Editorial

JOURNAL OF HEPATOLOGY

Non-alcoholic fatty liver disease: A risk factor for myocardial dysfunction?

Christopher D. Byrne[1,2,*], Gianluca Perseghin[3,4]

[1]Nutrition and Metabolism, Faculty of Medicine, Institute of Developmental Sciences (IDS), MP887, University of Southampton, Southampton General Hospital, Southampton SO16 6YD, UK; [2]Southampton National Institute for Health Research Biomedical Research Centre, University Hospital Southampton, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK; [3]Department of Medicine and Surgery, Università degli Studi di Milano Bicocca, Milan, Italy; [4]Department of Medicine and Rehabilitation, Unit of Metabolic Medicine, Policlinico di Monza, Monza, Italy

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There is mounting evidence that besides increasing the risk of cirrhosis, end-stage liver disease and hepatocellular carcinoma, non-alcoholic fatty liver disease (NAFLD) also affects risk of disease in organs beyond the liver.[1] For example, NAFLD is an independent risk factor for cardiovascular disease (CVD),[2] type 2 diabetes[3] and chronic kidney disease,[4] and NAFLD also increases risk of cardiac arrhythmias and aortic valve disease.[1] However, whether NAFLD is a risk factor for impaired myocardial function is uncertain.

In a study of 308 asymptomatic subjects recruited from attendees at a Health Promotion Centre in a University-affiliated tertiary care hospital in the Republic of Korea,[5] the authors have identified subjects with (n = 118) and without (n = 190) NAFLD. In their analyses, the authors tested whether hepatic steatosis and hepatic fibrosis are associated with abnormalities of fasting myocardial glucose uptake, as potentially causative of, or related to cardiac diastolic dysfunction and left ventricular (LV) remodelling.

Fasting myocardial glucose uptake was evaluated using [18F]-fluorodeoxyglucose-positron emission tomography (18FDG-PET). Hepatic steatosis and fibrosis were assessed using the controlled attenuation parameter (CAP) measurement and liver stiffness measurement (LSM), respectively. Both measurements were obtained by transient liver elastography (Fibroscan®). Hepatic fibrosis was defined by measurements of liver stiffness within the highest quartile of LSM. Cardiac structure and function were examined by echocardiogram.

The investigators included 53 subjects (17%) with diabetes and 255 subjects without diabetes. They excluded individuals who had abnormal renal or hepatic functions, a history of CVD including myocardial infarction, and heart failure. They also excluded subjects with a coronary artery calcium score >400, evaluated by coronary computed tomography (CT) angiography, as indicative of subclinical coronary artery disease. It is also important to note that the authors measured abdominal fat by CT measurement at the level of the L4 vertebra, to adjust for the presence of visceral fat as a potential confounder in their analyses. Multivariable linear regression analysis was undertaken to determine whether there were independent associations between E/e' (as a measure of LV filling pressure which reflects diastolic dysfunction), and hepatic steatosis (CAP), hepatic fibrosis (liver stiffness), and fasting myocardial glucose uptake.

Thirty-eight percent of participants had NAFLD. Compared to those subjects without NAFLD, subjects with NAFLD had alterations in cardiac remodelling, manifested by increased LV mass index, LV end-diastolic diameter, and left atrial volume index. Hepatic steatosis was significantly associated with E/e' ratio. Those without NAFLD were more likely to have higher fasting myocardial glucose uptake compared to those with NAFLD. E/e' ratio was independently associated with hepatic fibrosis, but not with hepatic steatosis, after adjusting for measures of adiposity. Fasting myocardial glucose uptake showed a significant relationship with diastolic function in the regression models, although its association with the E/e' ratio became non-significant after adjustment for diabetes status, or measures of body fat.

The authors are to be congratulated for this excellent study. However, there are important limitations of the study design that need to be highlighted before we can conclude that hepatic fibrosis in NAFLD is a risk factor for diastolic dysfunction. Future studies addressing the limitations may help confirm (or refute) that NAFLD, and in particular liver fibrosis, is an independent risk factor for impaired diastolic function.

A weakness of the present study is that myocardial glucose uptake was assessed by ^{18}FDG-PET in the fasting state only and myocardial insulin resistance with respect to glucose disposal should really be measured in the dynamic insulin-stimulated state. A second limitation relates to potential confounding by diabetes status (or drugs used to treat diabetes). In the diabetes sub-set, a significant association between liver stiffness and E/e' ratio was observed in the unadjusted regression model, but the association was not present in the fully adjusted model. It is possible that this non-significant result may have occurred because the study was underpowered to test associations only in subjects with diabetes. It is important to note that the beta

Received 3 December 2017; accepted 4 December 2017

☆ DOI of original article: http://dx.doi.org/10.1016/j.jhep.2017.11.023.

* Corresponding author. Address: Nutrition and Metabolism, Faculty of Medicine, Institute of Developmental Sciences (IDS), MP887, University of Southampton, Southampton General Hospital. Southampton SO16 6YD, UK.
E-mail address: c.d.byrne@soton.ac.uk (C.D. Byrne).

coefficients in the regression models for the associations between liver stiffness and the E/e' ratio were similar in the group with diabetes, to that without diabetes. Of the 53 patients with diabetes, although the majority of subjects were drug naïve (n = 33), 14 subjects were treated with metformin, five with thiazolidinediones, five with dipeptidyl peptidase 4 inhibitors, and five with insulin. The authors have attempted to show that the association between liver stiffness and the E/e' ratio was not confounded by drugs; and, in separate analyses adjusted for medications used to treat diabetes. However, that said, the number of subjects with diabetes is small and the numbers taking drugs from each specific drug class, are also very small. Given that many outcomes (including CVD) are worse in patients with NAFLD who also have type 2 diabetes,[6,7] we suggest that further study is necessary in greater numbers of patients who have NAFLD and also type 2 diabetes. It should then be possible to elucidate the impact of diabetes status (and associated medications used to treat diabetes) on cardiac function. Only then will we be able to elucidate whether relationships between NAFLD and impaired cardiac function, are confounded by the presence of co-existing type 2 diabetes.

Thirdly, although transient elastrography has acceptable sensitivity for diagnosing liver fibrosis in most patients with NAFLD, is it questionable that identifying the presence of hepatic fibrosis using the threshold for the highest quartile of LSM (>5.3 kPa), is specific for liver fibrosis in all subjects in whom LSM was above that threshold. It is important to note that in subjects with NAFLD, the LSM was 4.9 ± 1.3 kPa (mean ± SD), compared to 4.5 ± 2.4 kPa in subjects without NAFLD.

Assuming that the results in this paper are verified by other investigators, what is the biological explanation for these findings? Why might liver fibrosis be associated with impairment in diastolic function? To address this question, it is important to consider the pathogenesis of both non-alcoholic steatohepatitis (NASH) and myocardial dysfunction. Hepatokines produced by the liver in NAFLD might have a direct impact on the heart and contribute to diastolic dysfunction. For example, it has been shown that serum fetuin-A level is associated with liver/vessel fibrosis-related markers in patients with NAFLD. Circulating fetuin-A could be a useful serum biomarker for predicting liver and vascular fibrosis progression in NAFLD,[8] and fetuin-A levels have been shown to be associated with diastolic dysfunction.[9] It is also plausible that oxidative stress within hepatocytes could induce cellular apoptosis and increase production of pro-inflammatory and chemotactic cytokines and chemokines, to promote a fibrogenic response both in the liver and heart. In a very large Korean occupational cohort, it has previously been shown that increased gamma glutamyl transferase (GGT) concentration was associated with increased all-cause mortality.[10] In the general population, increased GGT concentrations are probably a marker of increased oxidative stress and the authors of the paper in question investigated differences in GGT concentrations between subjects with and without NAFLD. As expected, they showed that GGT concentration was increased in subjects with NAFLD, but the association between E/e' ratio and GGT concentration was not significant.

It is also possible that activation of the renin–angiotensin–aldosterone system with increased reactive oxygen species production could mediate increased predisposition to liver fibrosis and diastolic dysfunction. Whilst the numbers of subjects taking these medications was too small to investigate specific associations between inhibitors/blockers of the renin–angiotensin–aldosterone system and the E/e' ratio; the authors showed that the association between liver stiffness and the E/e' ratio was not confounded by treatment with these drugs.

Patients with NAFLD are usually very insulin resistant and have many of the features of the metabolic syndrome. It is possible that tissue mitochondrial dysfunction occurring early in the liver,[11] the heart[12] and possibly the pancreas could be a common unifying factor in patients with NAFLD, who have insulin resistance or overt type 2 diabetes and impaired myocardial function. Diastolic dysfunction in cardiomyopathies can occur via impairment in mitochondrial function and the muscle protein degradation by the stimulation of the ubiquitin-proteasome proteolytic pathway.[13]

Finally, it is possible that external factors beyond the liver (*e.g.* dysbiosis or adipose tissue dysfunction) may influence both progression of liver disease, and cardiac function. The intestinal microbiota produces molecules such as trimethylamine (TMA), pCresyl and indole from dietary nutrients such as choline, phenylalanine/tyrosine and tryptophan, respectively. After further metabolism in the liver by oxidation or sulphation, ionically charged water soluble molecules, such as trimethylamine-N-oxide (TMAO), pCresyl sulphate and indole sulphate, are produced that are excreted in the urine.[14] The potentially deleterious impact of TMAO on the vasculature has been highlighted recently, since it has been proposed that inhibition of TMA production could be a potential treatment for atherosclerosis.[15] Additionally, adiponectin is a key adipokine secreted by adipose tissue that can affect disease progression in NAFLD. Adiponectin exerts anti-inflammatory, anti-fibrotic and anti-atherogenic properties, and low levels of adiponectin are associated with NASH and increased risk of CVD,[16] potentially mediating a link between adipose tissue dysfunction, NASH and cardiac dysfunction.

In conclusion, the paper by Lee *et al.* in this issue is an important contribution to the field. The data provide more evidence to support the growing assertion that NAFLD is a liver disease with important consequences in organs beyond the liver, such as the vasculature and the heart.

Financial support

CDB. is supported in part by the Southampton National Institute for Health Research Biomedical Research Centre.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Author contributions

Both authors researched the data for the article, provided substantial contributions to discussions of its content, wrote the article and undertook review and/or editing of the manuscript before submission.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2017.12.002.

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