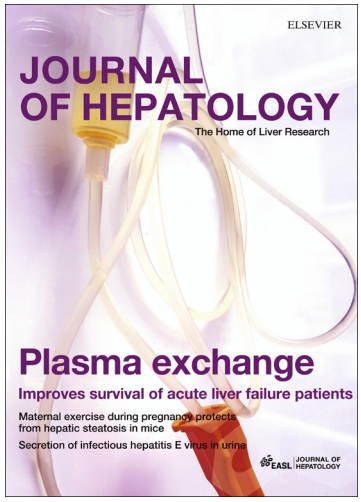
Adams LA, Anstee QM.

A fatty liver leads to a broken heart?

Journal of Hepatology **2016, 65(1), 14-16.**



A Fatty liver leads to a broken heart?

Leon A. Adams, Quentin M. Anstee

PII: S0168-8278(16)30085-X
DOI: http://dx.doi.org/10.1016/j.jhep.2016.03.012
Reference: JHEPAT 6051

To appear in: *Journal of Hepatology*

Received Date: 17 March 2016
Accepted Date: 20 March 2016

Please cite this article as: Adams, L.A., Anstee, Q.M., A Fatty liver leads to a broken heart?, *Journal of Hepatology* (2016), doi: http://dx.doi.org/10.1016/j.jhep.2016.03.012

Journal of Hepatology editorial

A FATTY LIVER LEADS TO A BROKEN HEART?

Leon A. Adams[1] & Quentin M. Anstee [2]

1. School of Medicine and Pharmacology, The University of Western Australia, Nedlands, Australia.
2. Liver Research Group, Institute of Cellular Medicine, The Medical School, Newcastle University, Framlington Place, Newcastle-upon-Tyne, NE2 4HH, U.K.

Contact Details:

Leon A. Adams MBBS, PhD, FRACP
M503
School of Medicine and Pharmacology, UWA
QEII Medical Campus
Verdun St
Nedlands, WA 6009
Australia

T: +61 8 6151 1052
F: +61 8 6151 1028
Email: leon.adams@uwa.edu.au

Dr Quentin M. Anstee BSc, MB BS, PhD, MRCP(UK)

Senior Lecturer & Honorary Consultant Hepatologist,
Institute of Cellular Medicine,
The Medical School,
Newcastle University,
4th Floor, William Leech Building,
Framlington Place,
Newcastle-upon-Tyne, NE2 4HH, Great Britain.

Telephone: + 44 (0) 191 208 7012
Fax: + 44 (0) 191 208 0723

Email: quentin.anstee@ncl.ac.uk

Word Count: 1023 Figures: 0 Tables: 0

Abbreviations: NAFLD, non-alcoholic fatty liver disease; CVD, cardiovascular disease; cIMT, carotid intimal media thickness; FLI, Fatty Liver Index; GGT, gamma glutamyl transferase

Keywords: NAFLD, cardiovascular disease, carotid intimal media thickness

Conflict of Interest: Nil

Financial Support: Nil

Authors Contributions: LAA and QMA both contributed equally to the data review and interpretation for this editorial, the manuscript writing and editing.

Non-alcoholic fatty liver disease (NAFLD) typically exists in a milieu of disturbed metabolism, including increased total body adiposity, insulin resistance, impaired glucose tolerance and dyslipidemia[1]. Cumulatively, these factors increase the risk for cardiovascular disease (CVD), and so it is not surprising that CVD is the leading cause of death in NAFLD patients.[2] The challenge over the past decade has been to tease apart the complex and inter-dependent relationships between NAFLD and these etiological factors, to establish whether NAFLD *per se* increases the risk of developing CVD. The validation of NAFLD as a significant additional risk factor would have direct relevance for primary preventative strategies against cardiovascular disease.

In this edition of the journal, Pais and colleagues present both new cross-sectional and longitudinal evidence that NAFLD is an important and independent risk factor for the development of atherosclerosis and therefore CVD.[3] In a cross-sectional analysis of 5671 individuals attending a cardiovascular disease primary prevention clinic, the presence of fatty liver was associated with greater cardiovascular risk, independent of traditional risk factors including age, sex, smoking, hypertension, diabetes and C-Reactive Protein. Cardiovascular risk was determined by carotid intimal media thickness (cIMT), which is a validated predictor of myocardial infarction and stroke.[4] Furthermore, repeat assessment in 1,872 individuals after a mean follow-up of eight years, demonstrated that incident fatty liver was associated with a greater increase in cIMT and baseline fatty liver predicted the development of carotid plaques after adjustment for a range of cardiovascular risk factors.

Although this data strongly suggests NAFLD confers an increased risk over and above its association with traditional cardiac risk factors, a few caveats are worth noting. The diagnosis of NAFLD was based on the Fatty Liver Index (FLI), a calculated score that combines body mass index, waist circumference, serum triglycerides and gamma-glutamyl transferase (GGT) to provide a composite value ranging from 0-100.[5] Whilst the use of non-invasive tests like FLI is a frequent and necessary compromise in large-scale retrospective studies of this type, validation of the FLI against magnetic resonance spectroscopy which is the gold standard for hepatic fat quantification, has demonstrated a score >60 is specific but only modestly sensitive for a diagnosis of NAFLD.[6] Moreover, of the FLI components, waist circumference was the dominant driver of the association between the FLI and cIMT and so is a potential confounding variable. Nevertheless, these results are supported by other cross-sectional population-based studies and meta-analysis that have demonstrated NAFLD to be independently associated with predictors of cardiovascular disease reflecting structural and functional vascular abnormalities including endothelial dysfunction, arterial stiffness and myocardial dysfunction.[7-10]

It should not be surprising that NAFLD plays a likely role in the genesis of CVD. The normal glucose and lipid homeostasis within the liver becomes disturbed with the accumulation of hepatic fat, resulting in hepatic insulin resistance, increased fasting glucose levels and an atherogenic lipid profile.[1] Moreover, weight gain in NAFLD subjects, exacerbates the adverse cardiovascular risk profile when compared with non-NAFLD subjects who have equivalent body fat mass and weight gain.[11] The fatty liver is also a producer of a number of inflammatory pro-atherogenic cytokines, hyper-coagulable factors and adhesion molecules, which have been implicated in the pathogenesis of myocardial dysfunction and atherosclerosis[12].

On this background of evidence demonstrating biological plausibility and cross-sectional association between NAFLD and CVD, the longitudinal findings of Pais *et al*, add a further critical piece of information by confirming that subjects with fatty liver were more likely to develop carotid plaque over time. A number of other studies also support the notion that NAFLD is predictive of incident cardiovascular disease and cardiovascular mortality.[13-17] However, some of these cohort studies have suggested that that the increase in CVD risk may be limited to sub-groups of NAFLD patients, such as those with advanced fibrosis[13], type 2 diabetes[15] or men with an elevated GGT[8]. Thus, there are likely to be other factors that modify the association between NAFLD and CVD. One such modifying factor may be genetic variation. An example is the *TM6SF2* gene, where minor allele carriage has been identified as a risk factor for NAFLD and hepatic fibrosis[18], but is also associated with a reduced risk of cardiovascular events.[19-21] Animal studies suggest TM6SF2 may be involved in lipid efflux from the liver: overexpression spares the liver from triglyceride accumulation but leads to higher circulating lipid levels, whereas deletion induces NAFLD but lowers peripheral lipid levels.[22]

Taken as a whole, the bulk of evidence suggests NAFLD increases CVD risk, although this relationship may be modified by other factors. The clinical implications of this paradigm may alter the decision to institute primary prevention strategies with anti-platelet, lipid lowering or anti-hypertensive drugs. Current recommendations for CVD prevention in the general population involve the calculation of future cardiovascular risk using algorithms such as the Framingham risk calculator or the SCORE risk assessment system that are based on traditional risk factors including age, blood pressure, cholesterol and smoking, but not NAFLD. Decisions to institute primary preventative pharmaco-therapy are then based on a calculated future risk of CVD, often defined as a 10-year absolute risk of ≥ 20%.[23] Although the Framingham risk score has been validated as a useful tool in NAFLD patients[24], it is not yet established whether the addition of NAFLD as a predictive factor in this or other CVD risk calculators, would increase their accuracy for determining future cardiovascular events.

A further intriguing thought is whether fatty liver can be a therapeutic target for cardiovascular risk reduction? Although causality can not be established, the PIVENS randomized controlled trial examining pioglitazone, vitamin E or placebo demonstrated that NASH resolution was associated with an improvement in atherogenic lipid profiles regardless of treatment group, as well as improved Framingham risk score.[25]

To summarize, the study by Pais *et al* provides further support for the view that NAFLD is an independent risk factor for atherosclerosis and therefore CVD. Clinicians should be aware of the increased cardiovascular risk in patients with NAFLD and consequently screen for conventional cardiovascular risk factors and use accepted risk calculators to make decisions regarding preventative pharmacotherapy, including statins. Additional prospective studies will be needed to determine what other factors modify the association between NAFLD and CVD.

References

[1] Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol 2013;10(6): 330-344.

[2] Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 2005;129(1): 113-121.

[3] Pais R, Giral P, Khan J-F, Rosenbaum D, Housset C, Poynard T, et al. Fatty liver as an independent predictor of early carotid atherosclerosis: Results from a large transversal and long-term follow-up. Journal of hepatology 2016.

[4] Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007;115(4): 459-467.

[5] Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 2006;6: 33.

[6] Cuthbertson DJ, Weickert MO, Lythgoe D, Sprung VS, Dobson R, Shoajee-Moradie F, et al. External validation of the fatty liver index and lipid accumulation product indices, using 1H-magnetic resonance spectroscopy, to identify hepatic steatosis in healthy controls and obese, insulin-resistant individuals. Eur J Endocrinol 2014;171(5): 561-569.

[7] Long MT, Wang N, Larson MG, Mitchell GF, Palmisano J, Vasan RS, et al. Nonalcoholic fatty liver disease and vascular function: cross-sectional analysis in the Framingham heart study. Arterioscler Thromb Vasc Biol 2015;35(5): 1284-1291.

[8] Huang RC, Beilin LJ, Ayonrinde O, Mori TA, Olynyk JK, Burrows S, et al. Importance of cardiometabolic risk factors in the association between nonalcoholic fatty liver disease and arterial stiffness in adolescents. Hepatology 2013;58(4): 1306-1314.

[9] VanWagner LB, Wilcox JE, Colangelo LA, Lloyd-Jones DM, Carr JJ, Lima JA, et al. Association of nonalcoholic fatty liver disease with subclinical myocardial remodeling and dysfunction: A population-based study. Hepatology 2015;62(3): 773-783.

[10] Oni ET, Agatston AS, Blaha MJ, Fialkow J, Cury R, Sposito A, et al. A systematic review: burden and severity of subclinical cardiovascular disease among those with nonalcoholic fatty liver; should we care? Atherosclerosis 2013;230(2): 258-267.

[11] Fabbrini E, Yoshino J, Yoshino M, Magkos F, Tiemann Luecking C, Samovski D, et al. Metabolically normal obese people are protected from adverse effects following weight gain. The Journal of clinical investigation 2015;125(2): 787-795.

[12] Vanni E, Marengo A, Mezzabotta L, Bugianesi E. Systemic Complications of Nonalcoholic Fatty Liver Disease: When the Liver Is Not an Innocent Bystander. Semin Liver Dis 2015;35(3): 236-249.

[13] Kim D, Kim WR, Kim HJ, Therneau TM. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. Hepatology 2013;57(4): 1357-1365.

[14] Targher G, Bertolini L, Poli F, Rodella S, Scala L, Tessari R, et al. Nonalcoholic fatty liver disease and risk of future cardiovascular events among type 2 diabetic patients. Diabetes 2005;54(12): 3541-3546.

[15] Haring R, Wallaschofski H, Nauck M, Dorr M, Baumeister SE, Volzke H. Ultrasonographic hepatic steatosis increases prediction of mortality risk from elevated serum gamma-glutamyl transpeptidase levels. Hepatology 2009;50(5): 1403-1411.

[16] Hamaguchi M, Kojima T, Takeda N, Nagata C, Takeda J, Sarui H, et al. Nonalcoholic fatty liver disease is a novel predictor of cardiovascular disease. World journal of gastroenterology 2007;13(10): 1579-1584.

[17] Pisto P, Santaniemi M, Bloigu R, Ukkola O, Kesaniemi YA. Fatty liver predicts the risk for cardiovascular events in middle-aged population: a population-based cohort study. BMJ Open 2014;4(3): e004973.

[18] Liu YL, Reeves HL, Burt AD, Tiniakos D, McPherson S, Leathart JB, et al. TM6SF2 rs58542926 influences hepatic fibrosis progression in patients with non-alcoholic fatty liver disease. Nature communications 2014;5: 4309.

[19] Holmen OL, Zhang H, Fan Y, Hovelson DH, Schmidt EM, Zhou W, et al. Systematic evaluation of coding variation identifies a candidate causal variant in TM6SF2 influencing total cholesterol and myocardial infarction risk. Nat Genet 2014;46(4): 345-351.

[20] Dongiovanni P, Petta S, Maglio C, Fracanzani AL, Pipitone R, Mozzi E, et al. Transmembrane 6 superfamily member 2 gene variant disentangles nonalcoholic steatohepatitis from cardiovascular disease. Hepatology 2015;61(2): 506-514.

[21] Kahali B, Liu YL, Daly AK, Day CP, Anstee QM, Speliotes EK. TM6SF2: catch-22 in the fight against nonalcoholic fatty liver disease and cardiovascular disease? Gastroenterology 2015;148(4): 679-684.

[22] Anstee QM, Seth D, Day CP. Genetic Factors That Affect Risk of Alcoholic and Non-Alcoholic Fatty Liver Disease. Gastroenterology 2016.

[23] Zhao D, Liu J, Xie W, Qi Y. Cardiovascular risk assessment: a global perspective. Nat Rev Cardiol 2015;12(5): 301-311.
[24] Treeprasertsuk S, Leverage S, Adams LA, Lindor KD, St Sauver J, Angulo P. The Framingham risk score and heart disease in nonalcoholic fatty liver disease. Liver Int 2012;32(6): 945-950.
[25] Corey KE, Vuppalanchi R, Wilson LA, Cummings OW, Chalasani N. NASH resolution is associated with improvements in HDL and triglyceride levels but not improvement in LDL or non-HDL-C levels. Aliment Pharmacol Ther 2015;41(3): 301-309.