)
Hypertension	Blood pressure ≥ 130/85 mmHg or drug treatment for hypertension

tion. By TDI the maximum velocity of movement of the region of interest throughout the cardiac cycle is visualized and can be quantified in real-time. Nuclear magnetic resonance imaging (MRI) is known as an accurate and reproducible method of calculating cardiac volumes and ejection fraction, regardless of patient anatomy, being one of the most innovative imaging diagnosis methods of the heart, but more difficult to access due to high cost.

Research in this field showed that patients with non-alcoholic fatty liver disease present an increase in the mass of the left ventricle, a higher end-diastolic volume of the left ventricle and an increase in its relative thickness[10,11]. In addition, it was shown that patients with non-alcoholic hepatic disease present a reduced early diastolic relaxation (e' tissue velocity), a reduced E/A ratio, and increased left ventricular filling (E/e' ratio), which imply the presence of the subjacent subclinical diastolic dysfunction[11-12]. Moreover, using speckle-tracking techniques, it was found that patients with non-alcoholic liver disease have a reduced longitudinal systolic function of the left ventricle despite having a normal ejection fraction[13]. The association between these echocardiographic changes at the level of the left ventricle and non-alcoholic fatty liver disease appears to be independent of several metabolic variables, including traditional cardiovascular risk factors. Myocardial strain measured by speckle-tracking echocardiography is an important predictor of morbidity and mortality. Identifying subclinical left ventricular dysfunction through these methods may help identify patients with non-alcoholic hepatic disease with increased cardiovascular risk[14,15].

VanWagner and colleagues demonstrated an increase in left atrial volume independently associated with non-alcoholic liver disease, after adjusting for traditional risk factors, including obesity[13]. Left atrium volume is an indicator of the severity of left ventricular diastolic dysfunction, and the size of the left atrium has been shown to be a strong predictor of cardiovascular events in certain conditions such as myocardial infarction, severe aortic stenosis, and chronic heart failure. Therefore, the left atrium volume may represent in future a predictor of symptomatic heart failure in patients with non-alcoholic fatty liver disease.

There is currently limited data on changes in left ventricular structure and function in normotensive, non-diabetic patients with metabolic syndrome and non-alcoholic fatty liver disease, because most studies have included diabetic patients. Several studies (**Tabla 2**)[10-18] have shown that non-diabetic patients with non-alcoholic liver disease have an early impairment of diastolic left ventricular function[10,11]. Fotbolcu *et al.*[11] analyzed 35 patients with non-alcoholic fatty liver disease, normotensive, non-diabetic and experienced an impairment of the left ventricular systolic and diastolic function; however, this study has its limitations, including the reduced number of patients and the fact that silent ischemia damage could not be ruled out because patients were not subjected to a stress test before inclusion.

Perseghin *et al.*[19] showed that non-diabetic male patients with increased intrahepatic fat content measured by MRI spectroscopy had a significant impairment of myocardial energy metabolism (low creatine phosphate-to-ATP [PCr/ATP] ratio) compared to those with a lower intrahepatic fat content In any case, these changes in myocardial energy metabolism have been detected despite similar changes in morphology and function of left ventricle by cardiac MRI. In a recent Magnetic Resonance Imaging study involving male patients with type 2 diabetes mellitus without inducible myocardial ischemia, Rijzewijk *et al.*[20] found that those with increased intrahepatic fat content had a reduction in myocardial perfusion, a reduced level of PCr/ATP ratio at myocardial level, and similar changes in morphology and function of left ventricle. Lautamäki *et al.*[21] in a study involving patients with type 2 diabetes and known ischemic heart disease found that patients with higher intrahepatic fat content had reduced functional coronary capacity; however, measurements of left ventricular function have not been performed in this study.

Rijzewijk *et al.*[22] showed that the level of intramyocardial fats detected by MRI spectroscopy was significantly higher in men with type 2 diabetes than in subjects in the non-diabetic control group and was associated with impairment of diastolic left ventricular function detected by cardiac MRI. Interestingly, the same authors also noted a significant association between fat content at the liver and myocardial level. In contrast, McGavock *et al.*[23] showed that, although intramyocardial fat accumulation was higher in patients with type 2 diabetes, there was no significant association between myocardial steatosis and the left ventricular ejection fraction or early diastolic filling.

These findings suggest the complex relationship between non-alcoholic fatty liver disease, myocardial steatosis and diastolic dysfunction of the left ventricle, and further research is needed to elucidate

Table 2. Echocardiography studies in adults with non-alcoholic fatty liver disease.

Authors	Patients characteristics	Findings
Goland S *et al.*[10]	38 non-DM NAFLD pts. and 25 age- and sex-matched controls.	Increased LV mass index. Increased prevalence of diastolic dysfunction. Reduced e' independently associated with NAFLD.
Fotbolcu H *et al.*[11]	35 non-DM, normotensive NAFLD pts. vs. 30 controls.	Increased prevalence of systolic and diastolic dysfunction (TDI).
Fallo F *et al.*[12]	Newly diagnosed untreated hypertensive pts. (non-obese, non-DM): 48 NAFLD vs 38 controls.	Increased prevalence of diastolic dysfunction correlated with degree of steatosis.
VanWagner *et al.*[13]	2,713 participants (10% with NAFDL)	Participants with NAFLD had lower early diastolic relaxation (e') velocity, higher LV filling pressure, and worse absolute GLS. When adjusted for HF risk factors or body mass index, NAFLD remained associated with subclinical myocardial remodelling and dysfunction.
Mantovani *et al.*[16]	222 type 2 DM pts. (158 had NAFLD).	NAFLD was associated with a three-fold increased odds of mild and/or moderate LV diastolic dysfunction after adjusting for confounders.
Bonapace *et al.*[17]	50 type 2 DM pts. (32 with NAFLD)	Increased prevalence of LV diastolic dysfunction. No differences in LV mass and systolic function.
Trovato *et al.*[18]	660 NAFLD and 791 non-NAFLD subjects	Left ventricular mass significantly greater in NAFLD. Ejection fraction is slightly smaller only in men with NAFLD. No significant difference for the E/A ratio.

DM, diabetes mellitus; e', mitral annular tissue doppler early diastolic velocity; GLS, global longitudinal strain; HF, heart failure; LV, left ventricular; NAFLD, non-alcoholic fatty liver disease; pts, patients; TDI, tissue Doppler imaging

the mechanisms by which non-alcoholic fatty liver disease could contribute to the development of diastolic dysfunction. Under these conditions, it is essential for patients with non-alcoholic fatty liver disease to have a rigorous control of cardiovascular risk factors as well as careful monitoring to prevent left ventricular systolic and diastolic dysfunction.

Imaging indices of right ventricular dysfunction in NAFLD

Although non-alcoholic fatty liver disease is clearly associated with the impairment of left ventricular function and an increased risk of cardiovascular disease, its impact on the right ventricular function remains unclear. Some patients with non-alcoholic liver disease experience dyspnea, low tolerance for exertion and peripheral edemas, suggesting that the right ventricular function should be evaluated in all these patients. Increased liver size may affect anatomically the right ventricular function; also, the increased preload due to elevated hepatic venous pressure may contribute to the occurrence of right ventricular dysfunction.

There are few studies focused on right ventricular function assessed by echocardiography in NAFLD, and the number of patients included is small. Bekler and colleagues[24] compared 32 individuals with NAFLD (59% were with grade I hepatosteatosis, 41% with grade II-III hepatosteatosis) to a control group of 22 subjects without hepatosteatosis. Right ventricular systolic and diastolic function were assessed by conventional and tissue Doppler echocardiography. Right ventricular global function was assessed by myocardial performance index (MPI). There were no differences in chamber diameter and standard Doppler parameters between the two groups, but tissue Doppler parameters were lower (Ea and Ea/Aa), and isovolumetric relaxation time (IVRT) and MPI were significantly higher in the patient group. Furthermore, the grade of hepatosteatosis was positively correlated with right ventricular isovolumetric relaxation time and MPI ($r=0.295$, $p=0.03$, $r=0.641$, $p<0.001$, respectively).

In addition to conventional echocardiographic

parameters, new techniques such as speckle-tracking echocardiography can detect subclinical right ventricular dysfunction. Sunbul *et al.*[25] showed that right ventricular dysfunction is common in patients with non-alcoholic fatty liver disease, although conventional echocardiographic parameters such as TAPSE (tricuspid annular plane systolic excursion) have normal value, right ventricular global longitudinal strain (GLS) is decreased in about half of patients with non-alcoholic fatty liver disease. In addition, the NASH score is an independent predictor of right ventricular dysfunction in patients with non-alcoholic fatty liver disease. However, the possibility that liver fibrosis may be a consequence rather than a cause of right ventricular dysfunction cannot be excluded.

Biological markers of myocardial injury and dysfunction in patients with NAFLD

Troponins (T and I) and NT-proBNP (N-terminal portion of the natriuretic peptide) are biomarkers with established value for the identification of myocardial damage and cardiac dysfunction. Troponins are widely used in the acute care system to diagnose myocardial infarction. However, recent studies have shown that low levels of cardiac troponins measured using new high-sensitivity tests (hs-cTnT and hsCTnI) may reflect chronic subclinical myocardial injury, and it has been recently proved that they improve the prediction of cardiovascular morbidity and mortality in subjects with stable coronary disease, but also in patients with no clinically evident cardiovascular disease. NT-proBNP, secreted by ventricular myocytes in response to increased parietal stress and ventricular filling pressure, is also a biomarker of subclinical ventricular dysfunction, being associated with cardiovascular mortality.

These markers of myocardial injury and dysfunction have been studied in liver diseases, especially in liver cirrhosis[26]. There is one study which analyzed NAFLD patients. Lazo and colleagues[27] in a cross-sectional analysis of 8668 participants from the Atherosclerosis Risk in the Communities (ARIC) Study without clinical evidence of cardiovascular disease found that higher levels of ALT, AST and GGT were significantly and independently associated with detectable (hs-cTnT > 3 ng/L) and elevated (hs-cTnT ≥ 14 ng/L) concentrations of Troponin T. Contrary to expectations, alanine transaminase (ALT) and aspartate transaminase (AST) levels were inversely correlated with NT-proBNP, thus suggesting reduced cardiac impairment among patients with non-alcoholic fatty liver disease. The authors proposed an alternative plausible mechanism to explain this reverse association: the direct metabolic effects of BNP comprising an increase of mitochondrial biogenesis, lipolysis of adipose tissue, and the phenomenon of "browning" of fat cells. It should be noted that in this study NAFLD diagnosis was not based on imaging, but on liver enzymes as surrogate markers.

CONCLUSIONS

Through complex interrelations with insulin resistance, lipid metabolism, proinflammatory, thrombogenic and vasoactive molecules, non-alcoholic fatty liver disease could be associated with left or right ventricular dysfunction. Non-invasive imaging techniques such as echocardiography or magnetic resonance imaging, as well as biomarkers are useful in detecting early systolic or diastolic cardiac dysfunction in these patients, supporting prompt therapeutic measures.

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