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In search of the optimal management strategy for non-alcoholic fatty liver disease in type 2 diabetes patients

Non-alcoholic fatty liver disease (NAFLD) is present in over two-thirds of individuals with type 2 diabetes. Diabetes increases the risk of NAFLD progression, especially the development of non-alcoholic steatohepatitis, advanced fibrosis (AF; defined as fibrosis stage ≥3) and hepatocellular carcinoma[1]. In contrast, NAFLD also puts patients at a higher risk of cardiovascular diseases[2]. Driven by the rising prevalence of both obesity and type 2 diabetes, and increasing life expectancy of patients with type 2 diabetes consequent to the improved standard of care, it is envisioned that NAFLD will soon become a major diabetic complication.

It is now recognized that liver fibrosis, rather than non-alcoholic steatohepatitis, is the key determining factor of long-term adverse outcomes in NAFLD, including all-cause and liver-related mortality[3]. Therefore, most NAFLD guidelines recommend the early identification of those at risk of AF, although none has specifically issued recommendations on the best strategy to screen for AF in patients with type 2 diabetes, despite their high propensity for NAFLD progression. Serum alanine aminotransferase (ALT) level is an insensitive marker of NAFLD. Indeed, Tanabe *et al.*[4] showed that the optimal ALT cut-off to indicate the presence of NAFLD in patients with poorly controlled type 2 diabetes could be as low as 28 U/L in men and 20 U/L in women. An algorithm recently proposed by Bril and Cusi[3] suggested that patients with type 2 diabetes who have either confirmed or risk factors of NAFLD should receive non-invasive assessments, such as magnetic resonance elastography, transient elastography (TE) or fibrosis biomarker panels to estimate their severity of liver fibrosis for risk stratification.

Given the large volume of patients with type 2 diabetes comorbid with NAFLD, it is often difficult to translate these recommendations into real-world clinical practice. For instance, although magnetic resonance elastography reduces sampling error and has the highest area under the receiver operating curve of 0.96 in predicting AF in NAFLD[5], it is costly and time-consuming. Similarly, although TE offers a quick assessment with accurate and reproducible results (area under the receiver operating curve 0.88 and 0.85 for M and XL probe, respectively)[5], it is not available in most clinics that provide primary or specialist care for patients with type 2 diabetes. Furthermore, although several commonly used serum-based fibrosis scores perform reasonably well in the general NAFLD population (Table 1), their performance is less satisfactory when applied in populations with exclusively type 2 diabetes patients. For instance, although the area under the receiver operating curves of the NAFLD Fibrosis Score and Fibrosis-4 Index were both 0.84 in the general NAFLD population, they dropped to just 0.64 and 0.78, respectively, in patients with type 2 diabetes[6].

A few commercially available multimarker panels, such as Fibrotest, Hepascore and Enhanced Liver Fibrosis (ELF) test, have also been used for non-invasive assessment of hepatic fibrosis. ELF, for instance, is a serum-based fibrosis panel recommended by the National Institute of Health and Care Excellence guidelines, and comprises hyaluronic acid, tissue inhibitor of metalloproteinase 1 and N-terminal procollagen type III peptide. Although a recent meta-analysis showed that ELF is a promising fibrosis marker, especially if applied in populations with a high prevalence of AF[7], its performance in populations with exclusively type 2 diabetes patients remains to be confirmed. Furthermore, ELF is also limited by its high cost and accessibility.

Table 1 | Commonly used serum-based fibrosis panels for detection of advanced fibrosis in non-alcoholic fatty liver disease

	Variables	AUROC reported in general NAFLD population†
NFS	Age, BMI, hyperglycemia, platelet count, albumin and AST/ALT ratio	0.84
FIB-4	Age, platelet count, AST and ALT	0.84
APRI	Platelet count and AST	0.77
BARD	BMI, diabetes, AST and ALT	0.76

†Data from Xiao *et al.*[5] ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver operating curve; BMI, body mass index; FIB-4, Fibrosis-4 index; NAFLD, non-alcoholic fatty liver disease; NFS, non-alcoholic fatty liver disease fibrosis score.

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Various adipokines, such as adiponectin, fibroblast growth factor 21 and adipocyte fatty acid-binding protein, have been investigated as potential fibrosis markers in NAFLD. This is in part related to the common soil that is shared between obesity and NAFLD, such as adipose tissue inflammation, lipotoxicity and insulin resistance[8,9]. Recently, Miyauchi *et al.*[10] also showed that circulating levels of insulin-like growth factor-1, shown to stimulate hepatic stellate cells in mice, were inversely associated with liver fibrosis markers, including Fibrosis-4 Index and 7S domain of type IV collagen, in patients with type 2 diabetes and NAFLD. However, there is still a long road before these adipokines or hepatokines can be used outside the research laboratories as commercially available fibrosis markers in clinical practice. Therefore, to avoid a flood of referrals to hepatology clinics for TE or further investigations, a simple and cost-effective strategy is eagerly awaited to facilitate AF risk stratification in patients with type 2 diabetes and NAFLD.

Patients with type 2 diabetes and AF should be jointly managed by diabetologists and hepatologists. Although lifestyle modification is an important first step in patients with NAFLD, it should be noted that to attain an improvement in hepatic fibrosis, patients might have to achieve >10% weight loss and engage in 75 min per week of vigorous physical activity. Diabetologists should therefore assess if patients require pre-exercise medical clearance and more frequent monitoring of their glycemic control, especially for those who have baseline cardiovascular diseases or are at high cardiovascular risk, or on a complex antidiabetic regimen. Furthermore, their antidiabetic agents should be streamlined to those with proven beneficial effects in NAFLD, such as pioglitazone, glucagon-like peptide-1 receptor agonists especially liraglutide[11] and sodium–glucose cotransporter 2 inhibitors. Indeed, a recent meta-analysis reported that sodium–glucose cotransporter 2 inhibitors could significantly reduce serum ALT levels and hepatic steatosis on magnetic resonance imaging in patients with type 2 diabetes[12] Inoue *et al.*[13] also showed that treatment with canagliflozin for 12 months reduced serum type IV collagen. Interestingly, in a randomized trial comparing pioglitazone, dapagliflozin and glimepiride in patients with type 2 diabetes and NAFLD, both pioglitazone and dapagliflozin significantly reduced their serum ALT levels to a similar extent. The reduction of type IV collagen levels, although not significant, was also comparable between pioglitazone and dapagliflozin[14]. Patients should be monitored by hepatologists for cirrhosis-related complications, such as the development of esophageal varices and hepatocellular carcinoma. Recent recommendations suggested that regular hepatocellular carcinoma screening by ultrasound should be offered to NAFLD patients who had severe liver stiffness ≥16.1 kPa on TE and documented AF by another non-invasive test[15].

In summary, there are clearly gaps between clinical guidelines and real-world practice. With the increasing number of patients with type 2 diabetes comorbid with NAFLD, all stakeholders of the healthcare system should work together to optimize AF detection by improving the accessibility of screening tools at a lower cost, so that timely treatment and surveillance can be provided to those at risk of long-term adverse liver outcomes.

DISCLOSURE

The authors declare no conflict of interest.

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