Nonalcoholic fatty liver disease represents a continuum of histopathologic and biochemical features, progressing from simple steatosis to a more marked inflammatory condition, termed nonalcoholic steatohepatitis, which can cause liver fibrosis. Basic scientists and clinicians alike are significantly invested in understanding mechanisms underlying the development of steatosis, as well as identifying triggers for the transition of simple steatosis to nonalcoholic steatohepatitis, which contributes significantly to liver-related morbidity. The presence of fatty liver disease in patients has been shown to increase the risk of cardiovascular disease. In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Ndumele et al identify an association between hepatic steatosis, as assessed by noninvasive abdominal ultrasound, and high-sensitivity C-reactive protein (hs-CRP). Importantly, this association was independent of and additive to obesity and metabolic syndrome. hs-CRP is an acute phase protein that is an indicator of systemic inflammation and is used clinically to predict adverse cardiovascular events. This observation strongly suggests that inflammation sits at the crossroads between fatty liver disease and cardiovascular disease, highlighting the need for increased scientific engagement across the fields of hepatology, gastroenterology, cardiology, and endocrinology to better investigate, prevent, and manage these interconnected diseases.

**See accompanying article on page 1927**

Is fatty liver disease a consequence of increased inflammation, or does inflammation increase hepatic steatosis? The studies of Ndumele et al provide an association between hepatic steatosis and elevated levels of hs-CRP, a protein produced predominately by the liver under conditions of inflammation. Hepatic steatosis may exaggerate the synthesis of hs-CRP or other mediators by the liver, thereby increasing systemic hs-CRP levels (see Figure). Numerous laboratory studies have shown that inflammation is not simply a consequence of steatosis, but rather its cause. For example, resident macrophages of the liver (ie, Kupffer cells) are required for hepatic steatosis in mice fed a high-fat diet. Moreover, chemokines such as monocyte chemoattractant protein-1 also contribute to hepatic steatosis. Thus, in patients with metabolic disease, the inflammatory response likely functions as an amplification loop contributing to hepatic steatosis and systemic change that increases the risk of cardiovascular disease (see Figure). The observation that hepatic steatosis is independently associated with increased hs-CRP levels suggests the possibility that fatty liver disease contributes to cardiovascular disease by promoting an inflammatory response. Studies determining the relative contribution of the fatty liver to the overall systemic inflammatory response in metabolic syndrome will be important. However, the fact that the liver is discretely engaged in a number of metabolic and endocrine processes may present challenges in interpreting the relative contribution of hepatic steatosis.

From a basic liver scientist perspective, the connection between fatty liver disease and cardiovascular disease, such as that presented by Ndumele et al, should shift the paradigm of model selection when studying hepatic steatosis in rodents. Wild-type C57Bl/6 mice fed a high-fat diet develop hepatic steatosis and are routinely used to evaluate the effects of genetic or pharmacological manipulation on the development of hepatic steatosis. In contrast, hypercholesterolemia and atherosclerosis are most commonly evaluated in mice on this background lacking either the low-density lipoprotein receptor (LDLr) or apolipoprotein E. Previous studies have found that fatty liver disease developed in conjunction with hypercholesterolemia and atherosclerosis in LDLr−/− mice and apolipoprotein E−/− mice, suggesting that these mouse models could be promising for studies evaluating interconnection between these disease processes. Of importance, hepatic inflammation is increased in LDLr−/− mice compared with wild-type C57Bl/6 mice, suggesting that the liver may be a more important contributor to systemic inflammation in these mice than was previously thought. Indeed, features of liver disease in LDLr−/− mice fed a high-fat diet resemble those observed in patients with nonalcoholic steatohepatitis. Insofar as LDLr−/− mice fed a high-fat diet also develop nonalcoholic fatty liver disease/nonalcoholic steatohepatitis, this mouse model provides ample opportunity to examine the connection between hepatic steatosis and systemic inflammation in the context of numerous features of metabolic syndrome. Identifying interventions that reduce both hepatic steatosis and atherosclerosis in mouse models could pinpoint interactions between these disease processes and lead to the development of new therapies.

In summary, the work of Ndumele et al is a call for collaboration between basic scientists and clinicians with expertise in fatty liver disease and cardiovascular disease. The association between fatty liver disease and hs-CRP levels strongly suggests that assessing, preventing, and treating...
nonalcoholic fatty liver disease development is one potential strategy to reduce systemic inflammation and the risk of adverse cardiovascular outcomes in patients with metabolic syndrome.

Disclosures

None.

References


KEY WORDS: cytokines ■ diabetes mellitus ■ obesity
Steatosis DeLIVERs High-Sensitivity C-Reactive Protein
James P. Luyendyk and Grace L. Guo

Arterioscler Thromb Vasc Biol. 2011;31:1714-1715
doi: 10.1161/ATVBAHA.111.230722
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/31/8/1714

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/