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EDITORIAL

The Liver and the Cardiovascular System: Two of a Kind?

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With an estimated prevalence in the adult population of roughly 25%, nonalcoholic fatty liver disease (NAFLD) has become the most prevalent chronic liver disease worldwide.[1] Being closely related to "metabolic" factors, most notably overweight/obesity, insulin resistance, and dyslipidemia, its prevalence and incidence continue to increase, given the epidemic of obesity and diabetes mellitus in societies with a so-called "western" lifestyle. The accumulation of liver fat associated with insulin resistance and overweight might be limited to isolated steatosis in the vast majority of cases, but 10% to 20% of patients develop signs of liver cell damage and inflammation, defining nonalcoholic steatohepatitis (NASH). The latter is considered more severe, as it drives liver-related complications (ie, progressive fibrosis that can lead to NASH-related cirrhosis and the complications hereof). Also, NAFLD is associated with an increased risk of developing a hepatocellular carcinoma, with probably the highest risk in cirrhotic patients but also occurring with less severe disease.[2]

See Article by Sinski et al.

Besides this obvious liver-related morbidity and mortality, NAFLD has also been associated with increased cardiovascular disease (CVD).[3] This issue is a matter of ongoing debate, as the relationship between NAFLD and CVD is not so easy to establish. The pathophysiological characteristics of NAFLD and NASH are in themselves not completely understood, but it has become clear that the liver disease is not just a simple consequence of metabolic overload, with adipose tissue dysfunction and insulin resistance as the main disease driving mechanisms.[4] The relationship between the liver and other organs is clearly multidirectional, and liver diseases, such as chronic hepatitis C and NAFLD, contribute to the development of disturbances of glycemic control and diabetes mellitus.[5]

We have gained many insights into how the chronically diseased liver might have an impact extrahepatically and by several mechanisms can contribute to the development of CVD. Briefly, by the release of inflammatory mediators and hepatokines, impact on the lipid profile, release of prothrombotic and angiogenic factors (Figure),[6] and indirectly by its effect on glycemic control, the diseased liver can contribute to the development of atherosclerotic lesions and other structural and functional abnormalities of the cardiovascular system.[3] Of note, functional and structural vascular alterations also contribute to the development of the liver disease, in early and advanced disease stages, illustrating again the multidirectional nature and complexity of the mechanisms involved.[7-9]

Although preclinical and mechanistic data have increased our understanding of the liver–cardiovascular system axis, proving unequivocally this independent role of NAFLD in the development of CVD, and hence putting it forward as a substantial risk factor for CVD, is challenging for many reasons. NAFLD and CVD share many risk factors, and this common ground will explain at least in part any association that is observed. Furthermore, although the diagnosis of NAFLD can be

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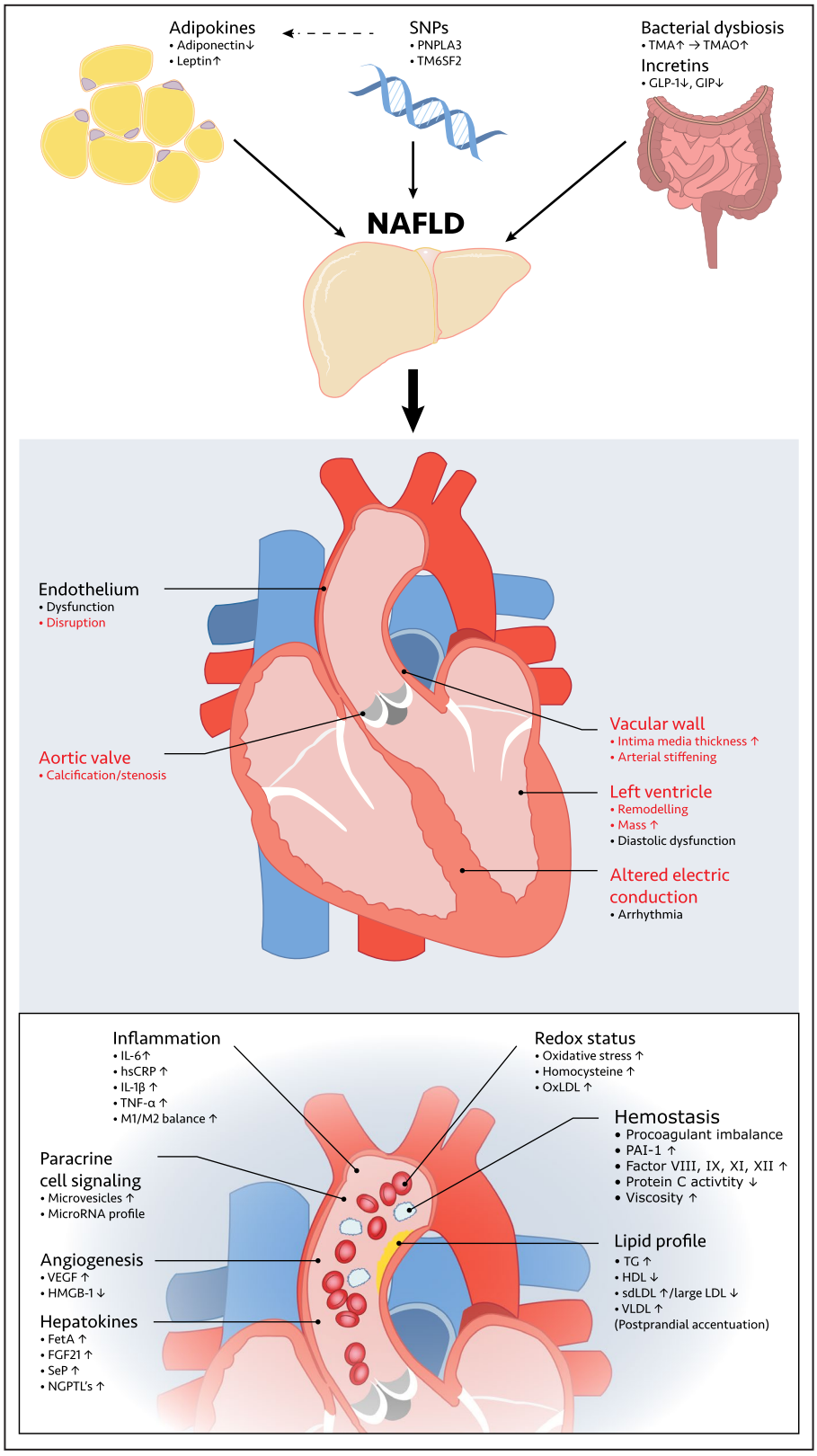

reliably done based on noninvasive techniques and imaging in particular, the assessment of its severity requires more sophisticated techniques. The diagnosis of NASH, of the severity of NASH in terms of the activity of hepatocyte damage and inflammation, and of the degree of steatosis still has the liver biopsy as gold standard, and no technique has been validated to replace the liver biopsy for the complete set of

Figure. Summary of potential pathophysiological mechanisms responsible for increased cardiovascular disease (CVD) in nonalcoholic fatty liver disease (NAFLD).
NAFLD drives multiple mechanisms that ultimately lead to CVD. These mechanisms are summarized in this figure. Genetic background, adipose tissue, and the gut all contribute, in part via the liver (direct effects also exist but are not within the scope of this review). Structural alterations of the cardiovascular system are marked in red. ANGPTL indicates angiopoietin-like protein; FetA, fetuin-A; FGF21, fibroblast growth factor 21; GIP, gastric inhibitory peptide; GLP-1, glucagon-like peptide 1; HDL, high-density lipoprotein; HMGB-1, high-mobility group box 1; hs-CRP, high-sensitivity C-reactive protein; IL-1β, interleukin 1β; IL-6, interleukin 6; LDL, low-density lipoprotein; M1/M2, macrophage phenotype 1/2 ratio; OxLDL, oxidized LDL; PAI-1, plasminogen activator inhibitor 1; PNPLA3, patatin-like phospholipase domain containing protein 3; sdLDL, small dense LDL; SeP, selenoprotein P; SNP, single-nucleotide polymorphism; TG, triglycerides; TM6SF2, transmembrane 6 superfamily member 2; TMA, trimethylamine; TMAO, trimethylamine-N-oxide; TNF-α, tumor necrosis factor α; VEGF, vascular endothelial growth factor; and VLDL, very-LDL. Reproduced from Francque et al[6] with permission. Copyright ©Elsevier, 2016.

information it provides. Liver biopsy remains an invasive procedure, and although complication rates are low in experienced hands, it does not come without risks and costs. As a consequence, series with liver biopsy as the most accurate assessment of the liver status may experience selection bias, as they tend to include patients with signs of more significant liver disease and a higher a priori likelihood of advanced disease, resulting in patient series skewed toward the more severe end of the liver disease spectrum. These series also mainly come from specialized referral centers. These series are also small compared with the number of patients required for CVD outcome studies. For the latter, patients must also be followed up for a sufficiently long time period, which increases the risk of confounding by several interventions and intercurrent events over the observed time period. Noninvasive assessments of steatosis by ultrasound are used for studies of more epidemiological design and size but lack an accurate assessment of the precise disease status. Variability in terms of the definition of the (composite) cardiovascular outcomes or events, or for subclinical cardiovascular lesions, the technique used, further hampers the interpretation of the data, the comparisons across studies, and the performance of meta-analysis.

Taking into account these methodological issues and related data quality, the current data point toward a clear and independent contribution of NAFLD to the development of CVD, with the strongest arguments for events related to accelerated atherosclerosis, but also cardiomyopathies and arrythmias are increased in patients with NAFLD, independently from the presence of potentially confounding cofactors that are risk factors for both diseases.[3] Especially, the more severe subtype of NASH seems to be more prone to the development of CVD events, with an odds ratio of 1.65 (95% CI, 1.26–2.13) for fatal and nonfatal CVD events in 34 045 adult individuals from 16 observational studies diagnosed with NAFLD, increasing to 2.58 (95% CI, 1.78–3.75) in patients with NASH.[10] Data on subclinical CVD, assessed with a variety of techniques, are more univocally supporting a causal link between presence and severity of NAFLD and the development of CVD, with more robust associations.

In the current issue of the *Journal of the American Heart Association* (*JAHA*), Sinski et al[11] provide interesting data that help to solve the issue. In patients with morbid obesity referred for bariatric surgery, they assessed, regardless of any a priori suspicion of both liver disease or CVD, by per-operative liver biopsy and by detailed cardiac ultrasound. Of course, the fact that they studied only morbidly obese patients undergoing bariatric surgery represents a selection bias and implies that the findings cannot be generalized to the overall population with NAFLD without further study. It is well known that obesity is a risk factor for NAFLD, but not all patients have NASH, and advanced fibrosis is rather uncommonly reported in more recent series.[12] Nevertheless, the risk of a more skewed patient group cannot be excluded. On the other hand, the approach is unbiased in the way that it systematically looks into the liver, regardless of any preset selection criterion. In this way, many sources of potential selection bias are avoided, and this is an important strength of the current study, as many findings in selected cohorts with NASH could not be reproduced in less selected cohorts and are hence of questionable relevance for the average patients with NAFLD.[13] And, this approach resulted in 58 of 171 patients with a normal liver, constituting, from a liver perspective, an internal control group. The latter is again a methodological strength of the study, as it avoids the need to compose an external control cohort that should then be matched for several potential confounders whilst at the same time disposing of all necessary data of the same quality. Furthermore, the prevalence of advanced liver fibrosis was low, resulting in an overall well-balanced representation of the different disease stages.

Although several differences between the groups (comparing mainly patients with a normal liver, patients with steatosis but not NASH, and patients with NASH) were observed in cardiac morphological characteristics and function, most of the differences were not significant when adjusted for potential important confounders, such as age or body surface area, although trends remained. Intriguingly, despite the relatively young age of the patients, some parameters of left ventricular remodeling, such as indexed left ventricular end-diastolic

diameter and left ventricular wall thickness, were different in NAFLD compared with patients with normal liver, and with more pronounced alterations in patients with NASH compared with those with isolated steatosis. Given the young age of the patients who did not have any history of cardiac disease, these data further highlight the potential of the liver to contribute to significant cardiovascular abnormalities long before clinical events occur. Together with the previous data, this has important clinical implications, as it incites looking for NAFLD in patients with CVD and, conversely, assessing CVD benefit of NASH treatments by measures of subclinical CVD in NASH clinical trials.[8]

Another interesting finding of the study by Sinski et al in this issue of *JAHA*[11] brings us back to the inverse of the liver-cardiovascular axis (namely, the role of vascular alterations early in the development of NAFLD and the progression from isolated steatosis to NASH).[8] We have shown previously,[7,14] and it was subsequently confirmed by others,[15] that steatosis induces an increase in the intrahepatic vascular resistance, reducing sinusoidal liver flow. We hypothesized that this will accentuate the physiological oxygen gradient over the liver lobule, resulting in centrolobular hypoxia, triggering processes that will ultimately lead to liver cell damage and inflammation, hence steatohepatitis.[8] The increased intrahepatic vascular resistance leads to an increase in portal pressure in rodents and also, as we could demonstrate, in humans.[14] In rodents, we could also demonstrate a hyperdynamic circulation (which is typically seen in severe portal hypertension and cirrhosis).[16] In the study by Sinski et al[11] patients with NASH, despite the signs of ventricular remodeling, had a higher cardiac index than patients with normal liver or with isolated steatosis, even after adjusting for confounders, like the use of β blockers. This suggests the presence of a hyperdynamic circulation in line with liver blood flow impairment and subsequent portal hypertension and hence adds to the translation of the previously mentioned preclinical data. These findings are thus supportive of the impact of NAFLD on liver blood flow and the relevance of this for disease progression.

In conclusion, in a cohort of morbidly obese but otherwise unselected patients, Sinski et al[11] elegantly demonstrate in an unbiased approach the independent association of NAFLD and particularly NASH with cardiac abnormalities in a population at young age, but also add to the evidence of impairment of liver blood flow early in the development of liver disease. Not only do these findings increase our insight in the complex entanglement between NAFLD and the cardiovascular system, but they are also clinically relevant for physicians taking care of patients experiencing or at risk for these diseases.

ARTICLE INFORMATION

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Disclosures

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