Abstract
Non-alcoholic fatty liver disease (NAFLD) is one of the most common forms of chronic liver disease in the Western world. There is a close association with the metabolic syndrome and NAFLD is considered to be the hepatic manifestation of the metabolic syndrome. The components of the metabolic syndrome include hypertension, obesity and insulin resistance which are well established cardiovascular risk factors. The mortality rate of NAFLD patients from myocardial infarction is higher than that in the general United States population and there is also an increased risk of non-fatal cardiovascular events. This article reviews the cardiovascular complications associated with NAFLD. In order to provide comprehensive care of NAFLD patients, physicians need to be aware of, and search for, the cardiac morbidity associated with NAFLD.

KEYWORDS: Cardiovascular; Diastolic dysfunction; Sleep apnea; Palatin-like phospholipase domain containing 3 gene; Non-alcoholic fatty liver disease

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome. Due to the overlapping cardiovascular risk factors in the metabolic syndrome, there are cardiovascular consequences linked to the presence of NAFLD in a patient. We review these complications and also a less well appreciated complication of diastolic dysfunction that is intimately associated with NAFLD. Physicians looking after NAFLD patients need to be aware of these complications and actively search for and treat them.

INTRODUCTION
Non-alcoholic fatty liver disease (NAFLD) is now considered to be one of the most common forms of chronic liver disease in the Western world. NAFLD refers to a clinicopathologic spectrum of conditions ranging from simple steatosis (simple fatty liver) to non-alcoholic steatohepatitis (NASH), involving inflammation and some evidence of liver cell damage, and in some cases, cirrhosis. It occurs in an estimated 25% to 30% of the United States general population, whereas its potentially progressive form, NASH, is reported in 2%-3% of the population[1].
**Table 1 Definitions of the metabolic syndrome**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>NCEP ATP III</th>
<th>IDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolutely required</td>
<td>None</td>
<td>Central obesity (waist circumference) $\geq 94$ cm in males or $\geq 80$ cm in females European origin $\geq 90$ cm (men), $\geq 80$ cm in females</td>
</tr>
<tr>
<td>Obesity</td>
<td>Waist circumference $&gt; 40$ inches in males, or $&gt; 35$ inches in females</td>
<td>Central obesity plus two of the four criteria below</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>$\geq 100$ mg/dL or treated for DM</td>
<td>Fasting glucose $\geq 100$ mg/dL</td>
</tr>
<tr>
<td>TG</td>
<td>$\geq 150$ mg/dL or treated for dyslipidemia</td>
<td>$\geq 150$ mg/dL or treated for dyslipidemia</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>$&lt; 40$ mg/dL in males, or $&lt; 50$ mg/dL in females</td>
<td>HDL cholesterol $&lt; 40$ mg/dL in males, or $&lt; 50$ mg/dL in females</td>
</tr>
<tr>
<td>Hypertension</td>
<td>$&gt; 130$ mmHg systolic or $&gt; 85$ mmHg diastolic or treated for HTN</td>
<td>$&gt; 130$ mmHg systolic or $&gt; 85$ mmHg diastolic or treated for HTN</td>
</tr>
</tbody>
</table>

NCEP ATP III: National cholesterol and education program-adult treatment panel III; IDF: International diabetes federation; TG: Triglycerides; HDL: High density lipoprotein; HTN: Hypertension.

Natural history studies of NAFLD showed that 1%-5% of patients with simple steatosis developed cirrhosis\(^1,2\), while patients with NASH showed pathological progression of fibrosis in 15%-39% within 10 years\(^3,4\). NASH can potentially progress to cirrhosis and its complications including decompensated liver disease and hepatocellular carcinoma. The mortality rate of NAFLD patients in the community was higher than that in the general ultrasound (US) population\(^5\). Death occurred ranging from 13% to 45% with mean follow up of 8-11 years and coronary artery disease (CAD) was the leading cause of death (25%-28% of mortality)\(^5,6\).

It is the purpose of this article to review the cardiovascular consequences of NAFLD and to suggest a diagnostic approach.

**GENETICS**

Advances in genome analysis, including the development of informative genetic markers, improved physical mapping methods and improvements in high throughput genotyping technologies, have contributed to the understanding of the pathogenesis of complex diseases. The Dallas Heart Study carried out a genome-wide association study of liver fat content in 2111 people from different ancestry groups\(^7\). They found a connection between NAFLD evaluated by proton magnetic resonance spectroscopy, with the rs738409 G allele of the palatin-like phospholipase domain containing 3 gene (PNPLA3), also known as adiponutrin. The sequence variation is a C > G single nucleotide change which encodes for the 148 isoleucine to methionine protein variant (II48M) of PNPLA3.

The PNPLA3 GG genotype has been associated with a higher severity of carotid atherosclerosis in young patients with NAFLD\(^8\). However, recently a variant of the TM6SF2 gene (E167K0) has been shown to be linked to fatty liver due to reduced secretion of very low-density lipoprotein lipoproteins. This variant has also been shown to provide protection against cardiovascular disease\(^9\).

This suggests that there is likely to be an effect of multiple genetic polymorphisms in the development of NAFLD, which require further study in diverse populations.

**METABOLIC SYNDROME**

The metabolic syndrome (MS) is defined by differing criteria in the United States, Europe and Asia (Table 1). The essential components of the MS include visceral obesity, insulin resistance, dyslipidemia and hypertension. Along with the epidemic of obesity, the prevalence of MS is increasing worldwide, both in the developing and developed countries. MS is associated with a risk of cardiovascular disease and is a common early abnormality in the development of type 2 diabetes.

In patients with NAFLD, metabolic abnormalities have been reported in 33% to 100% of cases, depending on study methods and selection criteria of NAFLD patients\(^10,11\). MS components including central obesity, hypertension, hypertriglyceridemia, decreased high density lipoprotein cholesterol and impaired glucose test or type 2 diabetes mellitus are commonly found in NAFLD\(^10,12\). Diabetes and hypertension are present up to 15-fold in patients with NASH compared to those with steatosis alone independent of age or body mass index (BMI)\(^13\).

Thus the metabolic syndrome is strongly linked to NAFLD. Patients presenting with NAFLD need to be examined for the presence of the components of the metabolic syndrome and their complications.

**NAFLD AND CARDIOVASCULAR ABNORMALITIES**

Since the MS is linked to many well recognized cardiovascular risk factors, it is to be expected that there will be a high prevalence of cardiovascular morbidity in patients with NAFLD (Figure 1). Retrospective studies of cohorts of NAFLD patients have shown myocardial...
infarction to be the cause of death in 25% compared to 13% in patients with other liver diseases\textsuperscript{[5]}. Another study with biopsy-proven NAFLD found an increased mortality in patients with NASH but not with simple steatosis and that this was primarily due to cardiovascular disease and not liver-related causes\textsuperscript{[11]}. Similar results have been reported from other groups\textsuperscript{[6,11,14]}. These studies had small cohort sizes. In a study with a larger cohort size, cardiovascular disease remained the number one cause of death but there was no difference detected between those patients with NASH or simple steatosis.

Prospective studies are usually considered as of higher quality than retrospective studies. Several prospective studies have shown an increased risk of either non-fatal cardiovascular disease events or mortality\textsuperscript{[15-22]}.

Coronary artery disease in asymptomatic people can be detected by computed tomography. Several studies have found a connection between coronary artery calcification and NAFLD\textsuperscript{[23-27]}, but 2 studies did not find a significant association\textsuperscript{[18,29]}.

Patients with NAFLD have a higher prevalence of CAD independent of other risk factors, including glycermic control and MS components\textsuperscript{[10,20]}. The incidence of new CAD events in non-cirrhotic patients with NAFLD varied from 2\% to 11\% with the overall mortality of 12\%-13\%\textsuperscript{[6,10,16,19,30,31]}. The CAD related mortality ranged from 1\% to 3\% in NAFLD\textsuperscript{[19,31]}, and from 12\% to 16\% in patients with NASH\textsuperscript{[6,32]}.

The mechanism for the increase in atherogenesis in NAFLD is multi-factorial including genetic predisposition, insulin resistance and atherogenic dyslipidemia, oxidative stress, chronic inflammation, reduced levels of adiponectin, and altered production of pro and anticoagulant factors\textsuperscript{[33]}.

### NAFLD AND LEFT VENTRICULAR FUNCTION

Our group was the first to report an association between NAFLD and impaired left ventricular diastolic function\textsuperscript{[34]}. We examined 38 patients with NAFLD diagnosed by ultrasound less than 55 years of age, with a normal exercise test and no diabetes or hypertension. They were compared to an age and gender matched control group. The NAFLD patients had altered left ventricular (LV) geometry and early features of LV diastolic dysfunction. On multivariate analysis only early diastolic velocity, assessed on tissue Doppler imaging was found to be associated with NAFLD. This has also been found by other centers\textsuperscript{[35-41]}. Furthermore this may be an early consequence of NAFLD.

Fallu et al\textsuperscript{[35]}
reported diastolic dysfunction in a group of 48 never-treated hypertensive patients with ultrasound diagnosed NAFLD compared to 38 with no NAFLD, who just had LV hypertrophy (LVH). This was independently linked to NAFLD and HOMA on multivariate analysis.

Fotbolcu et al\textsuperscript{[36]}
examined 35 NAFLD patients by tissue Doppler imaging that did not have either hypertension or diabetes mellitus. They found a lower early diastolic velocity and also a higher systolic velocity. Another group has found a higher incidence of LVH in hypertensive NAFLD patients (diagnosed by ultrasound) compared to the hypertensive patients without NAFLD\textsuperscript{[42]}. The finding of early diastolic dysfunction in patients with NAFLD has also been found in a study comparing 38 diabetic patients with US diagnosed NAFLD to 18 diabetic patients without NAFLD. The patients with NAFLD had early features of diastolic dysfunction on tissue Doppler echocardiography, which was significant after adjusting for hypertension and other cardiometabolic factors\textsuperscript{[37]}.

Furthermore, in obese adolescents, the presence of NAFLD has been shown to be an early marker of cardiac dysfunction\textsuperscript{[43]}. A larger study of 180 obese adolescents compared to 68 healthy controls employing pulsed-wave Doppler echocardiography and pulsed-wave tissue Doppler imaging showed, the NAFLD group had normal LV systolic function, impaired diastolic function, and altered global systolic and diastolic myocardial performance compared to 68 healthy controls\textsuperscript{[44]}.

Another study on obese children and adolescents with NAFLD included 108 obese children, 54 with hepatic fat fraction over 5\% on magnetic resonance imaging and 18 lean and healthy subjects. Forty one of the NAFLD patients also underwent liver biopsy and 26...
**Table 2  Non-alcoholic fatty liver disease and cardiac structure and function**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goland et al(^{[40]})</td>
<td>38 patients with NAFLD, &lt; 55 years of age and normal exercise test, were compared with an age and sex-matched control group TT echo study including TDI</td>
<td>Patients with NAFLD have mildly altered LV geometry (increased thickness of the intraventricular septum, posterior wall, and larger LV mass), and early features of left ventricular diastolic dysfunction. Early diastolic velocity on TDI is the only index identifying the patients with NAFLD and metabolic syndrome. Patients with NAFLD had similar prevalence of LHV compared to patients without NAFLD, but a higher prevalence of diastolic dysfunction.</td>
</tr>
<tr>
<td>Fallo et al(^{[41]})</td>
<td>Left ventricular morphology/function, metabolic parameters and NAFLD in 86 never-treated essential hypertensive patients subdivided into two subgroups according to the presence (n = 48) or absence (n = 38) of NAFLD at ultrasonography</td>
<td>Patients with NAFLD have impaired LV systolic and diastolic function and lower E’ (early diastolic velocity on TDI) values were lower in NAFLD. TDI systolic velocity (S' on TDI) values were lower in NAFLD.</td>
</tr>
<tr>
<td>Fotbolcu et al(^{[34]})</td>
<td>35 non-diabetic, normotensive NAFLD patients and 30 controls. TT echo and TDI performed</td>
<td>Patients with NAFLD have impaired LV systolic and diastolic function and lower E’ (early diastolic velocity on TDI) values were lower in NAFLD. Early features of LV diastolic dysfunction may be detected in patients with type 2 diabetes and NAFLD.</td>
</tr>
<tr>
<td>Benapace et al(^{[35]})</td>
<td>50 patients with type 2 DM, US diagnosed NAFLD. 32 patients (64%) with NAFLD, compared to other 18 patients. TT echo and TDI performed</td>
<td>Subjects with both NAFLD and MetS had a higher E/Ea ratio and baPWV, and lower TDI Ea velocity (P &lt; 0.001). Subjects with either NAFLD or MetS also showed significant differences in TDI Ea velocity and baPWV (P &lt; 0.05). No significant differences of CIMT values.</td>
</tr>
<tr>
<td>Kim et al(^{[34]})</td>
<td>1886 participants without CVS disease. Stratified by the presence or absence of CT-diagnosed NAFLD, MetS. Assessed by TDI, carotid ultrasound and baPW</td>
<td>The heart rate recovery index is deteriorated in patients with NAFLD.</td>
</tr>
<tr>
<td>Ozveren et al(^{[36]})</td>
<td>59 patients with NAFLD and 22 healthy subjects as controls. Basal electrocardiography, echocardiography, and treadmill exercise testing were performed on all patients and controls</td>
<td>The heart rate recovery index is deteriorated in patients with NAFLD.</td>
</tr>
<tr>
<td>Sert et al(^{[37]})</td>
<td>80 obese adolescents and 37 lean subjects. NAFLD based on elevated transaminases</td>
<td>Diastolic posterior-wall thickness, left ventricular mass, relative wall thickness, left atrial volume, as well as ejection fraction, lower lateral TDI e’, E/A ratio and epicardial fat linked to severe liver fibrosis.</td>
</tr>
<tr>
<td>Mantovani et al(^{[38]})</td>
<td>116 consecutive patients with hypertension and type 2 diabetes. US diagnosed NAFLD, LVH diagnosed by TT echo</td>
<td>LVH higher among diabetic patients with NAFLD. NAFLD is associated with LVH independently of classical CVS risk factors. The disposition index ([β-cell function] and insulin sensitivity index were approximately 45% and about 70% lower, respectively, and whole body insulin resistance, was about 60% greater, in obese than in lean subjects, and about 30% and about 50% lower and about 150% greater, respectively, in obese subjects with NAFLD than those without NAFLD (P &lt; 0.05 for all).</td>
</tr>
<tr>
<td>Singh et al(^{[39]})</td>
<td>IHTG content (magnetic resonance spectroscopy), insulin sensitivity and β-cell function, and left ventricular function</td>
<td>Asymptomatic obese children with NAFLD exhibit features of early LV diastolic and systolic dysfunction, and are more severe in those with NASH.</td>
</tr>
<tr>
<td>Petta et al(^{[42]})</td>
<td>Anthropometric, biochemical and metabolic of 147 consecutive biopsy-proven NAFLD cases</td>
<td>Diabetic posterior-wall thickness, left ventricular mass, relative wall thickness, left atrial volume, as well as ejection fraction, lower lateral TDI e’, E/A ratio and epicardial fat linked to severe liver fibrosis.</td>
</tr>
<tr>
<td>Pacifico et al(^{[43]})</td>
<td>TDI, and MRI for measurement of HFF and abdominal fat mass distribution in 108 obese children, 54 with (HFF &gt; 5%) and 54 without NAFLD, and 18 lean healthy subjects. 41 of the children with NAFLD underwent liver biopsy</td>
<td>Asymptomatic obese children with NAFLD exhibit features of early LV diastolic and systolic dysfunction, and are more severe in those with NASH.</td>
</tr>
<tr>
<td>Kocabay et al(^{[44]})</td>
<td>55 biopsy-proven NAFLD patients and 21 healthy subjects. Categorized as simple steatosis, borderline NASH, definitive NASH.</td>
<td>LA-Res, LA-Pump and LA-SR(A) were lower in the NAFLD control. LA-Res and LA-pump significantly lower in NAFLD subgroups. There were significant differences in LA-SR(A) between healthy controls compared with simple steatosis and borderline.</td>
</tr>
<tr>
<td>Karabay et al(^{[45]})</td>
<td>55 NAFLD patients and 21 healthy controls. Biopsy-proven NAFLD. Categorized as simple steatosis, borderline NASH, definitive NASH. All had echocardiography</td>
<td>Patients with NAFLD and its subgroups have evidence of subclinical myocardial dysfunction in relation to the presence of insulin resistance. NAFLD had borderline significant association with higher end-diastolic thicknesses of left-ventricle edPW and right-ventricle wall in newly diagnosed patients with fatty liver, fat accumulated in the epicardial area and despite normal LV morphological features, systolic and diastolic functions, there was abnormal LV energy metabolism.</td>
</tr>
<tr>
<td>Gianotti et al(^{[46]})</td>
<td>171 subjects aged &gt; than 65 yr. US diagnosed NAFLD and TT echo</td>
<td>No significant differences of CIMT values.</td>
</tr>
<tr>
<td>Perseghin et al(^{[47]})</td>
<td>21 nondiabetic men with or without fatty liver matched anthropometrically features assessed by (1) cardiac MRI; (2) cardiac P-MRS; and (3) hepatic H-MRS to assess quantitatively the IHTG content</td>
<td>No significant differences of CIMT values.</td>
</tr>
<tr>
<td>Hallsworth et al(^{[48]})</td>
<td>19 adults with NAFLD were age-, sex-, and BMI-matched to healthy controls. Cardiac structure and function assessed by high-resolution cardiac MRI. High-energy phosphate metabolism was assessed using P-MRS</td>
<td>Early diastolic velocity on TDI is the only index identifying the patients with NAFLD and metabolic syndrome. Patients with NAFLD had similar prevalence of LHV compared to patients without NAFLD, but a higher prevalence of diastolic dysfunction.</td>
</tr>
</tbody>
</table>

NAFLD: Non-alcoholic fatty liver disease; TDI: Tissue Doppler imaging; DM: Diabetes mellitus; CT: Computed tomography; MetS: Metabolic syndrome; baPWV: Brachial-ankle pulse wave velocity; BMI: Body mass index; IHTG: Intrahepatic triglyceride; HFF: Hepatic fat fraction; NASH: Non-alcoholic steatohepatitis; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; CIMT: Carotid intima-media thickness; TT: Transthoracic; US: Ultrasound; CVS: Cardiovascular; LV: Left ventricular; LHV: Left ventricular hypertrophy.
were shown to have NASH. Diastolic dysfunction was again found in the patients with NAFLD and also the Tei index which reflects combined systolic and diastolic LV dysfunction was significantly higher in those children with NAFLD. Those patients with biopsy-proven NASH had a significantly lower e’ velocity and higher E-to-e’ and Tei index than those with only NAFLD.

The use of 2D speckle tracking echocardiography to determine left atrial deformation parameters was not found to be helpful in a recent study on 55 NAFLD patients and 21 controls from Turkey. These studies are summarized in Table 2.

A finding of NAFLD on ultrasound in the population aged more than 65 years of age may be valuable to alert for the coexistence of multiple cardiovascular risk factors and changes in cardiac morphology and diastolic dysfunction.

In newly diagnosed individuals with fatty liver, both systolic and diastolic LV functions were normal but there was abnormal LV energy metabolism. A cohort of 19 NAFLD adults compared to age, gender and BMI-matched controls were shown to have a thicker left ventricular wall in both systole and diastole as well as decreased longitudinal shortening than those without fatty liver.

One of the consequences of diastolic dysfunction is atrial fibrillation and NAFLD has been shown to have an increased risk (OR = 4.49) of atrial fibrillation which was independent of age, gender, hypertension, and left ventricular hypertrophy and pr interval.

Thus adults with NAFLD have changes in cardiac structure and function that may predate overt cardiac artery disease. We suggest that NAFLD patients undergo a routine transthoracic echocardiogram examination as part of their assessment.

**NAFLD AND OBSTRUCTIVE SLEEP APNEA SYNDROME**

Obstructive sleep apnea (OSAS) syndrome is a common condition with prevalence estimates of 2% to 4% in the general population. Amongst obese patients the prevalence is as high as 35%. OSAS is accompanied by proinflammatory cytokine production, platelet aggregation, endothelial dysfunction and metabolic dysregulation which can increase the risk of cardiovascular disease.

OSA has been shown to be a risk factor for insulin resistance and carotid intima media thickening, and in addition there are reports of ischemic hepatitis accompanying severe OSAS.

A study of 163 non-drinking OSAS patients found that the more severe the OSAS, sufferers had more insulin resistance and more steatosis and fibrosis. This was independent of weight. It has also been shown that continuous positive airway pressure (CPAP) therapy for OSAS improves cardiac function, decreases cardiovascular risk and improves insulin resistance.

Furthermore, OSAS is linked to NAFLD. This association is more than just a convergence of risk factors. There is evidence for a derangement of the immune system in such patients resulting in a low-grade chronic inflammation. Uncontrolled treatment studies of adults and children with OSAS receiving CPAP treatment and tonsillectomy have shown a decrease in liver enzymes.

In addition a proportion of NAFLD patients without severe obesity are at risk for OSAS and this is associated with the severity of the liver damage independently of BMI and other co-factors.

Thus the finding of NFALD should prompt physicians to inquire regarding symptoms of OSAS. In addition patients with OSAS need to be assessed for the presence of NAFLD.

**CONCLUSION**

NAFLD is considered to be the hepatic manifestation of the metabolic syndrome, although there are cases that do not fulfill the metabolic syndrome criteria. Patients with NAFLD have an increased risk for cardiovascular disease, which is in part due to the overlapping of the risk factors of the metabolic syndrome with the risk factors for cardiovascular disease. In addition, however, there are changes in left ventricular function both systolic and diastolic, endothelial function, arterial stiffness and a link with sleep apnea syndrome.

Physicians treating NAFLD patients need to be aware of these cardiovascular complications and actively search for them in order to provide the comprehensive care that patients deserve. We suggest that all patients with NAFLD have an echocardiogram performed in order to detect LVH, systolic and diastolic dysfunction which may increase the risk for cardiac mortality. The benefit of treatment of the metabolic syndrome and associated NAFLD likely extends to many aspects of the cardiovascular system as well. Thus an integrative approach considering all the possible organ complications of the metabolic syndrome is necessary for NAFLD patients.

**REFERENCES**


35 Fallo F, Dalla Pozza A, Sonino N, Lupia M, Tona F, Federspil G.


P- Reviewer: Dirchwolf M, Garcia-Martinez R, Maroni L, Peltee A, Souza-Mello V
S- Editor: Qi Y
L- Editor: A
E- Editor: Liu SQ