**Editorial on JHEPAT-D-21-01264**

# Why are there no Strategies for NAFLD?

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Non-alcoholic steatohepatitis (NASH) was first described approximately 40 years ago[1] and non-alcoholic fatty liver disease (NAFLD) is now estimated to affect a quarter of the world's adult population[2]. A further concern is that the epidemic of obesity, metabolic dysfunction and type 2 diabetes (T2DM) in young people will likely increase the prevalence and complications of NAFLD in the near future[3, 4]. NAFLD is a multisystem disease [5] that requires a multidisciplinary, holistic approach to its management [6]. NAFLD is an independent risk factor for several other diseases, including T2DM[7], chronic kidney disease[8] and non-hepatic cancers[9]. Although a little more controversial, the weight of evidence now suggests that NAFLD is also a risk factor cardiovascular and cardiac disease [10-12]. Importantly, the majority of people with NAFLD do not require specialist hepatology services and most patients with NAFLD are cared for in other services in primary and secondary care.

In this edition of the Journal, Lazarus *et al* have further developed and extended their European preparedness index[13] and have developed their 'index' to accommodate six domains (ref JHEPAT-D-21-01264). These domains covered: a) policy; b) guidelines; c) civil awareness and society engagement; d) epidemiology and data; e) detection and f) care. Responses were rated high, medium, and low; and a multiple correspondence analysis was then applied. The overall policy score for a country was scored from 0 (worst) to 100 (best). The authors reported the results of responses from representatives (mainly Hepatologists) from 102 countries, covering 86% of the global population (ref JHEPAT-D-21-01264). The highest scoring country was India (42.7) and 32 countries scored zero. The findings contained in their paper led the authors to conclude that 'although NAFLD is a pressing public health problem, no country was found to be well prepared to address it'. The authors then concluded with a call to arms stating 'there is a pressing need for a strategy to address NAFLD at national and global levels'.

Whilst none of the regular readers of this Journal are likely to disagree with the authors' call to arms, it is incumbent on all us, to reflect on why this state of affairs still exists in 2021. We would all acknowledge that there has been an explosion in knowledge (and publications) related to NAFLD over the last 20 years, and that research endeavour has facilitated many countries and Societies in developing their own guidelines. However, that there is a disconnect between availability of guidelines in some countries, and no country having a specific NAFLD Strategy, should prompt us to explore why this state of affairs still exists. Whilst the following is not intended to be a comprehensive list, there are several potential factors which have not helped our cause in recent years. These factors are: a) the presence of already existing strategies for addressing obesity and T2DM, as key risk factors for NAFLD and NAFLD progression; b) scepticism about the additional risk conveyed by NAFLD; c) perceptions that liver fat is not harmful; d) limited availability of non-invasive tests for monitoring liver disease resolution, or progression; e) limited evidence of effective interventions for amelioration of liver disease, beyond weight loss and lifestyle change; f) the challenge of managing co-existing multi-morbidities such as T2DM and cardiovascular disease (CVD), which are often more urgent for patient well-being and health and g) the lack of a licensed drug treatment for liver disease in NAFLD.

It is intriguing that India, received the highest score amongst participating countries. There are lessons that could be learned form this, but it is important to emphasize that the policy score was less then 50, and that all countries have substantial room for improvement. India's high score is likely a result of implementation of national policies such as the integration of NAFLD within the National Program on Prevention and Control of Cancer, Diabetes, Cardiovascular diseases and Stroke (NPCDCS)[14].

Since NAFLD is so common in primary care and in other specialist clinics, it would be important for the authors to engage with colleagues from primary care, diabetology and cardiology, most of whom are not expert researchers on liver disease. Exploring their views

on the approaches needed for primary and secondary prevention of NAFLD, and gaining their agreement and approval of what is needed is crucial; if we are to make progress. It is disappointing (but not surprising) to note that only 20 (24%) of the 83 countries who reported having guidelines for diabetes, mentioned NAFLD in these guidelines (ref JHEPAT-D-21-01264). This may be, because T2DM potentially affects almost every bodily organ system, and many diabetologists view ‘a little bit of liver fat’ as the least of the patients’ worries. To address questions about the significance of hepatic steatosis there is a need for researchers to generate the necessary data which provides the evidence for cost-effective strategies of case-finding for NAFLD. This will be particularly important in high-risk groups such as those with metabolic syndrome or T2DM who are higher risk of more severe liver disease and co-morbidities associated with NAFLD [15]. Such an effort has been conducted recently in the U.S and needs to be extended to other countries[16]. T2DM is a strong risk factor for liver fibrosis, cirrhosis and hepatocellular carcinoma and glucose-lowering drugs used in T2DM may benefit the liver in NAFLD[17]. Moreover, the co-existence of T2DM and NAFLD creates a vicious spiral of worsening disease that affects both conditions [18]. Thus, there is clearly scope for expanding diabetes guidelines to include evidence-based information to support NAFLD management in this patient group.

In the absence of validated surrogate end-points regulatory authorities have requested liver histological end points in order to achieve a provisional license for any new treatment for NASH, which has impacted on progress. Use of this `gold` standard (liver biopsy and histology) for staging liver disease is recognised to be impractical, costly, risky and not feasible for monitoring treatment responses in routine clinical practice, rendering it an impediment to non-hepatologists engaging with us to develop a NAFLD Strategy. The advances made in non-invasive testing and ability of these tests to provide an accurate assessment of disease severity and sequential changes and to predicting disease outcome may provide an opportunity to move beyond the biopsy in clinical trials and routine clinical practice.

There is a large evidence base demonstrating that lifestyle change focussed on weight loss, adoption of a Mediterranean diet that is low in saturated fat, and increased physical activity, not only benefits the early stages of liver disease, but also decreases risk of T2DM and CVD. These studies need to be extended to patients with more advanced NAFLD and over longer periods of time, to establish if they remain tractable and effective. Indeed, the use of such diets alongside pharmacotherapies in trials remains an under-studied area. That said, behaviour change is difficult to make in an obesogenic environment without intensive support, and few of our patients with NAFLD receive the necessary sustained support. Nevertheless, programmes focussed on behaviour change, such as the English NHS Diabetes Prevention programme, afford an opportunity to extend support to other groups (such as many of our patients with NAFLD), who may benefit from a similar approach and who would benefit from lifestyle change.

In summary, we congratulate the authors on their work. It is our wish that this Editorial now helps Hepatologists appreciate the issues, which are clearly impeding progress. It is vital that we achieve consensus and resolve these issues quickly. We must then reach out to our stakeholders and engage with them and other relevant and interested health care professionals, as only then might we make progress. Once our stakeholders and interested health care professionals endorse what we are trying to achieve, only then will we be able to contribute to, or lead, the development of NAFLD Strategies.

## REFERENCES

[1] Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980;55:434-438.
[2] Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15:11-20.
[3] Radulescu A, Dugan AJ, Killian M, Attia SL, Mouzaki M, Fuchs GJ, et al. Stratification by obesity class, rather than age, can identify a higher percent of children at risk for non-alcoholic fatty liver disease and metabolic dysfunction. Pediatric obesity 2021:e12862.

[4] Shapiro WL, Noon SL, Schwimmer JB. Recent advances in the epidemiology of nonalcoholic fatty liver disease in children. Pediatric obesity 2021;16:e12849.
[5] Byrne CD, Targher G. NAFLD: A multisystem disease. J Hepatol 2015;62:S47-S64.
[6] Targher G, Tilg H, Byrne CD. Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach. The lancet Gastroenterology & hepatology 2021;6:578-588.
[7] Mantovani A, Petracca G, Beatrice G, Tilg H, Byrne CD, Targher G. Non-alcoholic fatty liver disease and risk of incident diabetes mellitus: an updated meta-analysis of 501 022 adult individuals. Gut 2021;70:962-969.
[8] Mantovani A, Petracca G, Beatrice G, Csermely A, Lonardo A, Schattenberg JM, et al. Non-alcoholic fatty liver disease and risk of incident chronic kidney disease: an updated meta-analysis. Gut 2020.
[9] Mantovani A, Petracca G, Beatrice G, Csermely A, Tilg H, Byrne CD, et al. Non-alcoholic fatty liver disease and increased risk of incident extrahepatic cancers: a meta-analysis of observational cohort studies. Gut 2021.
[10] Mantovani A, Csermely A, Petracca G, Beatrice G, Corey KE, Simon TG, et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. The lancet Gastroenterology & hepatology 2021;6:903-913.
[11] Simon TG, Roelstraete B, Hagström H, Sundström J, Ludvigsson JF. Non-alcoholic fatty liver disease and incident major adverse cardiovascular events: results from a nationwide histology cohort. Gut 2021.
[12] Byrne CD, Targher G. Non-alcoholic fatty liver disease is a risk factor for cardiovascular and cardiac diseases: further evidence that a holistic approach to treatment is needed. Gut 2021.
[13] Lazarus JV, Palayew A, Carrieri P, Ekstedt M, Marchesini G, Novak K, et al. European 'NAFLD Preparedness Index' - Is Europe ready to meet the challenge of fatty liver disease? JHEP reports : innovation in hepatology 2021;3:100234.
[14] [cited; Available from: https://main.mohfw.gov.in/newshighlights-42
[15] Karlsen TH, Sheron N, Zelber-Sagi S, Carrieri P, Dusheiko G, Bugianesi E, et al. The EASL–Lancet Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality. The Lancet 2021.
[16] Noureddin M, Jones C, Alkhouri N, Gomez EV, Dieterich DT, Rinella ME, et al. Screening for Nonalcoholic Fatty Liver Disease in Persons with Type 2 Diabetes in the United States Is Cost-effective: A Comprehensive Cost-Utility Analysis. Gastroenterology 2020;159:1985-1987 e1984.
[17] Mantovani A, Byrne CD, Scorletti E, Mantzoros CS, Targher G. Efficacy and safety of anti-hyperglycaemic drugs in patients with non-alcoholic fatty liver disease with or without diabetes: An updated systematic review of randomized controlled trials. Diabetes Metab 2020;46:427-441.
[18] Byrne CD, Targher G. Non-alcoholic fatty liver disease-related risk of cardiovascular disease and other cardiac complications. Diabetes Obes Metab 2021.