The Role of Nonalcoholic Fatty Liver Disease on Cardiovascular Manifestations and Outcomes

Alexander J. Kovalic, MD[a], Sanjaya K. Satapathy, MBBS, MD, DM[b,c,*]

KEYWORDS

• Nonalcoholic fatty liver disease • NAFLD • Cardiovascular disease • Atherosclerosis
• Cardiac dysfunction • Conduction abnormalities • Atrial fibrillation
• Thromboembolic risk • Cardiovascular mortality

KEY POINTS

- There have been numerous studies confirming the association between nonalcoholic fatty liver disease (NAFLD) and atherosclerosis, cardiac dysfunction, conduction abnormalities, atrial fibrillation, and thromboembolic risk.
- NAFLD is associated with increased CV events and mortality.
- The key pathogenetic link between NAFLD and cardiovascular events appears to be related insulin resistance.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is rapidly becoming one of the most common forms of liver disease worldwide.[1] Given the concomitant increase in obesity and the metabolic syndrome, the number of patients with this disease will only increase in the

Author Contribution: A.J. Kovalic was responsible for the initial draft of the article, critical revision of the article, approval of the article S.K. Satapathy was responsible for the concept/design, drafting the article, critical revision of the article, approval of the article.
The authors have nothing to disclose.
[a] Department of Internal Medicine, Wake Forest Baptist Medical Center, Medical Center Boulevard, Winston-Salem, NC 27103, USA; [b] Transplant Hepatology, Methodist University Hospital Transplant Institute, University of Tennessee Health Science Center, 1211 Union Avenue, Memphis, TN 38104, USA; [c] Division of Surgery, Methodist University Hospital Transplant Institute, University of Tennessee Health Science Center, 1211 Union Avenue, Memphis, TN 38104, USA
* Corresponding author. Methodist University Hospital Transplant Institute, University of Tennessee Health Sciences Center, 1211 Union Avenue, Suite #340, Memphis, TN 38104, USA.
E-mail address: ssatat@uthsc.edu

Clin Liver Dis ■ (2017) ■–■
http://dx.doi.org/10.1016/j.cld.2017.08.011 liver.theclinics.com

years to come. It has been postulated that a leading cause of mortality among patients with NAFLD is due to cardiovascular (CV) disease, rather than complications directly from liver disease. As more effective and targeted treatment strategies emerge, not only will the size of the NAFLD patient population increase, but also their longevity. Therefore, the incidence of CV sequelae of this disease process will undoubtedly be increasing.

LITERATURE REVIEW

A comprehensive PubMed search was performed, which queried English articles among human patients through February 1, 2017. This literature search included patients with NAFLD, as defined by either "NAFLD," "NAFLD (MeSH Terms)," or "nonalcoholic fatty liver disease," and cross-referenced with other concomitant pathologies that will be listed here in detail. First, atherosclerosis was queried by searching for the terms "atherosclerosis," "coronary artery disease (CAD)," "carotid artery disease," "carotid artery stenosis," "aortic aneurysm," "abdominal aortic aneurysm (AAA)," "endothelial dysfunction," "intima media thickness," "peripheral vascular disease (PVD)," and "peripheral artery disease (PAD)." Upon searching the primary literature, cardiac dysfunction was defined as "cardiac dysfunction," "heart failure," "diastolic dysfunction," "diastolic heart failure," "heart failure with preserved ejection fraction (HFpEF)," and "left ventricular hypertrophy (LVH)." To assess thromboembolic risk, articles were queried for patients with NAFLD with "thromboembolism," "venothromboembolism (VTE)," "deep venous thrombosis (DVT)," or "pulmonary embolism (PE)." Most important, subjects with NAFLD were evaluated on their effect of CV events and mortality, as defined by "myocardial infarction (MI)," "acute coronary syndrome (ACS)," "cerebrovascular accident (CVA)," "transient ischemic attack (TIA)," or "stroke." The endpoint of mortality was assessed using the terms "mortality," "death," "cardiac arrest," or "cardiopulmonary arrest."

ATHEROSCLEROSIS

There are a litany of studies linking NAFLD to atherosclerosis. It is imperative to tease out the influence of NAFLD as an independent risk factor. **Table 1** outlines the current studies with the largest impact on the connection between these two entities.

Earlier systematic reviews provided a comprehensive outlook on studies, noting this association of NAFLD with atherosclerosis. The two reviews listed herein used a large sample size across a multitude of studies and ethnicities. In the review by Sookoian and colleagues,[2] NAFLD was correlated with carotid atherosclerosis. NAFLD was primarily established via ultrasound imaging, with 3 of the 7 studies implementing liver biopsy. In establishing the diagnosis of NAFLD, the liver biopsy remains the gold standard, not only for the detection of hepatic steatosis, but also to assess the presence of NASH. Although ultrasound imaging is a good, noninvasive tool to detect hepatic steatosis, its sensitivity is poor when the degree of hepatic steatosis is less than 30%.[3] Despite liver biopsy remaining the gold standard for the diagnosis of NAFLD, it too is limited by its invasiveness and potential sampling error. Nevertheless, 1 study in this review stratified their results based on liver histology and found that carotid atherosclerosis is more pronounced in cases of more severe NAFLD, such as NASH. The second systematic review by Oni and colleagues[4] validated this affiliation, not only between NAFLD and carotid atherosclerosis, but also coronary artery calcifications, endothelial dysfunction, and arterial stiffness. This systematic review implemented a large sample size including 27 different studies, but did not comment on the degree of atherosclerosis in relation to the