

The Interactions of Nonalcoholic Fatty Liver Disease and Cardiovascular Diseases

Hugo Perazzo, MD^{a,b}, Thierry Poynard, MD, PhD^{a,b,c},
Jean-François Dufour, MD^{d,e,*}

KEYWORDS

- Nonalcoholic fatty liver disease • Liver fibrosis • Cardiovascular disease
- Atherosclerosis • Insulin resistance

KEY POINTS

- Patients with nonalcoholic fatty liver disease present higher overall mortality, and cardiovascular disease is one of the leading causes of death.
- Individuals with fatty liver presented higher carotid and coronary plaques measured by surrogate markers of atherosclerosis.
- NAFLD is associated with new onset of cardiovascular events independently of confounding factors.
- A complex interaction among metabolic factors, adipose tissue lipolysis, insulin resistance, and excessive free fatty acids results in an inflammatory state, hypercoagulability, and endothelial dysfunction, which might explain the association between NAFLD and cardiovascular disease.

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^a Hepatology Department, Liver Center, Groupe Hospitalier Pitié-Salpêtrière (GHPS), Assistance Publique Hôpitaux de Paris (APHP), 47-83, Boulevard de l'Hôpital, Paris 75013, France; ^b Pierre et Marie Curie University (Paris 6), Inserm UMR_S 938, Paris, France; ^c Institute of Cardiometabolism and Nutrition (ICAN), Paris, France; ^d University Clinic for Visceral Surgery and Medicine, University of Bern, Inselspital, Freiburgstrasse, Bern 3010, Switzerland; ^e Hepatology, Department of Clinical Research, University of Bern, Bern, Switzerland

* Corresponding author. University Clinic for Visceral Surgery and Medicine, University of Bern, Inselspital, Freiburgstrasse, Bern 3010, Switzerland.

E-mail address: jean-francois.dufour@ikp.unibe.ch

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Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases worldwide.¹ This liver disease is characterized by presence of fat accumulation in at least 5% of hepatocytes without others causes of chronic liver disease, including alcohol-induced and drug-induced liver disease, autoimmune or viral hepatitis, and cholestatic or genetic liver disease.²

NAFLD presents a large clinical spectrum, ranging from simple steatosis to coexistent hepatocyte injury, nonalcoholic steatohepatitis (NASH), associated with fibrosis and cirrhosis and its complications.^{3,4} Simple steatosis usually presents a benign course; however, patients who progress to NASH may develop cirrhosis and suffer from liver-related mortality.^{5,6}

Patients with NAFLD usually present metabolic syndrome and its components, common risk factors for cardiovascular disease (CVD).⁷ More recently, some studies have reported a close relationship between NAFLD and increased atherosclerosis.⁸ This review focuses on the association between NAFLD and CVD, discussing the data linking these major diseases and the likely mechanisms underlying this interaction.

NAFLD AND SURROGATE MARKERS OF ATHEROSCLEROSIS

NAFLD might play an important role in the atherosclerosis complex process, reinforcing the relationship between fatty liver and CVD.⁹ Several studies have reported the association of NAFLD with surrogate markers of atherosclerosis as presence of carotid and coronary plaques and cardiac dysfunction.

Cardiac multislice computed tomography accurately assesses coronary plaques.¹⁰ This method calculates the coronary artery calcium (CAC) score, which reflects the underlying total plaque burden that accurately correlates to increased risk of coronary events.^{11,12} Individuals with NAFLD presented higher calcified and noncalcified plaques compared with matched controls. In addition, the presence of fatty liver was predictive of coronary artery disease (CAD) after adjustment for confounding factors.¹³ Studies have reported a strong relationship between NAFLD and CAC score.^{14,15} Increased CAC score was significantly associated with NAFLD independently of metabolic factors, including visceral adiposity.¹⁴ Furthermore, a study reported a strong association between NAFLD and presence of vulnerable plaques, increasing the risk of severe CV outcomes.¹⁶

Measurement of carotid intima-media thickness (CIMT) and plaque by ultrasonography is a validated method for diagnosing early atherosclerosis and prediction of CVD.^{17,18} Several studies have associated carotid with NAFLD independently of components of the metabolic syndrome.^{19–22} A systematic review involving 3497 individuals (7 studies) strongly correlated CIMT with fatty liver, showing an increase of up to 13% of CIMT and higher prevalence of plaques in patient with NAFLD.²³ Furthermore, a study reported that severity of histologic features seems to correlates with CIMT, agreeing with the hypothesis that patients with NASH carry a higher risk of CVD than individuals with simple steatosis.²⁴

A few studies have reported the relationship between NAFLD and cardiac dysfunction. Increased cardiac left ventricular (LV) mass index and diastolic dysfunction were associated with NAFLD.^{25,26} Hallsworth and colleagues²⁷ described significant changes in cardiac structure and function in NAFLD patients with NAFLD compared with an age-matched, sex-matched, and body mass index (BMI)-matched healthy population. In this study, patients with NAFLD presented thicker LV walls at systole and diastole as well as higher peak whole wall and peak endocardial circumferential strain. Fallo and colleagues²⁸ also reported a positive correlation between diastolic cardiac dysfunction and severity of fatty liver disease. Yilmaz and colleagues²⁹ reported a reduced coronary flow reserve, measured by echocardiography, in patients

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