

Non-alcoholic fatty liver disease and type 2 diabetes: An update

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ABSTRACT

The global prevalence of non-alcoholic fatty liver disease (NAFLD) is rising, along with the epidemic of diabetes. NAFLD is present in >70% of individuals with type 2 diabetes. Although the mutually detrimental relationship between NAFLD and type 2 diabetes has been well established, a multitude of recent studies have further shown that type 2 diabetes is closely linked to the development of cirrhosis, hepatocellular carcinoma, liver-related morbidity and mortality. In contrast, NAFLD also negatively impacts type 2 diabetes both in terms of its incidence and related adverse clinical outcomes, including cardiovascular and chronic kidney diseases. In response to these global health threats, clinical care pathways for NAFLD and guidelines for metabolic dysfunction-associated fatty liver disease have been developed. Several antidiabetic agents have been evaluated for their potential hepatic benefits with promising results. Furthermore, type 2 diabetes patients are increasingly represented in clinical trials of novel therapeutics for NAFLD. However, despite the wealth of knowledge in NAFLD and type 2 diabetes, lack of awareness of the disease and the potential weight of this problem remains a major challenge, especially among clinicians who are outside the field of hepatology and gastroenterology. This review therefore aimed to provide all diabetes care providers with a summary of the latest evidence that supports NAFLD as an emerging diabetic complication of increasing importance, and to present the current recommendations, focusing on the assessment and therapeutic strategies, on the management of NAFLD among type 2 diabetes patients.

INTRODUCTION

The global prevalence of diabetes continues to rise. According to the latest report from the International Diabetes Federation, 10.5% of the world adult population have diabetes. If these trends continue, one in eight adults will be living with diabetes by the year 2045¹. Similarly, non-alcoholic fatty liver disease (NAFLD) affects one-quarter of the global population².

NAFLD consists of a spectrum of hepatic disorders, ranging from isolated hepatic steatosis, to non-alcoholic steatohepatitis (NASH), advanced fibrosis (AF), cirrhosis, development of hepatocellular carcinoma (HCC) and liver-related mortality³. Among the multiple hits in the pathogenesis of NAFLD, obesity, insulin resistance and type 2 diabetes are the major drivers of its progression^{4,5}. In a recent meta-analysis, the global prevalence of NAFLD in type 2 diabetes patients was more than twice that in the general population, reaching almost 60%, and NASH was present in a third of

them⁶. Furthermore, among those who underwent liver biopsy, 17% had AF, which is the major determinant of all-cause mortality and adverse liver-related outcomes among the various stages of NAFLD^{7,8}. Therefore, with obesogenic lifestyle, aging population and the soaring prevalence of type 2 diabetes, it is projected that by 2030, there will be a 137% and 178% substantial increase in NASH-related HCC and liver deaths, respectively⁹.

Importantly, mathematical modeling has shown that type 2 diabetes patients with NASH will account for 1.27 million decompensated cirrhosis person-years, 479,000 HCC person-years, 29% of liver transplants, 812,000 liver-related deaths and 1.37 million cardiovascular deaths over the next two decades¹⁰. These alarming estimates call for a comprehensive public health response to fight this global health crisis, not only among hepatologists, but also other clinicians, especially primary care physicians, diabetes care providers and endocrinologists¹¹.

The present review summarizes recent important findings that have shaped NAFLD as an emerging diabetes complication of increasing importance, and provides a clinical update focusing on the assessment and therapeutic strategies in managing NAFLD in type 2 diabetes.

THE MUTUALLY DETRIMENTAL RELATIONSHIP OF NAFLD AND TYPE 2 DIABETES

The bidirectional relationship between NAFLD and type 2 diabetes has been well reported^{12,13}. Type 2 diabetes promotes NAFLD progression to cirrhosis, and elevates the risks of liver-related and all-cause mortality by two- to threefold^{5,14}. In a recent study involving 713 participants with biopsy-proven NAFLD (48% with type 2 diabetes), it was shown that each 1% increase in mean glycated hemoglobin (HbA1c) in the year preceding liver biopsy was independently associated with a 15% higher odds of harboring more severe stages of liver fibrosis, highlighting the effect of glycemia on fibrosis progression¹⁵.

In addition to mean HbA1c, it was found from another study that visit-to-visit HbA1c variability was also an independent predictor of the development of NAFLD¹⁶. Furthermore, type 2 diabetes is a major risk factor of HCC development^{17,18}. Among patients with NASH-related cirrhosis, type 2 diabetes was associated with a fourfold increased risk of incident HCC¹⁹. In a recent real-world study of 18 million European adults with NAFLD, the presence of diabetes was the strongest independent predictor for HCC²⁰.

In contrast, the presence of NAFLD also negatively impacts type 2 diabetes both in terms of its incidence and related adverse clinical outcomes. In an updated meta-analysis involving >500,000 middle-aged individuals (30% with imaging-defined or biopsy-confirmed NAFLD) from Asia, the USA and Europe, NAFLD was associated with a twofold increased risk of developing type 2 diabetes after adjustments for age, sex, adiposity parameters and other conventional metabolic risk factors. Importantly, the risk was greater with more severe hepatic steatosis and fibrosis²¹.

Consistently, a nationwide population-based study in Korea with >5 million young adults also showed that NAFLD increased incident diabetes by fivefold, and the associations were even stronger among those who were men, smokers, sedentary and obese with body mass index ≥ 25 kg/m²²². These epidemiological findings were in line with a recent Mendelian randomization study showing that genetically driven NAFLD, based on risk variants in the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) and transmembrane 6 superfamily member 2 (*TM6SF2*) genes, was causally related to incident diabetes²³.

NAFLD is also known to be associated with other extrahepatic conditions, including cardiovascular and chronic kidney diseases (CKD), which are classical macro- and microvascular diabetes complications, respectively²⁴. Two recent meta-analyses showed that NAFLD conferred a 45% increased risk of fatal and non-fatal cardiovascular diseases (CVD), as well as incident

CKD stage ≥ 3 . Importantly, these risks appeared to correlate positively with the severity of hepatic fibrosis^{25,26}. In a prospective community-based study involving >4,000 participants, both incident NAFLD and fibrosis progression, as determined by NAFLD fibrosis score (NFS), were associated with the development of CKD²⁷. In type 2 diabetes, liver stiffness (LS) measurements, which reflect liver fibrosis, on either vibration-controlled transient elastography (VCTE) or magnetic resonance elastography, were associated with increased cardiovascular risk and CVD^{28,29}. Similarly, advanced liver fibrosis had also been shown as an independent risk factor for both the presence and development of albuminuria in type 2 diabetes^{30–32}. Although a few studies had evaluated the relationship between NAFLD and diabetic retinopathy, the association remained controversial^{28,33}.

METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

In 2020, a consensus of international experts proposed a new disease entity “metabolic dysfunction-associated fatty liver disease” (MAFLD) hoping to more precisely define fatty liver disease³⁴. Notably, NAFLD is a diagnosis of exclusion, defined as the presence of fatty liver in the absence of excessive alcohol consumption; use of steatogenic medications, such as tamoxifen or methotrexate; viral hepatitis; and other chronic liver diseases. MAFLD, in contrast, is diagnosed based on the presence of hepatic steatosis in addition to any one of the three criteria, including overweight or obesity, presence of type 2 diabetes, or evidence of metabolic dysfunction³⁴. Therefore, in essence, all type 2 diabetes patients with fatty liver disease have MAFLD, but not necessarily belonging to the NAFLD population if they have excessive alcohol consumption and/or the presence of concomitant chronic liver diseases.

As expected, studies published since the proposal of the new diagnostic entity of MAFLD have shown considerable overlap between patients classified based on the two definitions, and further studies are required to clarify whether these two groups of patients differ in terms of their development of long-term adverse liver-related and extra-hepatic outcomes^{35,36}.

DYSFUNCTIONAL ADIPOSE TISSUE AS A COMMON SOIL FOR NAFLD IN TYPE 2 DIABETES

Nevertheless, the proposal of MAFLD as a disease entity has highlighted the impact of suboptimal metabolic health on fatty liver disease progression. Adipose tissue dysfunction and inflammation are key common initiating events in the pathogenesis of type 2 diabetes and NAFLD^{37,38}. Dysfunctional adipose tissue alters adipokine production toward the generation of a pro-inflammatory, diabetogenic and atherogenic profile, with increases in the pro-inflammatory adipokines and reductions in the anti-inflammatory adipokines³⁹. These pro-inflammatory adipokines activate c-Jun NH2-terminal kinase and nuclear factor kappa B pathways, participate in the vicious cycle of adipose tissue insulin resistance and inflammation, and contribute to the development of whole-body insulin resistance

and systemic inflammation. The high rate of spontaneous lipolysis enhances free fatty acid efflux, and in the presence of insulin resistance, which favors hepatic de novo lipogenesis, fuels the liver for fat accumulation⁴⁰. The gluco- and lipotoxicities that ensue, together with mitochondrial dysfunction, oxidative and endoplasmic reticulum stress, and altered gut microbiome, collectively promote hepatic inflammation and liver sinusoidal endothelial cells capillarization, leading to activation of the hepatic stellate cells, which drive liver fibrosis progression^{37,38}.

Several adipokines have been implicated in the pathogenesis of both NAFLD and type 2 diabetes⁴¹. Adiponectin is probably one of the oldest adipokines that has been well known for its insulin-sensitizing, anti-inflammatory and anti-atherogenic properties^{42,43}. Low circulating adiponectin levels have been associated with the development of type 2 diabetes in epidemiological studies^{44,45}. Furthermore, the circulating adiponectin level was inversely related to fibrosis stage among individuals with biopsy-proven NAFLD, and recombinant adiponectin treatment ameliorated NASH in mice^{46,47}.

The cross-talk between adipose tissue and the liver was also illustrated in a recent study showing that adipocyte pleckstrin homology domain leucine-rich repeat protein phosphatase 2 excess in obesity could reduce peroxisome proliferator-activated receptor alpha (PPAR α) activity and adiponectin secretion from the adipocytes, causing reduced hepatocyte fatty acid oxidation. Consistently, mice with adipocyte-specific ablation of pleckstrin homology domain leucine-rich repeat protein phosphatase 2 had higher adipocyte expression and circulating levels of adiponectin, and hence were protected from obesity-related fatty liver disease⁴⁸.

Adipocyte fatty acid-binding protein (AFABP) is a cytosolic protein abundantly secreted from the adipocytes to the circulation⁴⁹. It is also highly expressed in the macrophages, including the Kupffer cells in the liver^{50,51}. Elevated circulating AFABP level was associated with all the components of metabolic syndrome, including central obesity, insulin resistance, hypertension and atherogenic dyslipidemia, and was an independent predictor of the development of type 2 diabetes^{52,53}. A high circulating AFABP level was also shown to be independently associated with ultrasound-defined NAFLD in type 2 diabetes patients, as well as MAFLD based on the fatty liver index in a recent study of middle-aged and elderly Japanese individuals^{54,55}.

As a pro-inflammatory adipokine, the circulating AFABP level correlated with lobular inflammation and fibrosis stage among individuals with biopsy-proven NAFLD, even after adjustments for adiposity indices and glycemic status^{56,57}. A recent study further showed that AFABP expression was increased in liver sinusoidal endothelial cells in mice with liver fibrosis. AFABP enhanced liver sinusoidal endothelial cell capillarization and potentiated liver fibrosis through augmenting transforming growth factor beta-1 production in the hepatic stellate cells⁵⁸. Importantly, preclinical studies had shown that pharmacological inhibition of AFABP could alleviate both

NASH and liver fibrosis in mice, highlighting AFABP as a potential therapeutic target in NAFLD and type 2 diabetes^{51,58}.

Gremlin-1 is among the novel adipokines that are associated with both type 2 diabetes and NAFLD. It is a major secreted endogenous antagonist inhibiting the effect of bone morphogenetic protein 4 on adipose precursor cell commitment and differentiation, as well as induction of beige and brown adipogenesis. In a recent study, Gremlin-1 was found to impair insulin signaling and action in adipose tissue, muscle, and liver cells, with high serum levels observed in type 2 diabetes patients. Furthermore, among type 2 diabetes patients, those with biopsy-proven NASH had significantly higher liver GREMLIN1 messenger ribonucleic acid expression than those with isolated hepatic steatosis⁵⁹.

CLINICAL ASSESSMENTS

In response to this NAFLD/MAFLD epidemic, a multidisciplinary team of experts involving gastrohepatologists, endocrinologists and primary care physicians has devised a Clinical Care Pathway highlighting the key steps in screening, diagnosis and treatment of NAFLD⁶⁰. The Asian Pacific Association for the Study of the Liver has also issued the first clinical practice guidelines for the diagnosis and management of MAFLD⁶¹.

CASE DETECTION

The Clinical Care Pathway recommends screening all type 2 diabetes patients for hepatic steatosis⁶⁰. The Asian Pacific Association for the Study of the Liver MAFLD guidelines and the Asia-Pacific Working Party on NAFLD recommend consideration of screening all type 2 diabetes patients with ultrasound (USG) of the liver^{61,62}. VCTE was suggested by the latter as a screening tool to detect minor steatosis if available⁶². In contrast, the American Association for the Study of Liver Diseases guidelines do not recommend systematic screening for NAFLD partly due to concerns over cost-effectiveness³.

However, a recent cost-utility analysis using a Markov model showed that the approach of screening all type 2 diabetes patients initially with USG of the liver and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels, followed by VCTE to detect those who would most likely be harboring significant hepatic fibrosis to receive intensive lifestyle intervention, was in fact cost-effective⁶³. For the diabetes guidelines, the European Association for the Study of Diabetes, together with the European Association for the Study of the Liver and the European Association for the Study of Obesity recommends screening for NAFLD in high-risk populations, such as those with type 2 diabetes⁶⁴. Since 2019, the American Diabetes Association has also started to recommend screening for NASH and AF in those with elevated ALT levels or fatty liver found on USG⁶⁵.

FIBROSIS ASSESSMENTS

The prognostic importance of liver fibrosis in relation to long-term adverse outcomes has been well established^{7,8,66,67}. In a

recent prospective study involving 1,773 individuals with biopsy-proven NAFLD followed up for a median of 4 years, AF and cirrhosis almost doubled and quadrupled the risk of all-cause mortality, respectively⁶⁸. Therefore, recent guidelines recommend assessments for hepatic fibrosis in patients with fatty liver disease, in particular type 2 diabetes patients with NAFLD⁶². A two-tier screening algorithm has been proposed, with the use of non-invasive serum-based markers followed by VCTE assessments for those with intermediate risk^{60,69}. However, there have been concerns over the several commonly used serum-based fibrosis scores, such as NFS and Fibrosis-4 (Fib-4) index, which although they perform reasonably well in the general NAFLD population, become less satisfactory when applied in type 2 diabetes patients^{70,71}.

Indeed, in a recent cross-sectional study involving 162 type 2 diabetes patients who had NAFLD and with liver biopsy carried out, none of the conventional non-invasive fibrosis scores (NFS, Fib-4) performed better than plasma AST level alone⁷¹. A few groups have therefore developed diabetes-specific non-invasive fibrosis scores using cohorts of exclusively type 2 diabetes patients with biopsy-proven NAFLD^{71–73}. For instance, the Diabetes Liver Fibrosis Score was recently developed to identify AF based on six clinical variables, including age, hypertension, CKD, lipid-lowering medications, platelet count and serum AST levels, with an area under the receiver operating characteristic curve of 0.79⁷³.

There have also been suggestions on the direct use of VCTE in fibrosis risk stratification among type 2 diabetes patients⁷⁴. Several recent studies worldwide using VCTE assessments alone have reported a high prevalence of moderate-to-advanced liver fibrosis in type 2 diabetes patients, ranging from 15% to 27%^{75–78}. However, VCTE is not widely available in healthcare institutions, and even if it is, given the large volume of type 2 diabetes patients with NAFLD, it is still a challenge to provide timely assessments to all patients with type 2 diabetes in both primary and secondary care sectors.

Our group has recently developed and internally validated a non-invasive Diabetes Fibrosis Score to identify those who would have AF on VCTE with an area under the receiver operating characteristic curve of >0.80, based on five routine measurements in standard diabetes care: body mass index, platelet, AST, high-density lipoprotein cholesterol and albuminuria⁷⁹. Although further external validation is required, given the promising area under the receiver operating characteristic curve and a negative predictive value of >90% for AF, the Diabetes Fibrosis Score would be particularly useful to screen out those without AF in type 2 diabetes, and help facilitate early referral to hepatologists for further investigations.

PHARMACOLOGICAL MANAGEMENT

Lifestyle modification, in particular weight reduction, remains the cornerstone in the management of NAFLD and MAFLD. A dose–response relationship between weight loss percentage and the overall improvements in liver histology has been

reported, with ≥ 7 –10% of weight reduction required to achieve NASH resolution and improvement in hepatic fibrosis⁸⁰.

Although no pharmacological agents are currently approved for treating NAFLD or specifically, NASH, by the US Food and Drug Administration or the European Medicines Agency, a few classes of antidiabetes medications should be prioritized for use in type 2 diabetes patients with NAFLD, in particular those with NASH and significant fibrosis, either in view of their proven hepatic benefits from randomized controlled trials (RCT), or their significant weight-reducing properties beyond HbA1c lowering. Specifically, pioglitazone and glucagon-like peptide-1 (GLP1) receptor agonists have been recommended in the latest American Diabetes Association guidelines in 2022⁸¹. Furthermore, as NAFLD is closely related to the development of CVD and CKD, agents that offer cardiorenal protection should also be preferable (Figure 1).

PPAR AGONISTS

PPARs are ligand-dependent nuclear receptor proteins, functioning as transcription factors, which play major roles in lipid and glucose metabolism. All three PPAR isoforms – α , β/δ and γ – are implicated in the pathogenesis of NASH and hepatic fibrosis through different inter-related pathways⁸². In particular, PPAR γ maintains hepatic stellate cells in a quiescent state under normal conditions and, hence, its overexpression could reduce collagen production and fibrogenesis.

A meta-analysis involving eight RCTs showed that pioglitazone, a PPAR γ -agonist with potent insulin sensitizing properties, improved liver fibrosis, especially AF in patients with NASH⁸³. Interestingly, the beneficial effects of pioglitazone on liver fibrosis seemed to be more readily observed among type 2 diabetes patients⁸⁴. In type 2 diabetes patients with NASH, the addition of vitamin E 400 IU twice daily to pioglitazone did not provide additional improvement in liver histology compared with pioglitazone alone⁸⁵.

In addition to enhancing PPAR γ activity alone, combined PPAR agonism is another attractive potential therapeutic strategy in NAFLD. PPAR α is involved in fatty acid transport and β -oxidation, and PPAR β/δ modulates inflammatory activities in the macrophages and Kupffer cells. Therefore, combined PPAR agonism should in theory lead to improved hepatic steatosis, NASH and fibrosis⁸².

Although elafibranor, a PPAR α/δ dual agonist, failed to resolve NASH in its phase III development program, lanifibranor, which is a pan-PPAR agonist, showed promising results in a recent phase IIb RCT involving 247 participants with NASH (42% type 2 diabetes). In that study, a higher dose of lanifibranor 12,00 mg met its primary outcome with significant improvement in NASH and hepatic fibrosis. Peripheral edema was observed in 2% of the lanifibranor-treated participants. The increase of 2.7 kg (3.1%) of bodyweight from baseline with lanifibranor was also similar to those reported in studies with pioglitazone (2–5%)⁸⁶.

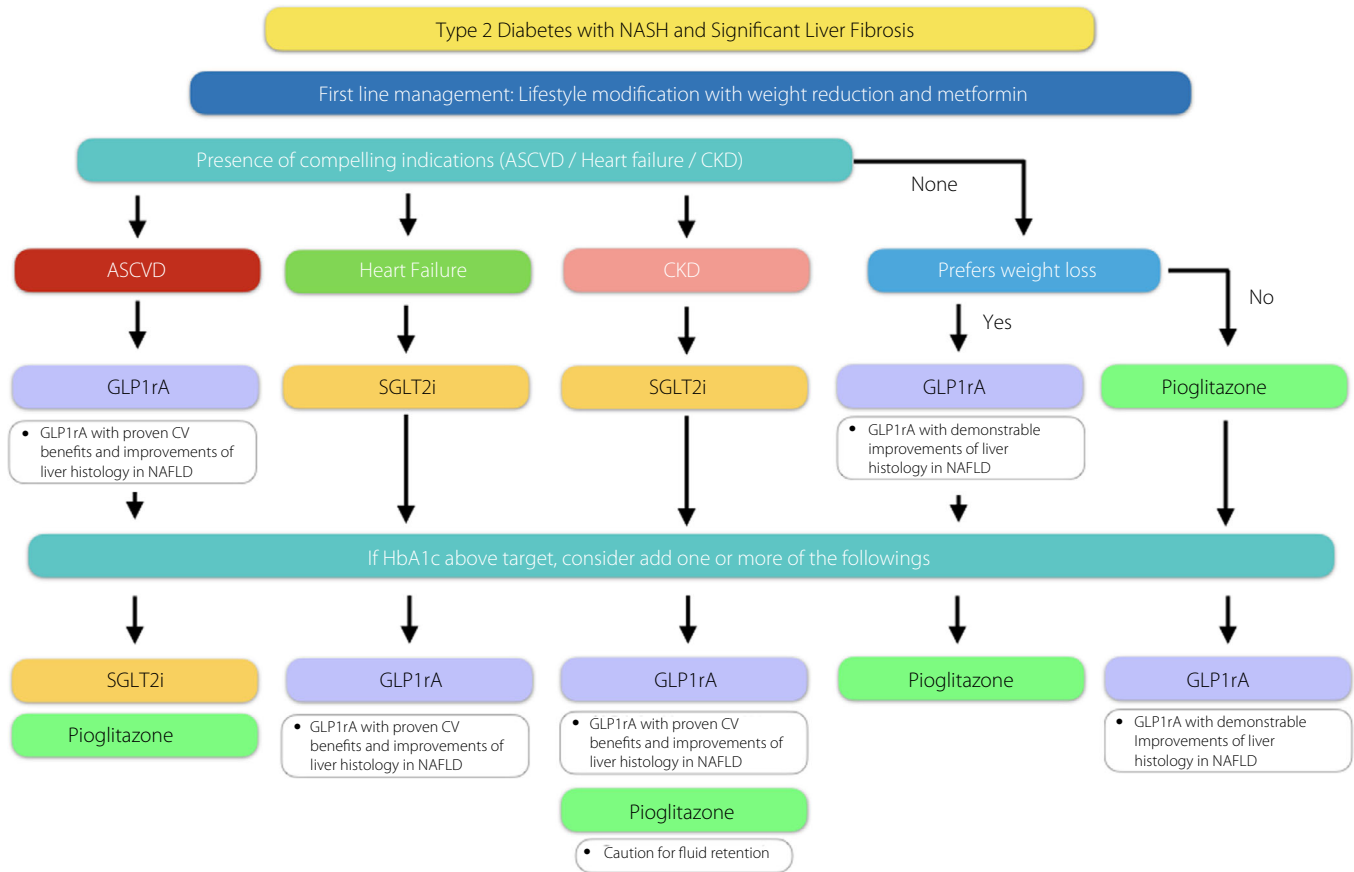


Figure 1 | Evidence-based pharmacological approach to glycemic control in patients with type 2 diabetes and non-alcoholic steatohepatitis (NASH) with significant fibrosis. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; GLP1rA, glucagon like-peptide-1 receptor agonists; HbA1c, glycated hemoglobin; SGLT2i, sodium–glucose cotransporter 2 inhibitors.

INCRETIN-BASED THERAPY

GLP1 receptor agonist is another class of antidiabetic agent that has shown hepatic benefits in NAFLD, in addition to glucose lowering and cardiorenal protection⁸⁷. In the Liraglutide safety and efficacy in patients with NASH (LEAN) study in 2016, which involved 52 participants with NASH (~30% with type 2 diabetes), treatment with liraglutide 1.8 mg daily for 48 weeks significantly resolved NASH, improved hepatic steatosis and reduced worsening of liver fibrosis compared with placebo⁸⁸.

In a recent RCT involving 320 participants with NASH (62% with type 2 diabetes; 49% with AF), treatment with subcutaneous semaglutide 0.4, 0.2 and 0.1 mg daily for 72 weeks all significantly increased the percentage of participants achieving resolution of NASH without worsening of liver fibrosis, compared with placebo, with an odds ratio 6.87, 2.71 and 3.36, respectively (all $P < 0.05$).

As GLP1 receptors are not present in the hepatocytes, it is generally agreed that GLP1 receptor agonists exert these beneficial effects indirectly through weight loss with alleviation of adipose tissue dysfunction and lipotoxicity, modulation of portal

and peripheral plasma insulin and glucagon levels, as well as improvement in hepatocyte mitochondrial function and hepatic insulin resistance⁸⁹.

Several other incretin-based therapies, which promote even more potent weight reduction than GLP1 receptor agonists, are in development. Clinical trials that evaluate their effects in NASH and NAFLD are eagerly awaited. Tirzepatide, a dual agonist of GLP1 and glucose-dependent insulinotropic polypeptide, was associated with a further 8.6 kg and 1.3% lowering of bodyweight and HbA1c, respectively, in a phase II study comparing it with dulaglutide⁹⁰. Furthermore, treatment with tirzepatide 15 mg daily also significantly reduced serum ALT and keratin-18 M30 fragment (a NASH marker), as well as the fibrosis marker procollagen III in type 2 diabetes patients⁹¹. More recently, treatment of type 2 diabetes patients with cotadutide, a dual agonist of GLP1 and glucagon receptor agonist, for 54 weeks was also shown to significantly improve ALT, NFS, Fib-4 index and procollagen III levels compared with placebo, in a phase IIb study⁹².

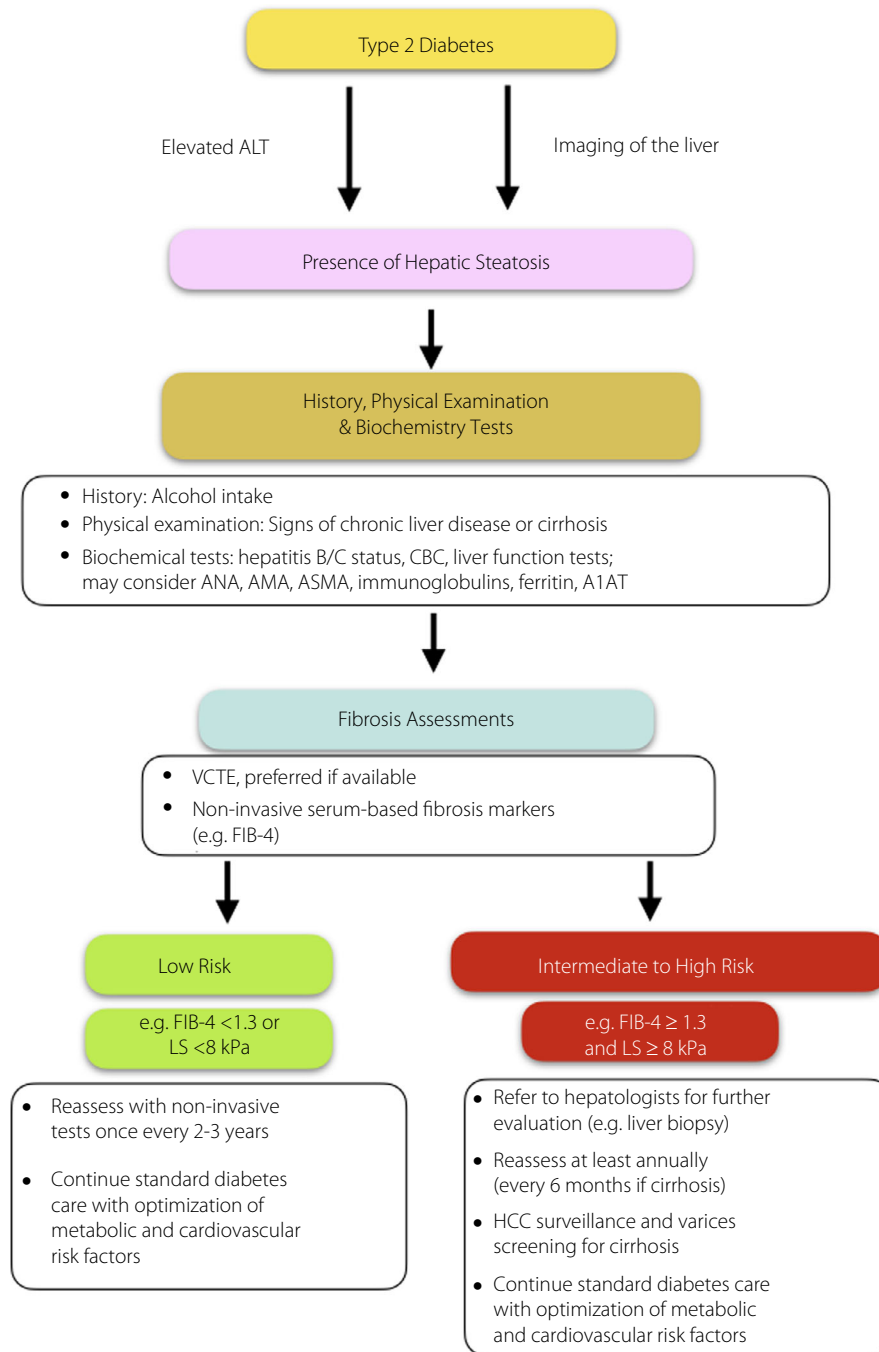


Figure 2 | Systematic evaluation for patients with type 2 diabetes and non-alcoholic fatty liver disease. A1AT, alpha-1 antitrypsin; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibody; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody; CBC, complete blood count; FIB-4, fibrosis 4 index; HCC, hepatocellular carcinoma; LS, liver stiffness; VCTE, vibration controlled transient elastography.

SODIUM–GLUCOSE COTRANSPORTER 2 INHIBITORS

Sodium–glucose cotransporter 2 inhibitor (SGLT2i) has been recommended widely for use in type 2 diabetes patients due to its substantial cardiorenal benefits, as shown in several large-scale RCTs^{93–100}. Although SGLT2i is likely a favorable drug in NAFLD due to its

weight-reducing property, RCT that involves participants with biopsy-proven NASH is lacking at present.

In a recent open-label, pilot study consisting of nine type 2 diabetes patients with NASH, compared with historical placebo, treatment with empagliflozin for 24 weeks significantly improved hepatic steatosis, hepatocyte ballooning and fibrosis,

in keeping with findings from preclinical studies on SGLT2i and NAFLD^{101,102}. A meta-analysis of six RCTs involving 309 type 2 diabetes patients concluded that SGLT2i significantly reduced serum ALT levels and magnetic resonance imaging proton density fat fraction¹⁰³.

Another RCT of 57 type 2 diabetes patients with NAFLD also showed that treatment with dapagliflozin for 24 weeks decreased LS measurements on VCTE and the improvement was significant among those with baseline LS ≥ 8.0 kPa¹⁰⁴. The two ongoing RCTs, namely, the Dapagliflozin Efficacy and Action in NASH (DEAN) and the Combined Active Treatment in Type 2 Diabetes with NASH (COMBAT_T2_NASH) studies will provide more insights and clarify the role of SGLT2i in type 2 diabetes patients with NAFLD.

MONITORING

The Asian Pacific Association for the Study of the Liver MAFLD guidelines recommend monitoring patients at regular intervals according to the presence of hepatic fibrosis at baseline⁶¹. A previous prospective study involving 52 NAFLD Chinese patients (50% with type 2 diabetes) with paired liver biopsies at 3 years showed that 27% had fibrosis progression by ≥ 1 stage¹⁰⁵. In another study of 80 Asian NAFLD patients with paired liver biopsies at 1 year, 11% developed fibrosis progression by ≥ 1 stage. The presence of type 2 diabetes was significantly associated with high-risk participants, defined in the study as those who had AF at baseline, but did not improve, and those who developed new AF after 1 year¹⁰⁶.

Using VCTE, in a recent study of 487 exclusively type 2 diabetes patients recruited from both primary care and hospital clinics, just 4.3% developed LS ≥ 10 kPa over a median follow-up period of 3.5 years¹⁰⁷. In contrast, our group recently showed that among 682 type 2 diabetes patients from hospital clinics, 8.8% developed AF (defined as LS ≥ 9.6 kPa) over a median follow-up period of 1.5 years. Those who were obese, with low platelet count and high hepatic steatosis on VCTE at baseline were at increased risk of incident AF⁷⁸. Therefore, it is recommended that patients with fibrosis at baseline should be monitored at least annually, whereas those without can be monitored every 2–3 years, provided there is no worsening of concomitant metabolic risk factors.

The surveillance protocol should also include routine biochemistry and evaluation of comorbidities, such as obesity, hypertension and dyslipidemia⁶¹. In a recent prospective study involving >100,000 patients with prediabetes or type 2 diabetes, it was shown that the achievement of metabolic goals, which included HbA1c <6.5%, blood pressure <130/80 mmHg and low-density lipoprotein-cholesterol <2.6 mmol/L, would help to attenuate the risk of CVD and CKD development regardless of the severity of concomitant NAFLD based on AST/ALT ratio¹⁰⁸. These findings emphasized the importance of optimizing metabolic parameters in type 2 diabetes patients with NAFLD to reduce the risk of CVD and CKD, which are major diabetes complications also closely related to NAFLD.

Type 2 diabetes patients with cirrhosis or at high risk of fibrosis progression from non-invasive assessments should be referred to hepatologists for further evaluation and monitoring at least every 6 months^{60,61}. These include consideration of liver biopsy, provision of varices screening and HCC surveillance. The latest recommendations also suggested that those with NAFLD and who had two non-invasive markers (serum-based fibrosis scores and elastography) concordantly showing evidence of AF or cirrhosis should be considered for HCC screening using USG of the liver, with or without α -fetoprotein, once every 6 months¹⁰⁹. Furthermore, with the long list of candidate compounds lining up in the therapeutic pipeline for NASH (e.g., farnesoid X receptor agonist, fibroblast growth factor 21 and 19 analogs, acetyl coenzyme A carboxylase inhibitor, GLP1-based co-agonists, thyroid hormone receptor-beta agonist etc.), type 2 diabetes patients with NASH can be considered for eligibility for recruitment to ongoing and upcoming clinical trials¹¹⁰.

CONCLUSION

Although it generally takes years for NAFLD to progress from isolated liver steatosis to adverse liver outcomes, such as cirrhosis and HCC, type 2 diabetes patients are now living longer given the improved standard of diabetes care, especially on their cardiovascular health^{111–113}. Therefore, it is timely to put more focus on NAFLD by increasing disease awareness among all diabetes care providers, and promoting the implementation of clinical care pathways through policy-makers and stakeholders in the government and healthcare institutions to enable more systematic evaluation (Figure 2). Finally, pharmaceutical companies should be engaged to invest in research on new therapeutics of NASH and liver fibrosis, with inclusion of more type 2 diabetes patients for better representation in the trial population. It is only then that we would be better prepared to fight against this emerging major diabetes complication.

DISCLOSURES

The authors declare no conflict of interest.

Approval of the research protocol: N/A.

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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