NAFLD: a multisystem disease that requires a multidisciplinary approach

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Non-alcoholic fatty liver disease (NAFLD) is often thought of as the hepatic manifestation of the metabolic syndrome and is frequently accompanied by type 2 diabetes, hypertension, dyslipidaemia and cardiovascular disease. Together with the obesity epidemic, NAFLD has reached epidemic proportions and is now the most common cause of chronic liver disease worldwide. Despite the epidemic of NAFLD, relatively few of these patients will die of liver disease and the leading cause of death among NAFLD patients is cardiovascular disease. Patients with NAFLD also experience significant morbidity from comorbid conditions, such as diabetes and chronic kidney disease. A liver-centric approach to the disease risks missing the forest for the trees.

In *Frontline Gastroenterology*, Moolla *et al*[1] illuminate one potential path through this forest by demonstrating the efficacy of a multidisciplinary approach to NAFLD in improving markers of liver, cardiac and metabolic health. This single centre, retrospective study examined a cohort of NAFLD patients referred to the Oxford University Hospital Metabolic Liver Clinic who were generally referred from the primary or secondary care setting with NAFLD and a NAFLD fibrosis score (NFS) in the intermediate to high range. Their multidisciplinary clinic was led by hepatologists and diabetologists or metabolic specialists and supported by a special service that provided patients with advice regarding weight loss, smoking cessation, alcohol reduction and accessing mental health services. Patients with a hepatic comorbidity, type 1 diabetes or bariatric surgery were excluded from the analysis. The primary outcome assessed was a change in alanine aminotransferase (ALT) from baseline to their most recent clinic visit. Other liver outcomes included changes in aspartate aminotransferase, transient elastography (TE), fibrosis-4 (FIB-4) and NFS. Metabolic and cardiovascular outcomes included changes in haemoglobin A1c (HbA1c), weight, lipid profile and QRISK3 cardiovascular risk score. In addition, they used the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model to model predicted changes in quality-adjusted life expectancy based on observed changes to patient cardiometabolic risk factors.

After a median of 13.3 months and two follow-up visits, the investigators noted a significant improvement in the primary outcome, ALT, by 11 IU/L. While the change in ALT is not prospectively validated to predict liver-related health outcomes, the evidence is accumulating that it may be a useful proxy. In a paired-biopsy study of lifestyle intervention in NAFLD, normalisation of ALT was associated with a significantly decreased risk (OR 0.21, 95% CI 0.08 to 0.58) of fibrosis progression.[2] Though fibrosis is the only independent predictor of liver-related mortality in NAFLD,[3] it is not unreasonable to hope improvement in ALT could translate to improved liver-related health outcomes.

Similarly, liver stiffness as assessed by TE significantly decreased by 1.3 kPa over the median 13.3 months of the study. Liver stiffness as assessed by TE is useful in the prediction of liver-related death or hepatic complications across chronic liver disease.[4] However, the relationship between change in TE score and liver-related outcomes is less well-studied, especially in NAFLD. For comparison, among patients with chronic hepatitis C treated with direct-acting antivirals, TE score decreased by a median of 4.1 kPa within 12 weeks of completing treatment.[5] While the improvement in TE score in this study is dramatically less than that seen in viral hepatitis, the duration of follow-up and likely the degree of improvement in hepatic inflammation makes a direct comparison difficult.

Improvement was also seen in cardiometabolic risk factors. Patients lost a median of 3.4% of their body weight. While weight loss of 5%–10% is required for resolution of NAFLD or nonalcoholic steatohepatitis (NASH), significant improvement in HbA1c can be achieved with more modest weight loss of 2.6%.[6] Indeed, in the present study, HbA1c was reduced by 14 mmol/mol among poorly controlled diabetics and by 4 mmol/mol among all patients with type 2 diabetes, which is similar to the 3.3 mmol/mol reduction seen with diet and physical activity intervention.[6] In addition, the 10-year relative risk of heart attack or stroke as estimated by QRISK3 score was modestly, but significantly, decreased from 2.1 to 2.0.

Perhaps more interesting than the modest improvement in cardiometabolic risk factors are the changes made in diabetes management and the potential impact of more individualised therapy in this population. In this study, 21% of diabetic patients were started on glucagon-like peptide-1 (GLP-1) receptor agonist therapy and 20% of patients initially on insulin were stopped. In a recent trial comparing the addition of a GLP-1 analogue versus insulin to patients with poorly controlled type 2 diabetes on metformin and a sulfonylurea, treatment with a GLP-1 analogue was associated with a 73% risk reduction of a composite major cardiac event.[7] Therefore, the improvement in cardiovascular risk estimated by QRISK3 score may be sorely underestimated.

For those interested in implementing a similar multidisciplinary NAFLD clinic at their own institution, several questions might arise.[2] How does the intervention work? Changes were made in diabetes medication and statin prescription that alone could have accounted for improvement in weight, HbA1c and lipid profile. If this is the case, one might see similar improvements just by incorporating a diabetologist into NAFLD clinic.[3] To what extent did patients take advantage of the *Here for Health* Service? If patients relied heavily on community services for weight management and mental health, this approach may not be implementable in places with a less robust ancillary support network.[4] Is this sustainable for long-term? With a median of 13.3 months of follow-up and 2 follow-up clinic visits, these patients have just embarked on what may be lifelong management of a complex disorder that requires long-term commitment to emerge from the forest, that is, NAFLD and its associated comorbidities.

Given the most common causes of morbidity and mortality in NAFLD are cardiovascular and metabolic disease and the lack of effective liver-directed therapy, NAFLD can be a frustrating

disease for the hepatologist. Moolla *et al* demonstrate that the addition of a diabetologist or metabolic physician and ancillary services to NAFLD clinic can result in improvement in surrogate markers not just for liver disease, but also for cardiometabolic disease. While long-term data are needed to confirm the sustainability, cost-effectiveness and improvement in meaningful clinical outcomes of such a model, they reinforce what we have long suspected; that the hepatologist can no longer afford to go it alone against the many-headed hydra of NAFLD and confirms the need for a multidisciplinary approach to the management of NAFLD.

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