Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach

Giovanni Targher, Herbert Tilg, Christopher D Byrne

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Department of Medicine, Section of Endocrinology, Diabetes, and Metabolism, Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy (Prof G Targher MD); **Department of Internal Medicine I, Gastroenterology, Hepatology, Endocrinology, and Metabolism, Innsbruck Medical University, Innsbruck, Austria** (Prof H Tilg MD); **Department of Nutrition and Metabolism, Faculty of Medicine, University of Southampton, Southampton, UK** (Prof C D Byrne MB BCh); **NIHR Southampton Biomedical Research Centre, University Hospital Southampton, Southampton, UK** (Prof C D Byrne)

Correspondence to: Prof Giovanni Targher, Department of Medicine, Section of Endocrinology, Diabetes, and Metabolism, Azienda Ospedaliera Universitaria Integrata Verona, 37126 Verona, Italy **giovanni.targher@univr.it**

Non-alcoholic fatty liver disease (NAFLD) is a public health problem worldwide. This narrative Review provides an overview of the current literature to support the notion that NAFLD is a multisystem disease. Convincing evidence shows a strong association between NAFLD and the risk of developing multiple extrahepatic complications such as type 2 diabetes, cardiovascular disease (ie, the predominant cause of mortality in people with NAFLD), chronic kidney disease, and some types of extrahepatic malignancies. The magnitude of this risk parallels the severity of NAFLD (especially the stage of liver fibrosis). There are probably multiple underlying mechanisms by which NAFLD might increase the risk of cardiovascular disease, type 2 diabetes, and extrahepatic complications. Addressing the growing burden of NAFLD will require setting up a multidisciplinary working group and framework to progress and embrace novel collaborative ways of working to deliver holistic, person-centred care and management of people with NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a public health problem worldwide that affects around 30% of the adult population, causing considerable liver-related and extrahepatic morbidity and mortality.[1–3] NAFLD is associated with an increased risk of all-cause mortality. The leading cause of mortality in patients with NAFLD is cardiovascular disease, followed by extrahepatic cancers, and liver-related complications.[1–3]

In the past 6 years, it has becoming increasingly evident that NAFLD is a multisystem disease,[4] which not only increases the risk of liver-related complications (non-alcoholic steatohepatitis [NASH], cirrhosis, or hepatocellular carcinoma), but also increases the risk of type 2 diabetes, chronic kidney disease, and some extrahepatic cancers (eg, colorectal cancer).[1,3,5] To further emphasise the systemic nature of NAFLD and the close links to other cardiometabolic diseases, in 2020, an international panel of experts proposed to change the terminology from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD).[6–11] Although the proposed change is still under discussion, the rationale of using the new terminology largely stems from a pathophysiological link between NAFLD and the presence of underlying metabolic abnormalities (namely overweight or obesity, type 2 diabetes, insulin resistance, or other metabolic risk factors). Additionally, MAFLD seems to be a more accurate definition than NAFLD to identify individuals with hepatic steatosis who are at high risk of disease progression or who have a higher risk of cardiovascular and chronic kidney disease.[12–15]

The importance of NAFLD is still underappreciated by primary care clinicians, specialists, and patients.[16,17] Thus, the main aim of this Review is to summarise new insights into NAFLD to facilitate improved health promotion, case identification, patient awareness, and health service delivery. We also provide a perspective towards building a framework for a person-centred, multidisciplinary, and holistic approach to manage patients with NAFLD.

Extrahepatic complications: epidemiological evidence

Meta-analyses of the excess of fatal and non-fatal events and diseases in people with NAFLD are summarised in table 1. We did not include the association between NAFLD and risk of other extrahepatic diseases such as primary hypothyroidism or polycystic ovary syndrome,[23,24] because the evidence available for such associations is not sufficiently robust.

Risk of cardiovascular disease

One meta-analysis[18] of 16 observational studies included approximately 34 000 individuals (mean age 52 years) with a median follow-up of 6·9 years and showed that people with NAFLD had a 64% higher risk of fatal or non-fatal cardiovascular disease events than those without NAFLD (table 1). Additionally, the risk of these incident events seemed to increase with greater severity of NAFLD (random-effects odds ratio 2·58, 95% CI 1·78–3·75), and remained statistically significant in studies where analysis was adjusted for traditional cardiovascular disease risk factors.[18] The risk of cardiovascular disease events might be linked to the underlying severity of NAFLD, and the stage of liver fibrosis is the strongest histological predictor of adverse liver-related events and cardiovascular disease outcomes in NAFLD.[25,26] Using a competing risk analysis, Henson and colleagues[27] showed that advanced liver fibrosis was associated with greater risk of incident cardiovascular disease events during a median of 5 years in a US cohort of around 300 individuals with biopsy-confirmed NAFLD, and this risk remained significant after adjusting for relevant covariates, including cardiovascular disease risk scores. Some cohort studies also reported that there was an association between NAFLD and the risk of coronary or carotid atherosclerosis progression, and most importantly, that improvement or resolution of NAFLD (on ultrasound examinations) was associated with a lower risk of carotid atherosclerosis development.[28,29]

	Study characteristics	Study outcomes	Random-effects OR or HR (95% CI)
Fatal and non-fatal cardiovascular disease events*			
Targher et al[18] (n=16 studies)	Longitudinal studies; involving 34 043 patients (36% with NAFLD); median follow-up of 6·9 years	Any fatal or non-fatal cardiovascular disease events	OR 1·64 (1·26–2·13)
Targher et al[18] (n=6 studies)	..	Fatal cardiovascular disease events	OR 1·31 (0·87–1·97)
Targher et al[18] (combined endpoint; n=5 studies)	..	Fatal and non-fatal cardiovascular disease events	OR 1·63 (1·06–2·48)
Targher et al[18] (n=5 studies)	..	Non-fatal cardiovascular disease events	OR 2·52 (1·52–4·18)
Targher et al[18] (n=3 studies)	Subgroup analyses in patients with more severe NAFLD†	Fatal cardiovascular disease events	OR 3·28 (2·26–4·77)
Targher et al[18] (combined endpoint; n=3 studies)	Subgroup analyses in patients with more severe NAFLD†	Fatal and non-fatal cardiovascular disease events	OR 1·94 (1·17–3·21)
Permanent atrial fibrillation			
Cai et al[19] (n=6 studies)	Longitudinal studies involving 614 673 individuals (40% with NAFLD); median follow-up of 10 years	Incident atrial fibrillation	HR 1·19 (1·04–1·31)
Type 2 diabetes			
Mantovani et al[20] (n=33 studies)	Longitudinal studies involving 501 022 individuals (31% with NAFLD); median follow-up of 5 years	Incident diabetes	HR 2·19 (1·93–2·48)
Mantovani et al[20] (n=9 studies)	Subgroup analyses in individuals with more severe NAFLD‡	Incident diabetes	HR 2·69 (2–08–3·49)
Mantovani et al[20] (n=5 studies)	Subgroup analyses in individuals with more severe NAFLD	Incident diabetes (NAFLD with increasing severity of fibrosis assessed by histology or fibrosis scores)	HR 3·42 (2·29–5·11)
Chronic kidney disease (stage ≥3)			
Mantovani et al[21] (n=13 studies)	Longitudinal studies involving 1 222 032 individuals (28% with NAFLD); median follow-up of 9·7 years	Incident chronic kidney disease (stage ≥3)	HR 1·43 (1·33–1·54)
Mantovani et al[21] (n=4 studies)	Subgroup analyses in individuals with more severe NAFLD‡	Incident chronic kidney disease (stage ≥3)	HR 1·67 (1·28–2·17)
Mantovani et al[21] (n=2 studies)	Subgroup analyses in individuals with more severe NAFLD	Incident chronic kidney disease (stage ≥3; severity of liver fibrosis assessed by histology)	HR 2·90 (1·62–5·18)
Colorectal tumours			
Mantovani et al[22] (n=11 studies)	8 cross-sectional and 3 longitudinal studies involving 91 124 (32% with NAFLD) asymptomatic individuals undergoing colonoscopy screening	Prevalent colorectal adenomas, n=7 studies using liver imaging techniques for NAFLD diagnosis; n=1 study using liver histology for NAFLD diagnosis	OR 1·28 (1·11–1·48); OR 1·61 (0·90–2·89)
Mantovani et al[22] (n=5 studies)	..	Prevalent colorectal cancer, n=4 studies using liver imaging techniques; n=1 study using liver histology for NAFLD diagnosis	OR 1·56 (1·25–1·94); OR 3·04 (1·29–7·18)
Mantovani et al[22] (n=3 studies)	..	Incident colorectal adenomas, n=3 studies using liver imaging techniques for NAFLD diagnosis	HR 1·42 (1·18–1·72)
Mantovani et al[22] (n=1 study)	.	Incident colorectal cancer, n=1 study using liver imaging techniques for NAFLD diagnosis	HR 3·08 (1·02–9·03)

HR=hazard ratio. NAFLD=non-alcoholic fatty liver disease. OR=odds ratio. *Fatal and non-fatal cardiovascular disease events were defined as cardiovascular death or non-fatal cardiovascular disease events (ie, acute myocardial infarction, angina, ischaemic stroke, or coronary revascularisation procedures), or both. †Defined by the presence of NAFLD on imaging techniques plus elevated serum γ-glutamyl transferase or a high NAFLD fibrosis score, high ^{18}F-fluorodeoxyglucose uptake on PET, or by increased severity of liver fibrosis on histology. ‡Defined by increasing ultrasonographic scores or by increasing liver fibrosis assessed using histology or non-invasive fibrosis scores.

Table 1: **Meta-analyses of the excess events and diseases in adults with NAFLD**

Risk of arrhythmias

The link between NAFLD and arrhythmia risk (mostly permanent atrial fibrillation) has gained interest.[30] In a meta-analysis[19] of six longitudinal studies (involving 615 000 individuals with and without type 2 diabetes), Cai and colleagues showed that NAFLD was associated with a moderately increased risk of incident atrial fibrillation, irrespective of shared cardiovascular disease risk factors (table 1). Studies[30,31] have also shown that the presence and severity of NAFLD (on ultrasound examination) was independently associated with a higher risk of QTc interval prolongation (on resting electrocardiogram), which predisposed to an increased risk of ventricular tachyarrhythmias and sudden cardiac death.

Risk of type 2 diabetes

In a comprehensive meta-analysis[20] including 33 longitudinal cohort studies with 501 022 individuals (30·8% had NAFLD) and a median follow-up of 5 years, Mantovani and colleagues found that individuals with NAFLD had a 2·19-times higher risk of incident type 2 diabetes than those without NAFLD (table 1). The risk of diabetes seemed to increase with greater severity of NAFLD (mostly the severity of liver fibrosis) and, most importantly, remained statistically significant in those studies where analysis was adjusted for age, sex, family history of diabetes, adiposity measures, and other common metabolic risk factors.[20] Notably, some observational studies[32,33] also reported that type 2 diabetes incidence

diminished over time following the improvement or resolution of NAFLD (assessed by ultrasound examinations), irrespective of the changes in bodyweight.

Risk of chronic kidney disease

Several observational studies reported an association between NAFLD and risk of chronic kidney disease. In a large meta-analysis[21] of 13 observational studies involving more than 1·2 million individuals from different countries, Mantovani and colleagues found that NAFLD was associated with a 1·43-times increased risk of incident chronic kidney disease (stage ≥3, defined as an estimated glomerular filtration rate <60 mL/min per 1·73 m²) over a median follow-up of 9·7 years, and this long-term risk appeared to be even greater among individuals with NAFLD and advanced fibrosis (table 1). However, further research is needed to better elucidate the complex link between NAFLD and chronic kidney disease, and to establish whether an improvement in NAFLD attenuates the development and progression of chronic kidney disease.

Risk of colorectal tumours and other extrahepatic cancers

In a meta-analysis[22] of eight cross-sectional and three longitudinal studies with aggregate data on around 91 000 asymptomatic adults (predominantly Asian descent) undergoing colonoscopy screening, NAFLD was associated with moderately increased prevalence and incidence of colorectal adenomas and cancer (table 1). These risks were independent of age, sex, smoking, body mass index, and type 2 diabetes (or metabolic syndrome). Further prospective studies, particularly in American and European populations, and mechanistic studies are needed to better understand the association between NAFLD and colorectal carcinogenesis.

In a US cohort study[34] with a median follow-up of 8 years, involving 4722 individuals with NAFLD and 14 441 age-matched and sex-matched healthy individuals, Allen and colleagues found that NAFLD was associated with around a doubling of risk of cancer (predominantly of the liver, gastrointestinal tract, and uterus). Notably, the association of increased cancer risk was stronger in NAFLD than in people with obesity, thereby suggesting that NAFLD might be a mediator of the obesity–cancer association. In another community-based cohort study[35] of approximately 54 000 Chinese men, NAFLD was associated with slightly increased risk of developing all cancers, thyroid cancer, and lung cancer. Furthermore, in men with NAFLD, higher serum aminotransferase concentrations were associated with higher risk of hepatocellular carcinoma and thyroid cancer. NAFLD also increased risk of colorectal and lung cancers in smokers, and risk of kidney cancer in men without type 2 diabetes. Finally, in a nationwide, matched cohort study[36] with a median follow-up of 14 years, that included 10 568 individuals with biopsy-proven NAFLD and 49 925 matched healthy individuals, Simon and colleagues found that all histological stages of NAFLD were associated with significantly increased overall mortality, and this risk increased progressively with worsening NAFLD histology (adjusted hazard ratio [HR] 1·71, 95% CI 1·64–1·79 for simple steatosis; 2·14, 1·93–2·38 for non-fibrotic NASH; 2·44, 2·22–2·69 for non-cirrhotic fibrosis; and 3·79, 3·34–4·30 for cirrhosis). Notably, the excess mortality was primarily from extrahepatic cancers, followed by cirrhosis, cardiovascular disease, and hepatocellular carcinoma.

Pathophysiological aspects in NAFLD

The pathophysiology of NAFLD is highly complex and involves diverse aspects such as metabolic disturbances, lipotoxicity, insulin resistance, chronic inflammation, fibrosis, intestinal function, and the gut microbiome.[37] The understanding of NAFLD genetics has improved in the past 4–5 years and many genome-wide association studies have shown links between NAFLD and genes such as *PNPLA3*, *TM6SF2*, and others.[38] NAFLD and related complications are frequently accompanied by low-grade metabolic inflammation (metaflammation), which is a hallmark of obesity-related disorders, type 2 diabetes, and NAFLD.[39] Specifically, inflammatory mediators might contribute to the liver phenotype and extrahepatic complications of NAFLD (figure 1).

Adipokine or cytokine imbalance and chronic inflammation

Adipose tissue inflammation is characterised by infiltration of various leucocytes; therefore, adipose tissue probably contributes substantially to chronic inflammation in obesity-related disorders such as NAFLD. This fact is important because adipose tissue-derived inflammation might affect inflammation at distal sites, such as the liver or vessels. Adipokines are mainly released by adipose tissue (especially visceral fat), whereas cytokines are mainly produced by leucocytes. The concept of adipokine or cytokine imbalance was established around 15 years ago, suggesting that an insufficiency in anti-inflammatory mediators (eg, adiponectin) and increased release of proinflammatory cytokines (eg, interleukin [IL]-1β, IL-6, or tumour necrosis factor [TNF]-α) might result in a proinflammatory local and systemic milieu in patients with NAFLD.[40] A potent anti-inflammatory adipokine, adiponectin, is one of the major products of adipose tissue, and obesity-related disorders (including NAFLD) are characterised by hypoadiponectinaemia. Expanded and dysfunctional adipose tissue exhibits massively increased production of several proinflammatory cytokines and decreased synthesis of some anti-inflammatory adipokines (eg, adiponectin) or cytokines (eg, IL-37). Adipose tissue can contribute by at least a third to circulating concentrations of IL-6, a major cytokine in obesity-related disorders mainly responsible for increased plasma C-reactive protein concentrations. Many preclinical

NAFLD studies have shown that neutralisation of either IL-1β or TNF abolished hepatic inflammation, steatosis, and associated pathologies. What remains unclear when considering NAFLD as a systemic chronic inflammatory disorder is which compartments in the body, besides adipose tissue and the liver, might contribute to chronic inflammation. Skeletal muscle has also been proposed as a site of synthesis of various mediators—ie, myokines with autocrine, paracrine, or endocrine effects.[41] To what extent muscle fibres contribute to the overall inflammatory load in NAFLD—eg, via production of myokine IL-6—is currently unclear.[42] Aerobic and resistance exercise are beneficial for people with NAFLD, and are accompanied by decreased insulin resistance and decreased circulating IL-6 concentrations. Skeletal muscle might also play a role in NAFLD by the release of metabolically beneficial myokines such as irisin.[43]

Microbiome and NAFLD

The gastrointestinal tract and its microbiota might contribute to NAFLD.[44] Large clinical studies[45,46] have shown that NAFLD is accompanied by dysbiosis, which is characterised by increased growth of some bacteria such as *Enterobacteriaceae*, *Escherichia coli*, and a decrease in *Faecalibacterium prausnitzii*. Recent data[46] also suggest that intestinal dysbiosis and microbiome instability exists over many years and might even precede the development of NAFLD and type 2 diabetes. Furthermore, emerging evidence has shown that bacterial components might be found in the liver of patients with NAFLD.[47] Intestinal microbiota converts nutrients such as choline or carnitine into trimethylamine, which is metabolised in the liver by flavin monoxygenases to trimethylamine *N*-oxide. Studies[48,49] have shown that trimethylamine *N*-oxide is associated with cardiovascular disease and can increase platelet responsiveness and thrombosis formation. Therefore, bacterial components and the associated production of intestinal-derived metabolites might contribute to the development of liver disease in NAFLD.[49]

Extrahepatic cancers in NAFLD: a proinflammatory environment

NAFLD is not only associated with hepatocellular carcinoma, but also with various other extrahepatic cancers. Chronic inflammation is a driving force in many malignancies. Several inflammation-related cancers arise from the gastrointestinal tract such as gastric cancer, pancreatic cancer, inflammatory bowel disease-related colon cancer, or liver cancer. A large biopsy-based cohort study[36] from Sweden showed that extrahepatic cancers were the most common reason for increased mortality in people with NAFLD, followed by liver-related and cardiovascular disease-related deaths. NAFLD is also associated with gastrointestinal and gynaecological cancers at a higher rate than the association with obesity.[34] A substantially higher rate of colorectal tumours[50] and oesophageal and stomach cancers have also been observed in patients with NAFLD. Furthermore, obesity and NAFLD are associated with a higher incidence of erosive oesophagitis, Barrett's dysplasia, and oesophageal adenocarcinoma.[34] Hepatocellular carcinoma is another typical cancer associated with chronic liver inflammation, resulting from various causes and observed in pre-cirrhosis stages of liver disease. This tumour is strongly influenced by the immune system and is characterised by cancer-promoting inflammation exerted by the underlying disease.[51]

Regardless of its origin, chronic inflammation at various sites of the body might have tumour-promoting effects.[52] Several key factors have been identified in the interplay of molecules in cancer-associated inflammation such as nuclear factor-kappa B; signal transducer and activator of transcription 3; and various proinflammatory cytokines such as IL-1β, IL-6, and TNF. Several dietary and genetic preclinical NAFLD models have shown that proinflammatory cytokines are crucial in liver oncogenesis.[53] A proinflammatory tumour-promoting environment might also be generated by the absence of key anti-inflammatory mediators such as adiponectin. Indeed, adiponectin seems to suppress tumour formation in preclinical studies. Adiponectin also exerts anticarcinogenic effects in vitro by inhibiting growth of

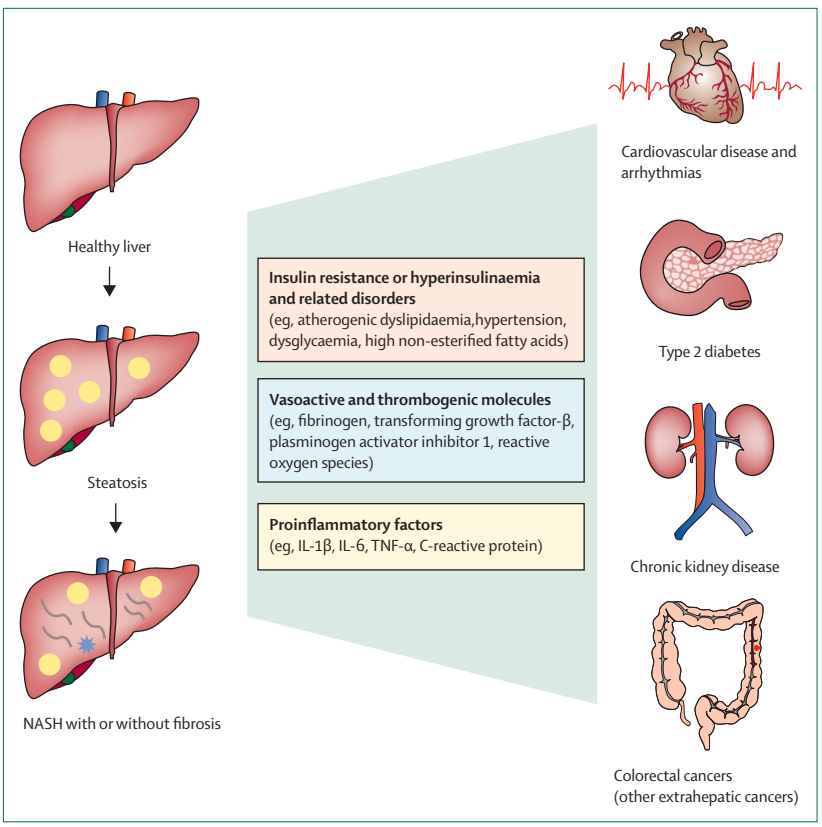

Figure 1: **NAFLD-related effects on cardiovascular disease, type 2 diabetes, and extrahepatic diseases**
IL=interleukin. NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic steatohepatitis. TNF=tumour necrosis factor.

colorectal cancer cells through initiation of adenosine monophosphate-activated protein kinase.[54] Adiponectin knockout mice and Adn$^{-/-}$APC$^{Min/+}$ mice not only show more inflammation, but also higher numbers and larger colorectal tumours after injection of dextran sodium sulphate.[55] Although there is evidence that NAFLD is associated with some extrahepatic cancers and many mechanisms have been explored, the precise mechanisms linking chronic inflammation and cancer development with NAFLD remain unknown.

Proinflammatory cytokines target vessels in NAFLD

Besides myocardial infarction and stroke, cardiac arrythmias and cardiomyopathy might also contribute to increased cardiovascular disease morbidity and mortality,[56] because of the proinflammatory environment in NAFLD. Proinflammatory cytokines such as macrophage-derived IL-1β induce arrhythmias in diabetic mice.[57] TNF, IL-6, and IL-17 have also shown potential to cause cardiac arrhythmias (mostly atrial fibrillation) in preclinical models. Increased serum IL-6 and C-reactive protein concentrations are correlated with a higher risk of atrial fibrillation.[58] In an experimental mouse model,[59] a specific NF-κB inhibitor abrogated cardiac inflammation and ameliorated arrhythmogenic cardiomyopathy. The CANTOS trial[60] showed that IL-1β has a major role in atherosclerosis; treatment with canakinumab (ie, an anti-IL-1β antibody) resulted in a significant reduction in recurrent cardiovascular disease events and mortality. However, clinical interventions targeting proinflammatory cytokines are needed to provide further evidence of a causal link between chronic inflammation, cardiovascular disease events, and cancers associated with NAFLD.

NAFLD, hepatocellular carcinoma, and extrahepatic complications

In NAFLD, liver disease is an independent risk factor for type 2 diabetes and cardiovascular disease (and potentially chronic kidney disease), suggesting that an unhealthy liver is a driving force in the worsening of NAFLD and type 2 diabetes (figure 2).[61,62] The liver also plays a key role in metabolic syndrome, which includes atherogenic dyslipidaemia, increased blood pressure, dysglycaemia, type 2 diabetes, and central obesity.[63] In people with newly diagnosed type 2 diabetes, the presence of metabolic syndrome is independently associated with incident cardiovascular disease.[64] Moreover, having more metabolic syndrome features at the time of a type 2 diabetes diagnosis is also associated with a linear increase in cardiovascular disease risk; when all features of metabolic syndrome are present, the risk of cardiovascular disease is five times greater than when one feature alone is present.[64] Metabolic syndrome is also common (around 20% of patients) in people without type 2 diabetes and cardiovascular disease, and is associated with an increased risk of these diseases (in men and women).[65] Since metabolic syndrome is more common in people with NAFLD (occurring in >50% of patients), it also potentially increases the risk of comorbidities (such as type 2 diabetes, cardiovascular disease, and chronic kidney disease) that all share similar cardiometabolic risk factors.[66–68]

Diagnosis and management of extrahepatic complications

Diagnosis of extrahepatic complications

Clinicians need to know how best to diagnose these related conditions (NAFLD, type 2 diabetes, cardiovascular disease, chronic kidney disease, and hepatocellular carcinoma). In people with NAFLD, the coexistence of metabolic syndrome and traditional cardiovascular disease risk factors such as age (>65 years), smoking, hypertension or atrial fibrillation (or both), and increased plasma LDL-cholesterol concentration should alert the clinician to the possibility of type 2 diabetes, cardiovascular disease, or chronic kidney disease, as these conditions share common risk factors. For those individuals with NAFLD who have cirrhosis and portal hypertension (based on clinical features, imaging techniques, or histology), there is a need for regular surveillance for hepatocellular carcinoma with ultrasound examinations.[69] Although most individuals with NAFLD and less severe liver disease can develop hepatocellular carcinoma, currently this group are not recommended to

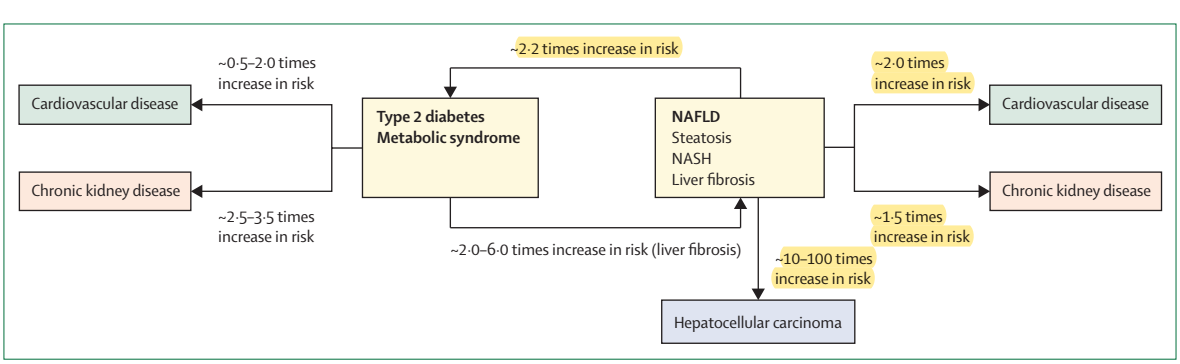

Figure 2: **Relationships between NAFLD, type 2 diabetes, and metabolic syndrome**
NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic steatohepatitis.

undergo regular surveillance. Similarly, screening tests are not recommended for extrahepatic cancers in people with NAFLD.

Diagnosis of type 2 diabetes, chronic kidney disease, and atrial fibrillation

The effect of a type 2 diabetes diagnosis on quality of life and health-related behaviour needs to be considered. In the past 10 years it has become easy to screen a patient at risk of type 2 diabetes by measuring HbA_{1c} (39–47 mmol/mol [5·7–6·4%] indicative of prediabetes and ≥48 mmol/mol [≥6·5%] indicative of diabetes). American Diabetes Association guidelines[70] recommend that HbA_{1c} testing should be done in all individuals (≥45 years) and in those of any age with overweight or obesity and with one or more risk factors for type 2 diabetes. HbA_{1c} has many advantages over previous diagnostic tests for type 2 diabetes that involved measurement of fasting plasma glucose or an oral glucose tolerance test. These advantages include greater convenience (fasting not required); greater preanalytical stability; and fewer day-to-day perturbations during stress, diet, or illness. However, the disadvantages include lower sensitivity of HbA_{1c} at the designated cut-point (≥6·5%) and greater cost. According to National Health and Nutrition Examination Survey-III data,[71] the HbA_{1c} test (diagnostic threshold of 48 mmol/mol) diagnoses approximately 30% of type 2 diabetes cases identified collectively using HbA_{1c}, fasting plasma glucose, or 2 h glucose concentrations (during an oral glucose tolerance test). Despite these caveats, the American Diabetes Association guidelines[70] recommend that the HbA_{1c} test should be repeated at minimum 3-year intervals. Similar to current standard practice common among primary care physicians and diabetologists for individuals with a type 2 diabetes diagnosis, we advocate that the following measures should be done in all individuals with NAFLD: adiposity, blood pressure, pulse rate, presence of metabolic syndrome, atrial fibrillation, chronic kidney disease, and cardiovascular disease risk calculations. Chronic kidney disease can be assessed by measurement of eGFR (normal ≥90 mL/min per 1·73 m²) and urinary albumin excretion (normal <30 mg/g). There are five GFR stages in chronic kidney disease, and when stage 3 to 5 occur, defined by a decreased concentration of eGFR, there is a further (at least ≥50%) increase in 10-year cardiovascular disease risk.

Although there are more than 100 cardiovascular disease risk prediction models and calculators, only 25 of these have been externally validated.[72] Notably, cardiovascular disease risk calculators are only able to generate estimates of the global (ie, absolute) risk. Calculators vary according to the database they are derived from, choice of clinical endpoints, and risk interval duration. Addition of other risk factors to traditional cardiovascular risk factors (age, sex, BMI, blood pressure, plasma lipid profile, smoking, and diabetes) does not substantially improve risk prediction performance, with the exception of the coronary artery calcium score (CACS), although this score still requires further study.[72] Whether addition of NASH, either with or without liver fibrosis, to a cardiovascular disease risk algorithm improves cardiovascular disease risk prediction is unknown. However, the use of a cardiovascular disease risk calculator without entering specific information about liver disease in individuals with NAFLD is better than not estimating the risk. Thus, we recommend that health-care professionals should use a cardiovascular disease risk calculator based on a risk prediction model derived from, or calibrated for, a population similar to the patient in question.[72] Generally, management of cardiovascular disease risk in people with NAFLD widely overlaps with guidelines for the treatment of cardiovascular disease risk factors, which are adopted for the general population.

CACS is a strong predictor of cardiovascular disease event rates in the general population for around 15 years of follow-up,[73,74] and assessment of CACS might improve cardiovascular disease risk prediction, particularly where there is uncertainty about individual risk. CACS is obtained from a high-resolution CT of the chest and is usually presented as the Agatston score. This score reflects the total area of coronary calcium deposits and density of calcium. When calcium is present, the score is higher, thus, cardiovascular disease risk is also higher. A score of 100–300 indicates moderate coronary plaque deposits and a score greater than 300 is a sign of high cardiovascular disease risk, particularly in people younger than 50 years. Addition of CACS to Framingham risk score leads to substantial reclassification of cardiovascular disease risk (net reclassification index >0·20) in those with multiple risk factors.[74] Additionally, a CACS of 400 or greater means a 15-year all-cause mortality rate higher than 20%, confirming the importance of follow-up length when defining higher risk status.[74]

One problem with multislice CT is the risk of cancer after exposure to ionising radiation, which is estimated at 12 cancers for every 10 000 screened individuals.[75] Additionally, although CACS is a well-established assessment for stratifying asymptomatic individuals by overall cardiovascular disease or coronary event risk, the prognostic value of CACS for incident ischaemic stroke is less clear. CACS might also be useful for assessing risk of stroke; in a meta-analysis[76] of 13 262 asymptomatic people without cardiovascular disease, the presence and severity of CACS was associated with increased risk of incident ischaemic stroke during a median follow-up of 7·2 years. Cholesterol management guidelines published in 2018[77] suggest that CACS testing should be considered in individuals aged 40–75 years without diabetes and with a plasma LDL-cholesterol of 70–189 mg/dL at a 10-year cardiovascular disease risk of 7·5–20% (ie, intermediate risk), particularly when there is uncertainty about whether medical treatment should be instigated. Thus, for asymptomatic individuals, calculation of CACS might

refine cardiovascular disease risk prediction and guide patient management, which might offset the minimal projected risk of cancer after exposure to ionising radiation.[75]

Management of cardiovascular disease, type 2 diabetes, and chronic kidney disease

Statin therapy is safe and recommended for patients with a high 10-year atherosclerotic cardiovascular disease risk, regardless of the presence of NAFLD. According to cholesterol management guidelines,[77] a CACS of 1–99 favours statin therapy, especially in people aged 55 years or older. A CACS of 100 or more indicates that statin treatment is required unless agreed otherwise in a clinician–patient discussion. In those with a high CACS, the challenge is to decide which patients require further investigation and which require intensive medical management, and in this situation advice from a cardiologist is important. Most asymptomatic individuals with elevated CACS scores do not need any further testing; however, they do require aggressive medical treatment—eg, low-dose aspirin, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, and lifestyle interventions.[78]

Lifestyle measures, such as increased physical activity and weight reduction, are effective in ameliorating early stages of liver disease in people with NAFLD, and in improving glycaemic control, resolution of type 2 diabetes, cardiovascular disease, and chronic kidney disease risk factors. Several studies[79,80] have investigated the role of physical activity, independent of dietary intervention, in people with NAFLD. A meta-analysis[79] of 16 randomised controlled trials with a total of around 700 individuals with NAFLD showed that exercise without dietary intervention improved liver fat content, as assessed by magnetic resonance-based techniques. Lifestyle measures are also effective in improving many cardiometabolic risk factors shared between NAFLD, type 2 diabetes, and cardiovascular disease. For example, weight reduction is effective at improving coexisting cardiometabolic risk factors, such as increased blood pressure, atherogenic dyslipidaemia, and at decreasing plasma glucose concentrations and promoting remission of type 2 diabetes.[81–84] How much weight reduction should be advocated will partly depend on the amount of overweight or obesity. Weight reduction of 10% or more induces NASH resolution and improves liver fibrosis by at least one histological stage,[81] and for most individuals this amount of weight loss should be advocated; however, weight reduction of 10% or more can be difficult to achieve and lower amounts of weight loss (eg, 5–10%) can also improve hepatic steatosis and NASH, as assessed by the histological NAFLD activity score.[81] Consequently, practice guidelines[85–87] for the management of NAFLD emphasise that in overweight or obese individuals with NAFLD, 5–10% weight loss is the goal of most lifestyle interventions and this amount of weight loss will have favourable effects on cardiometabolic risk factors. Notably, individuals with NAFLD who are not obese can also achieve improvements in liver disease with a weight reduction of 3–10% and are more likely than individuals with obesity to maintain weight loss (and normal serum liver enzyme concentration) over time. People with NAFLD should be recommended to avoid alcohol consumption, hepatotoxic drugs, cigarette smoking, and intake of high sucrose or fructose-containing drinks and food.[85,86]

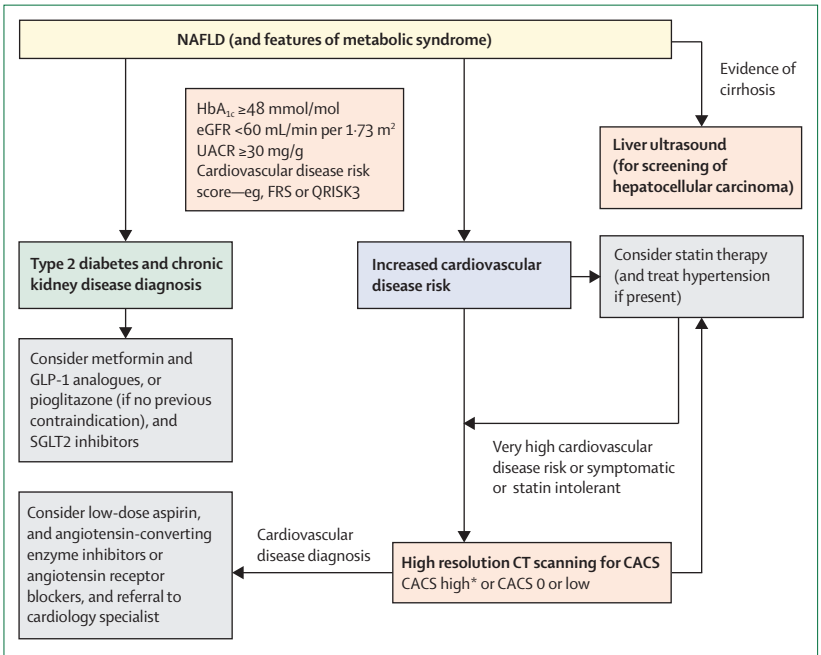

Figure 3: **Pragmatic approaches for the diagnosis and initial management of NAFLD complications**
CACS=coronary artery calcium score. FRS=Framingham risk score. eGFR=estimated glomerular filtration rate. NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic steatohepatitis. UACR=urine albumin to creatinine ratio. *Based on CACS. When score has increased (eg, ≥90 percentile adjusted for age and sex, or score >300), refer to cardiology because a person might be asymptomatic but have reversible cardiac ischaemia. Require high-dose statin treatment, and low-dose aspirin and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.

In the USA, the American College of Cardiology and American Heart Association guidelines[88] for primary prevention to reduce the risk of major atherosclerotic cardiovascular disease events recommend that adults should be categorised into low (<5%), borderline (5 to <7·5%), intermediate (≥7·5 to <20%), or high (≥20%) 10-year cardiovascular disease risk. Statin treatment to attenuate risk is advocated in people aged 40–55 years at borderline cardiovascular disease risk. In Europe, the threshold for medical intervention is not as low; however, the threshold for 10-year cardiovascular disease risk at which health-care professionals should advocate medical intervention to lower that risk remains unknown.

Although metformin treatment is the first-line oral therapy for people with type 2 diabetes, there is no convincing evidence that metformin confers a benefit on liver disease in people with NAFLD. Pioglitazone

has become a somewhat forgotten cost-effective, cardioprotective drug for type 2 diabetes[89] that can lower blood glucose and decrease progression from impaired glucose tolerance to type 2 diabetes; however, treatment with pioglitazone can also decrease risk of acute myocardial infarction and ischaemic strokes. Despite having some recognised side-effects, treatment with pioglitazone also produces benefits such as resolution of NASH and improvement in individual histological scores, including the fibrosis score in people who have NASH with or without type 2 diabetes.[90,91] Despite the recommendations from the American Association for the Study of Liver Diseases, European Association for the Study of the Liver, and the UK National Institute for Health and Care Excellence that pioglitazone treatment should be considered in people with NASH,[85–87] this drug is often not used in individuals who have NASH with or without type 2 diabetes.

Histological liver improvement depends on the amount of weight reduction rather than the intervention used to achieve this goal.[81] For example, drugs such as orlistat and GLP-1 receptor agonists (liraglutide and semaglutide) facilitate weight reduction and are associated with histological resolution of NASH and, in some cases, fibrosis regression.[81,92,93] Figure 3 shows a potential approach to diagnose and manage extrahepatic complications of NAFLD.

Areas of uncertainty

We believe that combating the growing burden of NAFLD and its multisystem complications (not only related to the liver) will require a multidisciplinary team to embrace collaborative ways of working and deliver holistic person-centred care and management for people with this condition. Care of a person with advanced liver disease and NAFLD has traditionally been the remit of hepatologists who liaise with primary care physicians, and many individuals with less severe liver disease are frequently patient attendees in other clinics (eg, diabetes, cardiology, renal) that are run by physicians who might know little about NAFLD, its complications, and management. We call for a more person-centred, multidisciplinary, and holistic approach involving health-care professionals (figure 4), with better advocacy for this patient group and the potential for earlier diagnosis and management of liver-related and extrahepatic complications to improve patient outcomes. How to best achieve this goal remains unclear, and we recommend that further work is needed to decide on the best structures of health-care delivery for people with NAFLD. This health-care delivery will likely be different across individual countries, because of the different structural organisation of health-care systems worldwide.

Whether individuals with non-cirrhotic NASH should undergo hepatocellular carcinoma surveillance remains unclear. For those with type 2 diabetes and NAFLD, metformin is the first-line oral treatment for hyperglycaemia. However, current evidence does not show a beneficial effect of metformin treatment on liver disease and further studies are needed to test the effect of metformin on risk of hepatocellular carcinoma. Although CACS assessment can be used in the general population to improve cardiovascular disease risk prediction, further studies are needed in people with NAFLD who might have features of metabolic syndrome, but who do not have type 2 diabetes. Although statins are safe in individuals with NAFLD, some might have serum aminotransferase concentrations that are very high (>2–3 times higher than the normal upper limit) and better evidence is needed regarding surveillance and long-term effects of statins on the liver in this population. There is increasing interest in the potential benefit of long-acting injectable GLP-1 receptor agonists in NASH, as a result of favourable data with semaglutide[93] and because these glucose-lowering agents facilitate weight reduction and decrease cardiovascular disease risk. However, it remains unknown whether any benefit on the liver in people with NASH is independent of weight reduction. Additionally, favourable data from 24-week treatment with the pan-peroxisome proliferator-activated receptor (PPAR) agonist lanifibranor—reported at the 2020 American Association for the Study of Liver Diseases meeting[94]—has placed the focus on the role of PPAR agonists in treatment of NASH and further data are awaited from an ongoing phase 3 trial (NCT03008070).

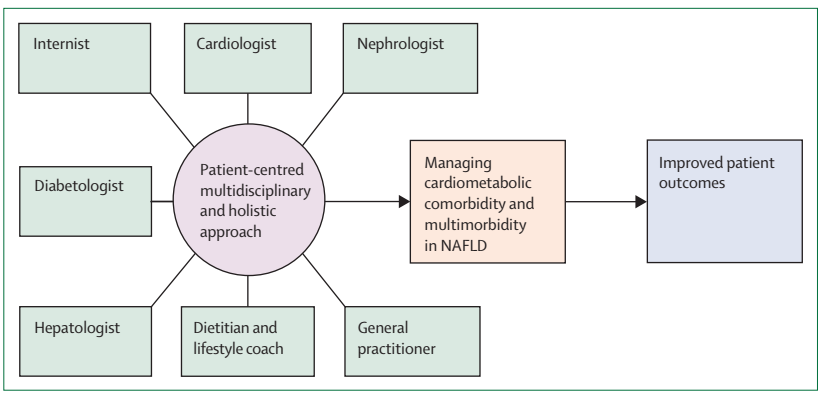

Figure 4: **Person-centred, multidisciplinary, and holistic approach to patients with NAFLD**
NAFLD=non-alcoholic fatty liver disease.

Conclusion

This Review outlines the strong association between the presence and severity of NAFLD and the risk of developing multiple extrahepatic complications. Despite growing evidence that links NAFLD with type 2 diabetes, cardiovascular disease, chronic kidney disease, and some extrahepatic cancers, a causal association remains to be established. Notably, existing guidelines from non-hepatological societies do not advocate screening

Search strategy and selection criteria

References for this Review were identified through PubMed using the search terms "nonalcoholic fatty liver disease" OR "NAFLD" AND "incident diabetes", "incident cardiovascular disease", "incident chronic kidney disease", OR "incident extrahepatic cancers", from the inception date to Dec 6, 2020. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

for NAFLD and liver-related complications in people with cardiovascular disease, chronic kidney disease, or type 2 diabetes, making the liver a potentially neglected organ and meaning that chronic disease progression to cirrhosis might be largely undetected. Conversely, existing guidelines from hepatological societies recommend screening patients with NAFLD for type 2 diabetes and cardiovascular disease, but do not recommend any specific screening for chronic kidney disease or extrahepatic cancers and do not define screening tests for cardiovascular disease complications. Currently, all individuals with NAFLD should undergo similar screening programmes for cardiovascular disease, type 2 diabetes, chronic kidney disease, and extrahepatic cancers to those usually adopted for individuals without NAFLD of similar age and sex. We also call for better advocacy and a multidisciplinary team approach for people with NAFLD. Improved collaborative ways of working among health-care professionals caring for this patient group will hopefully achieve earlier diagnosis and better management, not only of liver disease, but also of extrahepatic complications arising from NAFLD.

Contributors

All authors contributed equally to this manuscript.

Declaration of interests

We declare no competing interests.

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