Optimising referral pathways for patients with NAFLD in the United Kingdom

Key Points

The burden of NAFLD is increasing, and advanced liver fibrosis is the main predictor of worse clinical outcomes.

The principle aim of clinical pathways is to identify patients with advanced fibrosis and who may benefit from specialist management.

Implementation of a two-step NAFLD Referral Pathway in primary care using a combination non-invasive score (i.e. Fib-4) and specialist biomarker (i.e. ELF^{TM}) reduced inappropriate referrals by 80% and increased the detection of advanced fibrosis 5 fold.

Healthcare modelling suggests that implementing a NAFLD Referral Pathway can lead to significant cost-savings.

Future adoption of artificial intelligent testing (such as iLFT) could provide an efficient, safe and cost-effective approach to diagnosis and risk-stratification of patients with NAFLD in primary care.

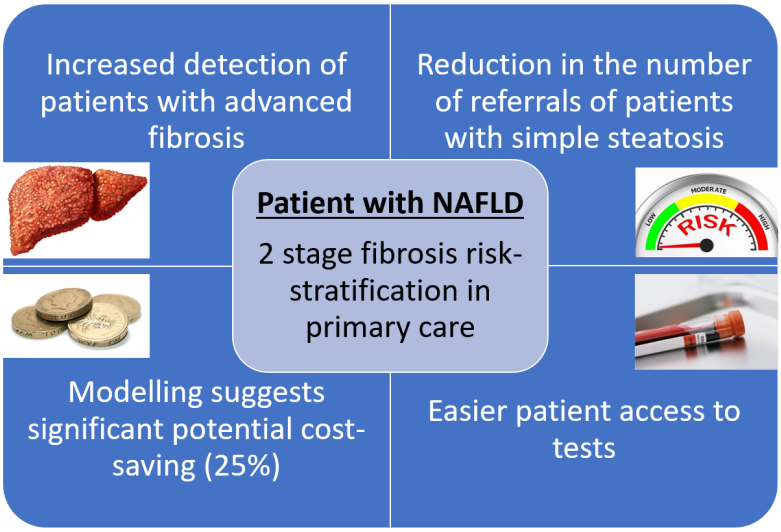

Figure 1 – schematic of the potential benefits of a two-step fibrosis risk stratification in primary care for patients with NAFLD. Comparison made to a "standard of care" system with no formal risk stratification system in place.

Background

The burden of chronic liver disease is growing and demands a coordinated approach from primary and secondary care physicians (1). Liver disease results in over 62,000 years of lost working life every year in the UK and deaths from liver disease have increased by over 400% since 1970 (2). Whilst alcohol-related liver disease (ARLD) remains the commonest indication for liver transplantation in the UK, non-alcoholic fatty liver disease (NAFLD) is the commonest cause of abnormal liver blood tests in primary care (3) with an estimated prevalence of 20-30% of all consultations? Or tests? (4). The number of liver transplants being undertaken for NAFLD is increasing (5) and in the USA, NAFLD is the second commonest indication for liver transplantation (6) highlighting the need for better diagnosis and management of NAFLD.

NAFLD is an umbrella term describing the spectrum of fatty liver disease seen in conjunction with the metabolic syndrome, in the absence of significant alcohol consumption affecting 20-30% of the UK population[ref]. Obesity and/or insulin resistance lead to increased free fatty acids within the liver and subsequent triglyceride deposition which is termed steatosis (7). In combination with steatosis, the presence of inflammation and hepatocyte injury (indicated by hepatocyte ballooning on histology) denote the presence of non-alcoholic steatohepatitis (NASH) (8) that may develop in X-Y%[refs]. NASH may be accompanied by the development of fibrosis, which confers a higher chance of progression to cirrhosis and end-stage liver disease (9) which effects 5% of cases of NAFLD.

There are currently no licensed pharmacological therapies for NAFLD or more specifically the advanced forms of NASH fibrosis and cirrhosis. The mainstay of management for the vast majority is lifestyle intervention, including weight loss (diet, exercise) and smoking cessation, with pharmacological optimisation of other metabolic risk factors including hyperglycaemia, hypertension and hyperlipidaemia of paramount importance. Indeed, weight loss targets of 5, 7 and 10% have been reported to improve steatosis, NASH and even fibrosis, respectively (10). If patients develop cirrhosis, secondary care management focuses specifically on the monitoring for complications including portal hypertension (ascites, varices, encephalopathy), muscle wasting (sarcopenia) and hepatocellular carcinoma. Some centres may provide access to clinical drug trials, in addition to multi-disciplinary team (MDT) clinics (i.e. hepatology, endocrinology/bariatric medicine, dietetics and sports medicine) for optimal management of aspects of the metabolic syndrome in parallel to the underlying liver disease.

The NAFLD epidemic represents a significant healthcare challenge. The majority of patients only develop steatosis without progression to NASH. Such patients have minimal liver-related morbidity and require cardiovascular and metabolic risk factor modification in primary care. However, patients

with NASH (estimated prevalence between 1-2% (4)) are at risk of progressive fibrosis. Identifying patients who have advanced fibrosis (defined as Kleiner stage 3 or 4, also known as "bridging fibrosis or "cirrhosis" respectively) is key, as they represent a critical group with an increased risk of liver-specific and all-cause mortality (9). These patients in particular will benefit from specialist management and secondary care follow-up. However, a dependence on "routine" liver blood tests, which lack sensitivity for fibrosis (11), and the asymptomatic nature of liver fibrosis until patients develop the complications of end-stage of disease mean patients may progress silently in primary care. When patients presents with an episode of hepatic decompensation (ascites, encephalopathy, jaundice, variceal haemorrhage) or advanced hepatocellular cancer, the treatment options are often limited to either palliation or liver transplantation. A retrospective UK study analysing NAFLD patients listed for liver transplantation revealed 64% (52/81) initially presented to medical services with a cirrhotic decompensation event, highlighting that patients often present too late for reversal of their underlying liver disease (12). The emergence of non-invasive fibrosis tests has created the opportunity to improve case-finding in primary care with the aim of targeted referral of the higher risk patients with advanced liver fibrosis.

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Risk-stratification of patients

Until recent years, identifying cases of NAFLD with advanced fibrosis in primary care challenging. Two scoring systems have been widely adopted although not universally applied in secondary care: namely the NAFLD Fibrosis Score (NFS) (13) and Fib-4 score (initially devised for viral liver disease) (14). Both scores use basic clinical parameters (Fib-4 - age; NFS – age, diabetes, body mass index (BMI)) and common blood tests (Fib-4 and NFS – AST, ALT, platelets; NFS only – albumin) to assess the risk of advanced liver fibrosis.

With the use of appropriate thresholds, both NFS and Fib-4 perform well in secondary care to rule-out advanced fibrosis, with negative predictive values (NPV) well in excess of 90% (15), thereby enabling patients with low-risk NAFLD to be readily identified and discharged safely to primary care. Limited data from primary care settings are restricted to a few studies but show even better NPVs due to the lower prevalence of advanced fibrosis in this setting as compared to secondary care. However, increasing the test threshold/cut-offs, with the aim of increasing the specificity for detection of advanced fibrosis comes at the expense of sensitivity. Therefore, a low threshold/cut-off is often chosen to ensure that cases of advanced fibrosis are not missed when using either NFS or Fib-4 in primary care. Although this does not result in many "false negative" cases of advanced fibrosis being left in primary care, the consequence of using these low thresholds means that the corresponding positive predictive value (PPV) of these tests (i.e. their ability to identify advanced fibrosis) is modest

at 30-70%, generating a high number of "false positives" which in turn runs the risk of unnecessary specialist referrals, investigations potential harm and patient anxiety. Additional specialist tools have therefore been established in secondary care to further assess the risk of advanced fibrosis in these patients, with the main focus on ultrasound-based transient elastography (Fibroscan^{TM}) and the Enhanced Liver Fibrosis (ELF^{TM}) test. ELF is a proprietary blood test in which the levels of three complex molecules (hyaluronic acid, procollagen III amino-terminal peptide and tissue inhibitor of matrix metalloproteinase 1) associated with turnover of liver matrix, and has been shown to perform well in excluding advanced liver fibrosis, but also in the identification of fibrosis (16). Other tools exist including the French-based serological panel 'Fibrotest', acoustic radiation force impulse (ARFI) and magnetic resonance elastography (MRE); however due to cost, specialist expertise and acquisition time the latter is largely restricted to research use only.

Traditional management has been to perform this second level of risk stratification using specialist non-invasive fibrosis tests in secondary care. Thereafter a proportion of patients can be reassured and discharged for metabolic risk management to primary care. The remainder often require further assessment in the form of a liver biopsy if there is discrepancy between the non-invasive fibrosis tests or if they have been identified at increased risk for advanced fibrosis or cirrhosis and require definitive disease staging to guide their further management such as screening for complications of cirrhosis or entry into clinical trials.

However with the diffusion of liver fibrosis tests into primary care there is an opportunity for second stage testing (e.g. Fibroscan, ELF) to be performed in community settings, reducing the need for secondary/tertiary care referrals of patients with insignificant fibrosis, thereby reducing footfall in hospital outpatient departments, duplication of tests and patient anxiety. Furthermore, this approach can ensure that a greater proportion of the patients with NAFLD and advanced fibrosis are referred to secondary care for appropriate treatment and specialist surveillance.

Implementation of a two-step risk stratification protocol in primary care

Srivastava and colleagues have described the experience of adopting a two-step liver fibrosis risk stratification pathway conducted entirely in primary care (17). The study evaluated the outcomes of a prospective longitudinal cohort of over 3000 patients in North London. Their "NAFLD Pathway" was evaluated in 1452 patients and compared to the "standard-of-care" which did not have protocolised risk assessment. The NAFLD Pathway used Fib-4 as the initial screening test for patients with a clinical diagnosis of NAFLD and a raised ALT. Continued management in primary care was recommended for those deemed to be at low risk of advanced fibrosis (i.e. Fib-4 <1.45) on initial testing. Those judged to be at high risk (Fib-4 >3.25) were recommended for referral to the local hospital based hepatology

service. An indeterminate result (1.45 - 3.25) triggered second-line testing using ELF. Patients with low (<9.5) ELF scores remained in primary care management, while those with high (>9.5) scores were referred to hospital. The study found that use of the two-step pathway led to an 81% reduction in inappropriate referrals to secondary care (patients judged to not have advanced fibrosis on expert hepatology review). At the same time the pathway led to referral of 5 times more cases of advanced fibrosis and cirrhosis than routine standard-of-care. The NAFLD Pathway, combining sequential protocolised use of simple and specialised non-invasive fibrosis tests in primary care not only reduced the burden on secondary care services, but also identified patients with significant liver disease before they developed end-stage or irreversible pathology.

Health economics

The potential healthcare cost-savings of any new pathway must be taken in the context of the cost of the pathway tests themselves. In the case of the NAFLD Pathway this requires additional general practitioner time and further phlebotomy to send the ELF test, which currently has a cost of around £45. In some areas, the AST may not form part of the routine liver blood test panel, and this may also require additional testing to permit calculation of FIB4 scores.

Cost-savings from the North London NAFLD Pathway can be attributed to two broad areas. The first is a reduction in the costs associated with unnecessary referrals to secondary care for patients with low risk NAFLD, who could appropriately be managed in primary care with lifestyle intervention and intermittent monitoring. The second is the savings associated with earlier detection of cases of advanced fibrosis and cirrhosis, ensuring that these patients are referred onwards to specialist care. This timely referral to specialist services ensures that those with more advanced disease have access to therapies to potentially prevent progression to end-stage liver disease. Patients with these most advanced forms of the NAFLD disease spectrum incur disproportionate healthcare costs. A reduction in healthcare costs by use of sequential simple and specialised non-invasive tests to risk-stratify patients with NAFLD has consistently been shown in simulated cohort analyses (18, 19). Fib-4 with sequential ELF testing (as used in the North London NAFLD Pathway) was associated with a significant reduction in total budget spend of 25% in comparison to the model's standard-of-care. This corresponded to a potential saving of £169,000 over one year in a simulated primary care population containing 1000 patients with NAFLD (18). Notably, all approaches including using Fibroscan, or ELF, alone or in combination with Fib-4, reduced unnecessary referrals, increased detection of advanced fibrosis and reduced healthcare costs.

One concern prior to the implementation of new primary care pathways was that although the number of inappropriate referrals to secondary care may reduce, the overall number of new referrals

might rise. Although the North London NAFLD Pathway did result in a slight increase in the total number of referrals to secondary care, this occurred in parallel with an increase in the number of patients coded with a diagnosis of NAFLD on primary care databases. Therefore, although the absolute number of NAFLD referrals increased, there was a decrease in the proportion of patients who were diagnosed with NAFLD referred from 13% to 10% across the whole catchment area despite only 48% of referrals being made on the pathway. This suggests that the NAFLD Pathway was helped to identify and risk stratify more of the total caseload of NAFLD in the community.

Developing and implementing new risk-stratification models

The successful implementation of the NAFLD Pathway in North London demonstrates that a two-step non-invasive test approach is effective, particularly in reducing the number of inappropriate referrals. Use of Fib-4 alone would still have identified all the cases of advanced fibrosis, Use ELF ensured that a significant proportion (40%) of those with intermediate Fib-4 scores were reassured and avoided referral. Given the over-stretched secondary care clinics, this is an important factor. Depending on local arrangements, community Fibroscan clinics in place of ELF could perform a similar role. This has been shown to be feasible in some parts of the country (20), and has the potential advantage of greater clinician familiarity with the technology. Disadvantages include the cost of the Fibroscan machine, operator variability in performance, technician costs and clinic space in the community.

The NAFLD Pathway in North London was initially devised in 2012 with multi-disciplinary input from primary care physicians, hepatologists, public health consultants, commissioners and patients. The pathway required a year to innovate in conjunction with local clinical commissioning groups (CCGs). The success of service developments such as these depends upon collaboration, considerable time and effort in the planning stages. However, the use of non-invasive fibrosis markers in primary care for risk stratification is now established in national and international guidelines (8, 21).

Challenges

The experience of the NAFLD Pathway in North London does also highlight some challenges with the adoption of new clinical pathways. Firstly, the NAFLD Pathway was only used in 48% of referrals to secondary care, despite being readily available to all primary care practitioners and a programme of education and training. This shows the importance of iterative education around the development and implementation of new pathways, in addition to reinforcing messages about the clinical impact of 'silent' advanced liver fibrosis. Secondly, using the NAFLD Pathway, only 55.3% of those deemed to be at high risk of advanced fibrosis in primary care were referred to secondary care. Whilst some reasons for this were explicable such as co-morbidities and patient choice, the reason for not referring

was not clear in many cases raising further questions about the barriers to effective implementation of a new pathways. Some primary care practitioners reported that they deviated from the pathway because of constraints on consultation time and limited phlebotomy capacity, which in turn results in reluctance to invite the patients back for the second tier of non-invasive fibrosis testing. As a consequence some North London GPs have opted to omit FIB-4 testing and rely on ELF testing of NAFLD patients alone, a strategy that is clinically more effective but slightly less cost-effective. Similarly patients may decline the option of a secondary care referral, especially if they do not uderstand the long-term implications of advanced liver fibrosis and lack of potential pharmacological therapies.

Areas for future development

The implementation of new referral pathways for NAFLD, or alterations to existing pathways, could ultimately form one facet of a new approach to managing liver disease in primary care which has been termed "intelligent" liver function testing (iLFT) (22). This approach, pioneered in Dundee, uses an automated investigation algorithm, that employees reflex testing to complete a liver screen followed by the provision of clinical advice tailored to the situation. This approach has been trialled in Scotland and was shown to increase the diagnosis of liver disease, also demonstrating cost-effectiveness. It is easy to see how a reflex fibrosis assessment could be incorporated into this design, perhaps even allowing a "one button" assessment of NAFLD with appropriate advice given at the end of the assessment which may include suggested referral to secondary care or management within primary care. Such an approach could form part of a strategy to improve the detection and management of liver disease in general, an important endeavour given the increasing prevalence of and mortality from liver disease in the UK in the 21st Century and is currently being evaluated by the iLFT team..

Summary

Historically, patients with NAFLD and underlying advanced fibrosis have gone undetected until symptoms of liver failure or malignancy become apparent and therapeutic options are limited. At the same time patients with incidental, non-specific abnormal liver blood tests and fatty liver on ultrasound have undergone unnecessary investigations and secondary care follow-up. The evolution of novel non-invasive fibrosis tests in recent years has resulted in earlier detection of advanced fibrosis and, for the vast majority, reassurance that either they have no liver damage or that their liver disease is in the early stages and reversible. Utilisation of validated NAFLD referral pathways is not only cost-effective and optimises the use of healthcare resources, but it streamlines the appropriate patients into surveillance programs for the complications of cirrhosis and for entry into novel clinical trials. The use of an automated intelligent testing system in primary care offers significant promise, but in order

to reduce the growing burden of liver disease in the UK they will require widespread adoption and uptake which will in turn depend on investment and education.

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