Diabetes and NAFLD

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Abstract

Type 2 diabetes and nonalcoholic fatty liver disease (NAFLD) are common diseases that often coexist and may act synergistically to drive adverse hepatic and extrahepatic clinical outcomes. NAFLD affects up to 70-75% of patients with type 2 diabetes and approximately 30–40% of adult patients with type 1 diabetes.

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E. Bonora, R. A. DeFronzo (eds.), *Diabetes Complications, Comorbidities and Related Disorders*, Endocrinology, https://doi.org/10.1007/978-3-319-44433-8_17

In patients with diabetes, the presence of NAFLD is associated with poorer glycemic control, more severe hyperinsulinemia, atherogenic dyslipidemia, and adipose tissue/hepatic insulin resistance compared with patients without NAFLD. The coexistence of NAFLD and diabetes increases the risk of developing both microvascular and macrovascular complications of diabetes as well as increasing the risk of developing more severe forms of NAFLD (nonalcoholic steatohepatitis, advanced fibrosis, and cirrhosis). In addition, patients with NAFLD and diabetes have an increased risk of all-cause and cause-specific (cardiovascular, cancer, and liver) mortality compared with those without NAFLD. The mainstay of NAFLD management among patients with diabetes is currently to maintain a healthy body weight, improve glycemic control and reduce the modifiable cardiometabolic risk factors. This chapter briefly discusses the diagnosis of NAFLD, the epidemiology, and natural history of NAFLD in patients with diabetes, the potential adverse effects of NAFLD on glycemic control, and the risk of chronic complications of diabetes (principally cardiovascular disease and chronic kidney disease). This chapter also critically evaluates the available treatment options for NAFLD, with the aim of helping to inform the reader as to the most pertinent issues when managing patients with coexistent NAFLD and diabetes.

Keywords
Fatty liver · Nonalcoholic fatty liver disease · NAFLD · NASH · Diabetes · Complications

Introduction

Nonalcoholic fatty liver disease (NAFLD) is increasingly diagnosed in many developed and developing countries, affecting about 25–30% of adults in the general population in Western countries, and is the most common cause of chronic liver disease among patients with type 2 diabetes (T2DM), occurring in up to 70–75% of these patients. In addition, NAFLD is likely to be the major underlying etiology for liver transplantation by 2020 in Western countries (Chalasani et al. 2012; Lonardo et al. 2015; EASL-EASD-EASO clinical practice guidelines 2016).

NAFLD is a spectrum of liver diseases that encompasses simple fatty infiltration in >5% of hepatocytes (simple steatosis or NAFL), fatty infiltration plus inflammation (nonalcoholic steatohepatitis, NASH), fibrosis, and ultimately cirrhosis that may, sometimes, progress to hepatocellular carcinoma (Chalasani et al. 2012; EASL-EASD-EASO clinical practice guidelines 2016).

NAFLD is strongly associated with abdominal overweight or obesity, insulin resistance, and other features of the metabolic syndrome. Given these strong associations, it is therefore unsurprising that there is also a link between NAFLD and T2DM. In recent years, many studies have clearly demonstrated that NAFLD is associated with a substantially increased risk of all-cause and cause-specific (cardiovascular-, cancer-, and liver-related) mortality in patients with T2DM. In addition, accumulating evidence suggests that NAFLD can be directly implicated in the

development and progression of chronic complications of diabetes (mainly cardiovascular disease [CVD] and chronic kidney disease [CKD]) (Anstee et al. 2013; Byrne and Targher 2015; EASL-EASD-EASO clinical practice guidelines 2016).

In this chapter, we will briefly discuss the diagnosis of NAFLD, the epidemiology and natural history of NAFLD in patients with diabetes, the evidence linking NAFLD with poorer glycemic control, and the prognostic role of NAFLD in the development of chronic vascular complications of diabetes. We will also briefly discuss the management of NAFLD in patients with diabetes as well as the current and potential future pharmacological options for this increasingly prevalent liver disease that is likely to have an important future global impact on the burden of ill health.

Diagnosis of NAFLD

Diagnosis of NAFLD is based on the following criteria: hepatic steatosis on imaging or histology, no excessive alcohol consumption (a threshold of 30 g/day for men and 20 g/day for women is conventionally adopted), and no competing causes for hepatic steatosis (e.g., virus, drugs, iron overload, autoimmunity) (Anstee et al. 2013; Chalasani et al. 2012; EASL-EASD-EASO clinical practice guidelines 2016).

The "gold standard" for the diagnosis of NAFLD remains liver biopsy, as this method is quantitative and is the only reliable way to assess disease severity within the spectrum of pathologic conditions that encapsulate NAFLD (simple steatosis, NASH, and cirrhosis). However, liver biopsy is invasive, potentially risky, patient-unfriendly, and subject to sampling error; therefore, this procedure is not suitable for the diagnosis of NAFLD in large cohorts or for patient monitoring (Chalasani et al. 2012; Rinella 2015; EASL-EASD-EASO clinical practice guidelines 2016).

Although liver ultrasonography remains the recommended first-line imaging modality in clinical practice, this imaging method provides a subjective and qualitative assessment of hepatic fat content, generally believed to be of only limited sensitivity (60–90%) when less than 20–30% of hepatocytes are steatotic (Chalasani et al. 2012; EASL-EASD-EASO clinical practice guidelines 2016). Computed tomography can also be used for diagnosing hepatic steatosis. The liver attenuation index is derived and defined as the difference between mean hepatic and mean splenic attenuation, and some investigators have used a liver attenuation index <5 Hounsfield units to identify $>5\%$ liver fat and diagnose NAFLD. To date, T1-weighted dual-echo magnetic resonance imaging and proton magnetic resonance spectroscopy have the best diagnostic accuracy in defining hepatic steatosis. Proton magnetic resonance spectroscopy enables quantitative assessment of hepatic triglyceride content (and potentially lipid composition), has excellent reproducibility and sensitivity, but is resource intensive, and still cannot reliably discriminate simple steatosis from NASH (Chalasani et al. 2012; EASL-EASD-EASO clinical practice guidelines 2016).

Hepatic steatosis is often associated with mild-to-moderate elevations of serum liver enzymes (mainly serum alanine aminotransferase and gamma-glutamyl-transferase levels), but, at best, the serum liver enzymes only identify people who are at increased risk of NAFLD and who will require further diagnostic tests.

A common clinical concern in patients with NAFLD is whether they have simple steatosis or NASH and, more importantly, what the stage of hepatic fibrosis is and whether the level of hepatic fibrosis has increased over time. Such concern is based on the fact that NAFLD patients with advanced fibrosis are at the greatest risk of developing complications of end-stage liver disease over time (Chalasani et al. 2012; Lonardo et al. 2015; EASL-EASD-EASO clinical practice guidelines 2016).

Although noninvasive methods for estimating hepatic fibrosis require further validation, they could be useful for selecting those patients with NAFLD who require a liver biopsy. The sensitivity and specificity of some noninvasive biomarkers for the assessment of hepatic fibrosis have recently been described. The enhanced liver fibrosis (ELF) score uses an algorithm and measurements of tissue inhibitor of matrix metalloproteinase-1, hyaluronic acid, and the aminoterminal peptide of pro-collagen III and has excellent performance for the diagnosis of severe fibrosis, good performance for moderate fibrosis, and fair performance for identifying people without fibrosis. The NAFLD fibrosis score has good performance for identifying people without fibrosis, but poorer performance for diagnosing advanced fibrosis. Thus, a combination of both tests might improve diagnostic performance to diagnose different stages of hepatic fibrosis in NAFLD, without having to resort to liver biopsy (Castera et al. 2013; Byrne and Targher 2015; EASL-EASD-EASO clinical practice guidelines 2016). However, whether the currently available fibrosis biomarkers are also useful for monitoring NAFLD progression (or regression) in patients with established diabetes is uncertain (Bazick et al. 2015). Future studies combining the clinical prediction rules with other noninvasive imaging methods need to be performed to further improve the diagnostic accuracy.

Hepatic fibrosis can be also staged using vibration controlled transient elastography (FibroScan®), which measures the velocity of a low-frequency elastic shear wave propagating through the liver. This velocity is directly related to tissue stiffness. The stiffer the tissue, the faster the shear wave propagates. The results are expressed in kPa and correspond to the median value of 10 validated measurements, ranging 2.5–75 kPa, with normal (healthy liver) values ~5.5 kPa. Advantages of transient elastography include a short procedure time (<5 min), immediate results, and the ability to perform the test at the bedside or in an outpatient clinic. However, accurate results require careful interpretation of data, based on at least 10 validated measurements to calculate a median value, a success rate (the ratio of valid measurements to the total number of measurements) >60%, and an interquartile range (IQR; reflects variations among measurements) of <30% of the median value (IQR/M <30%). The main limitation of ultrasonography-based transient elastography in clinical practice is its failure to obtain reliable liver stiffness measurements (~20% of cases, mainly severely obese patients), which diminishes its application in NAFLD (Castera et al. 2013).

Several other liver-elasticity-based imaging techniques are being developed, including 2D acoustic radiation force impulse imaging (ARFI), shear-wave elastography, and 3D magnetic resonance elastography (Castera et al. 2013).

Epidemiology and Natural History of NAFLD in Patients with Diabetes

Estimates of NAFLD prevalence may vary both by the population that is studied (for example, studies in patients with different ethnicities, sex, and comorbidities) and the sensitivity of the modality used for diagnosis (serum liver enzymes, imaging techniques or biopsy).

Hepatic fat content is strongly correlated with the number of the metabolic syndrome features and the levels of serum aminotransferases. However, it is known that patients with T2DM have a hepatic fat content that is approximately 80% greater and their serum liver enzymes levels are less representative of the severity of hepatic steatosis than age-, sex-, and body weight-matched nondiabetic controls. Moreover, patients with T2DM and NAFLD often have worse glycemic control than their counterparts without NAFLD, suggesting that NAFLD may hamper glycemic control in T2DM (Targher and Byrne 2013; Lonardo et al. 2015; EASL-EASD-EASO clinical practice guidelines 2016).

Based on these findings, it is not surprising that the prevalence of NAFLD is markedly increased in people with T2DM. As discussed in a recent review (Lonardo et al. 2015), the prevalence of NAFLD in patients with T2DM ranges from approximately 45% to 75% in large hospital-based studies and from approximately 30% to 70% in population-based studies. These wide interstudy variations might reflect differences both in the demographic features of patient cohorts and in the modality used to diagnose NAFLD. For instance, in the Valpolicella Heart Diabetes Study, involving 2839 Italian outpatients with T2DM (mean age 63 years, mean body mass index 27 kg/m^2), the prevalence of NAFLD on ultrasonography was 69.5% (Targher et al. 2007a).

Strong evidence indicates that patients with T2DM are at high risk of developing NASH and a twofold to fourfold higher risk of developing serious liver-related complications (Chalasani et al. 2012; Anstee et al. 2013; Targher and Byrne 2013). For instance, the prevalence of advanced hepatic fibrosis, detected by noninvasive methods, in patients with T2DM has been estimated to be approximately between 3% and 7%. Some recent studies in patients with T2DM using magnetic resonance imaging to assess the liver proton density fat fraction and magnetic resonance elastography to estimate hepatic stiffness demonstrated high rates of both NAFLD (steatosis) and advanced fibrosis: approximately 65% and 7%, respectively (Doycheva et al. 2016). Early studies using liver biopsy observed that patients with T2DM have more severe NAFLD based on histology with NASH rates up to 70% and advanced fibrosis in approximately 30–40% of patients (Castera et al. 2013; Byrne and Targher 2015; Lonardo et al. 2015). In a large prospective cohort study of approximately 1250 patients with biopsy-proven NAFLD, recently conducted by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-sponsored NASH Clinical Research Network, the prevalence of NASH and advanced fibrosis on liver histology in the subgroup of patients with T2DM (mean age and BMI of these patients: 52.5 years and 35.8 kg/m^2, respectively) was 69.2% and 41%, respectively (Bazick et al. 2015). The prevalence of histologically

proven NASH was found to be high (56%) also in a smaller study enrolling 103 obese T2DM patients with normal serum aminotransferase levels (Portillo-Sanchez et al. 2015). In addition, a recent study using a large administrative health database, involving almost 2.5 million people, has demonstrated that Canadian adults with newly diagnosed T2DM had an approximately twofold higher risk of developing serious liver disease (namely cirrhosis, liver failure, or liver transplantation) than matched individuals without diabetes over a follow-up period of 12 years (Porepa et al. 2010).

In addition to the presence of T2DM, other established clinical risk factors for NAFLD progression are older age (>45 years), obesity (body mass index >30 kg/m^2), insulin resistance, aspartate aminotransferase-to-alanine aminotransferase (AST/ALT) ratio >1, increased ferritin levels, and hypertension (Chalasani et al. 2012; Lonardo et al. 2015; EASL-EASD-EASO clinical practice guidelines 2016).

All these findings, together with the notion that patients with T2DM have an increased mortality risk from cirrhosis of any etiology, fully support screening for NAFLD and/or advanced fibrosis in people with T2DM.

Notably, it is important to note that most patients with T2DM and NAFLD (approximately 80%) have fairly normal serum liver enzyme levels, but this is not reassuring given that NASH, advanced fibrosis, and even cirrhosis may be found in patients with fairly normal serum liver enzymes. Therefore, normal serum liver enzyme levels should not preclude pursuing a histological diagnosis in high-risk groups of patients, especially if the presence of advanced liver disease is clinically suspected on the basis of transient elastography and/or noninvasive fibrosis biomarkers (Chalasani et al. 2012; Anstee et al. 2013; Targher and Byrne 2013; Portillo-Sanchez et al. 2015; EASL-EASD-EASO clinical practice guidelines 2016).

At present, there are very few data regarding the prevalence and natural history of NAFLD in adults with type 1 diabetes (T1DM). However, the epidemiological impact of both NAFLD and the metabolic syndrome seems to be greatly relevant also in T1DM adults, since the prevalence of the metabolic syndrome is steadily growing in these patients, being nowadays approximately 40%. Some recent studies have reported that NAFLD as detected by ultrasonography is present in approximately 30–50% of adult patients with T1DM (Targher et al. 2010a, b). In a longitudinal cohort of T1DM and T2DM patients who undergone a liver biopsy, it was also demonstrated that adult patients with T1DM had a high risk of developing severe liver complications (e.g., cirrhosis and portal hypertension), and that this risk was even comparable with that observed in patients with T2DM, who were matched for duration of diabetes, obesity, and other comorbidities (Harman et al. 2014).

Association Between NAFLD and Poor Glycemic Control

In patients with T2DM, the presence of NAFLD often makes it difficult to obtain a good glycemic control. In clinical practice, it is well established that patients with coexistent T2DM and NAFLD have a poorer quality of glycemic control and require a higher amount of insulin to get a good glycemic control than their counterparts

without NAFLD (Anstee et al. 2013; Targher and Byrne 2013). It is believed that the intrahepatic fat content is the major determinant in explaining the daily amount of insulin needed to achieve good glycemic control in T2DM patients with NAFLD. In fact, in insulin-treated T2DM patients with stable glycemic control, it has been demonstrated that intrahepatic fat content (as measured by proton magnetic resonance spectroscopy) is more closely correlated with the daily insulin dose and the ability of insulin to suppress hepatic glucose production and better explained the interindividual variation in insulin requirements. Moreover, some studies have observed a significant association between poor glycemic control and increased intrahepatic fat content in patients with T2DM, irrespective of age, sex, duration of diabetes, and body mass index. Moreover, in patients with T2DM, the coexistence of NAFLD is associated with more severe hyperinsulinemia and greater insulin resistance in the skeletal muscle, adipose tissue, and liver compared with their counterparts without NAFLD (Portillo-Sanchez et al. 2015). Additionally, when the relationship between NAFLD and peripheral glucose metabolism is explored in healthy individuals, the association between intrahepatic fat content and peripheral insulin sensitivity is stronger than the association with intramyocellular lipid content, visceral fat content, or subcutaneous fat content (Anstee et al. 2013; Targher and Byrne 2013). To date, clear evidence indicates that NAFLD can interact with the regulation of multiple metabolic and inflammatory pathways and is involved in the development of incident T2DM, possibly via its direct contribution to hepatic glucose production, hepatic/peripheral insulin resistance and the systemic release of multiple hepatokines (e.g., fetuin A, fetuin B, retinol-binding protein 4 and selenoprotein P) that adversely affect glucose metabolism and insulin action (Anstee et al. 2013; Targher et al. 2016a).

Collectively, therefore, these data suggest that increased intrahepatic fat infiltration is an important determinant of insulin resistance in the liver and affects both the daily dosage of glucose-lowering therapy and the achieving good glycemic control in patients with T2DM. These considerations also suggest that treatment strategies that decrease intrahepatic fat infiltration and improve insulin sensitivity might partly contribute to improved glycemic control in diabetic patients with NAFLD (Anstee et al. 2013; Byrne and Targher 2015).

Association Between NAFLD and Risk of Liver-Related Mortality and Morbidity

It is established that patients with NAFLD have a substantially increased risk of all-cause mortality, with a higher risk of mortality from CVD, malignancy, and liver-related diseases (Chalasani et al. 2012; Anstee et al. 2013; Rinella 2015; EASL-EASD-EASO clinical practice guidelines 2016). Particularly, the histological subgroup analysis indicates that simple steatosis seems to be a fairly benign condition, whereas NASH with varying degrees of hepatic fibrosis is more strongly associated with excess liver-related morbidity and mortality (Chalasani et al. 2012; Anstee et al. 2013; Rinella 2015). This relationship is well demonstrated also in a recent

multinational retrospective study of 619 patients with biopsy-proven NAFLD from 1975 through 2005 at medical centers in the United States, Europe, and Thailand (Angulo et al. 2015). Over a median follow-up period of 12.6 years, 193 (33.2%) of these patients died or underwent liver transplantation. In this study, patients with advanced hepatic fibrosis had shorter survival rates than patients without fibrosis. Moreover, the hepatic fibrosis stage, but no other histologic features of NASH, was strongly associated with the risk of all-cause mortality, liver transplantation, and liver-related events (Angulo et al. 2015).

As previously discussed, several studies indicate that T2DM, abdominal obesity, and insulin resistance are among the strongest clinical risk factors for the progression of NAFLD to NASH, advanced fibrosis, and cirrhosis. On the other hand, it is well known that the coexistence of chronic liver disease may also adversely influence the prognosis of diabetes. For example, in the Verona Diabetes Study, the risk of mortality from liver causes (mainly due to cirrhosis) was higher in the cohort of 7148 outpatients with T2DM than that observed in the age- and sex-matched general population (de Marco et al. 1999). Notably, the 5-year risk of mortality from liver causes was even higher than risk of mortality from cardiovascular causes. In fact, the standardized mortality rate in patients with T2DM was approximately 2.5 for liver causes and 1.3 for cardiovascular diseases (de Marco et al. 1999). These results were also confirmed in other large case-control studies. In all these studies, however, it was not possible to differentiate the various etiologies of chronic liver disease. Using a large electronic administrative database, Zoppini et al. recently analyzed all information available in death certificates in an entire region in northern Italy to investigate the etiology of chronic liver disease-associated mortality in people with diabetes ($n = 167{,}621$ diabetic individuals aged 30–89 years of the Veneto region) (Zoppini et al. 2014). Notably, these investigators found that diabetic individuals had an approximately threefold higher risk of dying of chronic liver diseases, mainly associated with a nonvirus and nonalcohol-related etiology, which is largely attributable to NAFLD (Zoppini et al. 2014). In agreement, a smaller community-based cohort study of 337 residents of Olmsted County (Minnesota) with diabetes mellitus reported that NAFLD (diagnosed by imaging or biopsy) had an approximately twofold increased risk of all-cause mortality (mainly due to CVD, malignancy, and liver-related complications) during a mean 11-year follow-up period (Adams et al. 2010). From all these studies, it is reasonable to assume that an early diagnosis and treatment of NAFLD, if any, may have a beneficial impact on survival rates of diabetic patients.

In the past decade, a marked increase in the incidence of hepatocellular carcinoma (HCC) has been observed internationally. Worldwide, most cases of HCC are related to chronic infection with viral hepatitis; however, over half of all cases of HCC in developed countries occur in patients who are not infected with viral hepatitis (Anstee et al. 2013; Reeves et al. 2016). Recent prospective studies have documented that there is a strong link among T2DM, NAFLD/NASH, and risk of HCC. It is known that the prevalence of HCC in patients with NAFLD is approximately 0.5% and increases to 3% in patients with NASH (Anstee et al. 2013; Michelotti et al. 2013). Studies also suggested that the prevalence of HCC is higher

in patients with T2DM and NAFLD. In fact, the coexistence of T2DM increases the risk of developing HCC (from 1.5 to 4.3-fold) (Anstee et al. 2013; Michelotti et al. 2013; EASL-EASD-EASO clinical practice guidelines 2016). A US-based population study reported in 2010 that NAFLD was the most common etiological factor in patients with HCC, as it was present in 58% of the 4406 patients with HCC who were surveyed. T2DM was the second most common factor, present in 35.8% of these patients. Furthermore, NAFLD remained the most common etiological factor in the subset of patients who only had a single risk factor for HCC, suggesting that this association was not simply through potentiation of other liver diseases. In a meta-analysis, patients with T2DM had a 2.5-fold increased risk of HCC than nondiabetic individuals (Anstee et al. 2013; Michelotti et al. 2013; Reeves et al. 2016).

Some evidence also suggests that the risk of HCC is increased in patients with a longer duration of diabetes and in those treated with sulfonylurea or insulin (Singh et al. 2013). Conversely, treatment with metformin appears to be associated with a lower risk of developing HCC (Zhang et al. 2012; Singh et al. 2013). However, these findings need further confirmation in large randomized clinical trials. To date, although viral cirrhosis and alcohol abuse are still the most important causes of primary liver cancers, NAFLD is becoming an emerging cause and, of course, will have an important impact on the development of this type of cancer in the next future.

All these considerations suggest again the need for close and intensive surveillance for advanced liver disease in diabetic patients with NAFLD.

Association Between NAFLD and Risk of Chronic Kidney Disease and Other Microvascular Diabetic Complications

In patients with T2DM, the presence of NAFLD is associated with an increased risk of microvascular diabetic complications, including CKD, retinopathy, and distal symmetric polyneuropathy.

In a large cohort study involving 2103 outpatients with T2DM (Targher et al. 2008a), it has been reported that patients with ultrasound-diagnosed NAFLD had remarkably higher age- and sex-adjusted prevalence rates of both nonproliferative and proliferative/laser-treated retinopathy and CKD than patients without NAFLD (Fig. 1). In logistic regression analysis, NAFLD was associated with increased rates of CKD (adjusted odds ratio 1.87; 95% CI 1.3–4.1) and proliferative/laser-treated retinopathy (adjusted odds ratio 1.75; 95% CI 1.1–3.7), independently of age, sex, body mass index, waist circumference, diabetes duration, hemoglobin A1c, plasma lipids, hypertension, smoking, and medication use (Targher et al. 2008a). Other studies in which NAFLD was diagnosed by either ultrasonography or histology have clearly shown that the presence and severity of NAFLD was strongly associated with an increased prevalence of abnormal albuminuria or decreased kidney function in patients with T2DM or prediabetes (Targher et al. 2014a). Some studies also showed that ultrasound-diagnosed NAFLD was associated, independently of

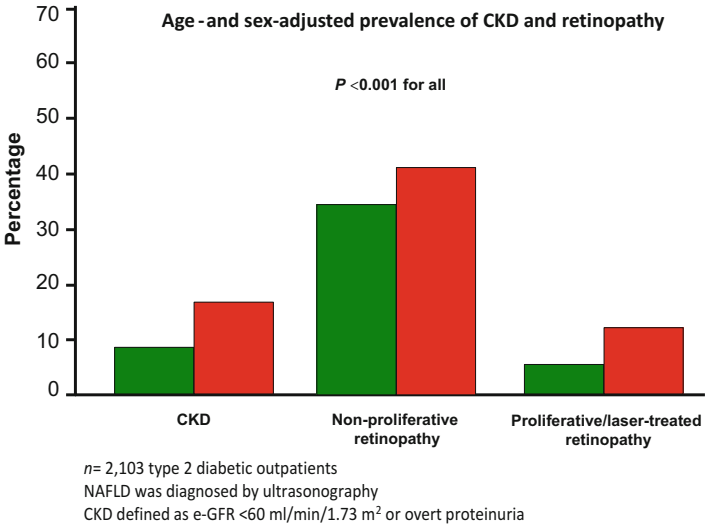

Fig. 1 Age- and sex-adjusted prevalence of chronic kidney disease (defined as estimated GFR <60 ml/min/1.73 m^2 or overt proteinuria), and diabetic retinopathy in type 2 diabetic adults with (red columns) and without (green columns) ultrasound-diagnosed NAFLD. (Data derived from Targher et al. 2008a)

multiple confounding factors, with a higher prevalence of CKD and retinopathy in adult patients with T1DM (Targher et al. 2010b).

To date, there is a paucity of published data regarding the risk of developing incident CKD in diabetic patients with NAFLD. The Valpolicella Heart Diabetes Study enrolled 1760 T2DM patients with normal or near-normal kidney function who did not have CVD, cirrhosis, and viral hepatitis at baseline (Targher et al. 2008b). During a mean follow-up of 6.5 years, 547 participants developed incident CKD (defined as estimated glomerular filtration rate [e-GFR] <60 ml/min/1.73 m^2 or overt proteinuria). Cox regression analysis revealed that ultrasound-diagnosed NAFLD was associated with a nearly 70%-increased risk of incident CKD (hazard ratio 1.69; 95% CI 1.3–2.6), independently of a broad number of coexisting cardio-renal risk factors (including also diabetes duration, hypertension, baseline e-GFR, albuminuria, and medication use) (Targher et al. 2008b).

In agreement, in a smaller follow-up study involving 261 T1DM adult patients with preserved kidney function and without overt proteinuria at baseline, who were followed for a mean period of 5.2 years, the presence of NAFLD on ultrasonography was associated with an increased incidence of CKD (hazard ratio 2.85, 95% CI 1.6–5.1). Adjustments for age, sex, duration of diabetes, hypertension, HbA1c, and baseline e-GFR did not appreciably attenuate this association. Results remained unchanged even after excluding those who had microalbuminuria at baseline (adjusted hazard ratio 1.85, 1.03–3.3). Notably, addition of NAFLD to traditional risk factors for CKD significantly improved the discriminatory capability of the regression models for predicting CKD (Targher et al. 2014b).

Finally, preliminary evidence also suggests that NAFLD is associated with an increased prevalence of distal symmetric polyneuropathy and cardiac autonomic dysfunction both in patients without diabetes and in those with T1DM or T2DM (Byrne and Targher 2015; Mantovani et al. 2016a). However, further studies are required to confirm this issue.

Despite the growing evidence that links NAFLD with CKD and other microvascular complications in patients with T1DM or T2DM, it remains to be definitively established whether a causal association also exists. There is uncertainty as to whether NAFLD poses an independent risk for diabetic nephropathy and retinopathy above and beyond that conferred by known risk factors. There is a suggestion in that direction, but studies are too few and are not methodologically rigorous. Additional large-scale prospective studies are needed to draw a firm conclusion about any independent hepatic contribution to the increased risk of developing microvascular complications observed among diabetic patients with NAFLD. In the meantime, however, all these studies suggest that diabetic patients with NAFLD need more careful surveillance and treatment to reduce the risk of developing CKD and other microvascular complications of diabetes.

Association Between NAFLD and Risk of Cardiovascular, Cardiac and Arrhythmic Complications

Over the last 10 years, growing epidemiological evidence has strongly documented that NAFLD, diagnosed either by imaging or by histology, is not only associated with an increased risk of liver-related morbidity and mortality but is also associated with an increased risk of developing CVD death and events both in patients without diabetes and in those with T1DM or T2DM. Indeed, clear evidence indicates that CVD is the leading cause of mortality among patients with NAFLD (Targher et al. 2010c; Byrne and Targher 2015; Rinella 2015; EASL-EASD-EASO clinical practice guidelines 2016).

Several cross-sectional studies have consistently shown that NAFLD is associated with both various markers of subclinical atherosclerosis (including also increased coronary artery calcium score) and clinically manifest CVD across a wide range of patient populations, including patients with diabetes (Byrne and Targher 2015; Mantovani et al. 2016a). For example, the Valpolicella Diabetes Heart Study reported that patients with T2DM and NAFLD had a higher age- and sex-adjusted prevalence of clinically manifest coronary, cerebrovascular, and peripheral vascular disease compared to their counterparts without NAFLD (Fig. 2). In logistic regression analysis, NAFLD on ultrasonography was associated with an increased risk of prevalent CVD independent of traditional CVD risk factors, hemoglobin A1c, metabolic syndrome features, and use of medications (Targher et al. 2007a). Similar findings were also found in adult patients with T1DM (Targher et al. 2010a). Moreover, in patients referred for clinically indicated coronary angiography, the presence of NAFLD was associated with a greater severity of coronary artery disease and with an increased prevalence of high-risk and vulnerable coronary

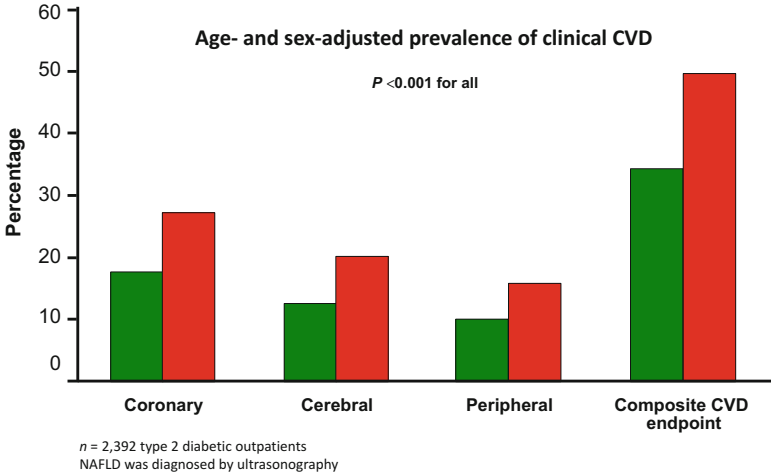

Fig. 2 Age- and sex-adjusted prevalence of coronary (defined as myocardial infarction, angina, or revascularization procedures), cerebrovascular (ischemic stroke, recurrent transient ischemic attacks, carotid endarterectomy, or carotid stenosis >70% as diagnosed by echo-Doppler scanning), and peripheral (intermittent claudication, rest pain, as confirmed by echo-Doppler scanning, lower extremity amputation, or revascularization procedures) in type 2 diabetic adults with (red columns) and without (green columns) ultrasound-diagnosed NAFLD. (Modified by Targher et al. 2007a)

artery plaques, independently of the extent and severity of coronary atherosclerosis (Byrne and Targher 2015; Mantovani et al. 2016a).

To date, convincing epidemiological evidence also substantiates the existence of a link of NAFLD with subclinical myocardial remodeling and dysfunction (i.e., left ventricular diastolic dysfunction and hypertrophy), valvular heart diseases (i.e., aortic-valve sclerosis and mitral annulus calcification), and increased risk of permanent atrial fibrillation both in patients without diabetes and in those with T2DM (Lonardo et al. 2016; Mantovani et al. 2016a). Preliminary evidence also supports a significant and independent association of NAFLD with heart rate-corrected QT interval prolongation on standard electrocardiograms in both nondiabetic and diabetic individuals, and with an increased prevalence of ventricular tachyarrhythmias on 24-h Holter monitoring (i.e., presence of nonsustained ventricular tachycardia, >30 premature ventricular complexes per hour, or both) in patients with T2DM (Lonardo et al. 2016; Mantovani et al. 2016a, b).

Although the cross-sectional associations of NAFLD with CVD and other cardiac and arrhythmic complications are strong and consistently demonstrated across different patient populations (including people with diabetes), the currently available data on whether NAFLD *per se* is simply a risk marker that coexists in people at increased risk of CVD, or is an independent risk factor for CVD is debatable. Moreover, uncertainty also exists about the prognostic value of NAFLD in risk stratification for CVD (Targher et al. 2010c; Lonardo et al. 2016).

However, with those caveats, a growing body of evidence now suggests that CVD is a serious threat to patients with NAFLD, and that CVD dictates the outcome(s) in

patients with NAFLD more frequently and to a greater extent than does the progression of liver disease (Targher et al. 2010c; Anstee et al. 2013; Byrne and Targher 2015; Rinella 2015; Lonardo et al. 2016; EASL-EASD-EASO clinical practice guidelines 2016).

In patients with NAFLD diagnosed by imaging techniques, several large hospital-based and population-based studies reported an increased incidence of fatal and nonfatal CVD events, independent of established CVD risk factors, both in patients with T2DM and in those without established T2DM (Targher et al. 2010c; Anstee et al. 2013; Byrne and Targher 2015; Lonardo et al. 2016; Mantovani et al. 2016a).

For instance, the Valpolicella Diabetes Heart Study, involving 2103 T2DM patients without prior CVD and secondary causes of chronic liver disease at baseline, reported that patients with ultrasound-diagnosed NAFLD had an approximately twofold increased risk of developing nonfatal ischemic heart disease (defined as myocardial infarction and coronary revascularization procedures), nonfatal ischemic stroke, or cardiovascular death (adjusted hazard ratio 1.87, 95% CI 1.2–2.6) compared with patients without NAFLD over a 6.5-year follow-up period. Notably, this relationship was independent of age, sex, body mass index, smoking, diabetes duration, hemoglobin A1c, low-density lipoprotein (LDL) cholesterol, metabolic syndrome features, and use of hypoglycemic, anti-hypertensive, lipid-lowering, and antiplatelet drugs (Targher et al. 2007b).

A recent systematic review and meta-analysis of 16 observational studies, involving approximately 34,000 individuals (36.3% of whom with NAFLD as detected by imaging or histology), confirmed that patients with NAFLD, irrespective of the presence of diabetes, had a higher risk of fatal and nonfatal CVD events than those without NAFLD (random-effects odds ratio 1.64, 95% CI 1.26–2.13). In addition, patients with more "severe" NAFLD (defined either by presence of hepatic steatosis on imaging *plus* either increased serum gamma-glutamyltransferase concentrations or high NAFLD fibrosis score or high ^{18}F-fluoro-2-deoxyglucose uptake on positron emission tomography, or by increasing fibrosis stage on liver biopsy) were also more likely to develop fatal and nonfatal CVD events (random-effects odds ratio 2.58; 95% CI 1.78–3.75) (Targher et al. 2016b).

Although the results of this large and updated meta-analysis provide robust evidence of the association between NAFLD and risk of developing major CVD events both in patients with and without T2DM, however, it is important to underline that the quality of published studies was not always high and that causality remains to be proven in high-quality intervention studies (Targher et al. 2016b). Moreover, the key question of whether the prognostic role of NAFLD in CVD development is restricted only to NASH (with varying amounts of liver fibrosis) or is also associated with simple steatosis remains still unresolved. More research is needed to address this issue.

Taken together, however, the current evidence from the published studies indicates that a diagnosis of NAFLD identifies a subset of individuals, which are exposed to at higher risk of CVD mortality and morbidity. This also implies that patients with NAFLD should undergo careful cardiovascular surveillance. In line with this implication, given that CVD complications frequently dictate the outcome(s)

of NAFLD, the EASL-EASD-EASO clinical practice guidelines have strongly recommended screening of cardiovascular system in all patients with NAFLD, at least by detailed risk factor assessment (EASL-EASD-EASO clinical practice guidelines 2016).

However, it is not yet established whether addition of NAFLD to the currently available risk assessment calculators significantly improves CVD risk prediction. Moreover, randomized controlled trials with major CVD outcomes that focus on treatments for liver disease in NAFLD are also needed in order to definitely establish a causal relationship between NAFLD and risk of developing CVD events.

Putative Mechanisms Linking NAFLD with Cardiovascular, Cardiac and Kidney Complications

It is beyond the scope of this chapter to discuss in detail the pathophysiological links between NAFLD and CVD/cardiac complications as well as the links between NAFLD and CKD. Detailed discussions of this topic have been published elsewhere (Targher et al. 2010c; Anstee et al. 2013; Mantovani et al. 2016a; Lonardo et al. 2016).

To date, a clear understanding of the pathophysiological pathways linking NAFLD to the development of CVD, cardiomyopathy, and CKD remains elusive, because of the intricate interactions among NAFLD, abdominal obesity, insulin resistance, chronic inflammation, and oxidative stress. NAFLD, cardiovascular/cardiac diseases, and CKD share many metabolic features and cardiovascular risk factors, leading to the concept that they belong to a complex multisystem disease with several organ manifestations and a complex interplay between the different diseases, with multiple bidirectional cause–effect relationships. The specific contribution of one disease to the others is therefore difficult to discern, and there might be substantial interindividual variability.

However, a growing body of evidence to date suggests that NAFLD is not simply a marker of both CVD and CKD, but is also implicated in the pathogenesis of these important extrahepatic complications (Targher et al. 2010c; Anstee et al. 2013; Mantovani et al. 2016a; Lonardo et al. 2016).

Figure 3 schematically summarizes the putative mechanisms linking NAFLD, expanded and inflamed adipose tissue, and altered gut microbiota with CKD and CVD complications in people with diabetes.

Both expanded/inflamed ("dysfunctional") visceral adipose tissue and altered intestinal microbiota (intestinal dysbiosis) may influence the development and progression of NAFLD, through the release and production of nonesterified fatty acids, proinflammatory adipocytokines (e.g., tumor necrosis factor-α and interleukin-6), short-chain fatty acids (SCFAs) (e.g., butyrate, propionate and acetate), incretins (e.g., glucagon-like peptide 1), thrombospondin-1, and decreased production of adiponectin levels. When NAFLD develops and when hepatic fat, inflammation, and fibrosis progress (NASH), many important alterations occur in the liver, resulting in the worsening of hepatic/systemic insulin resistance, the production of

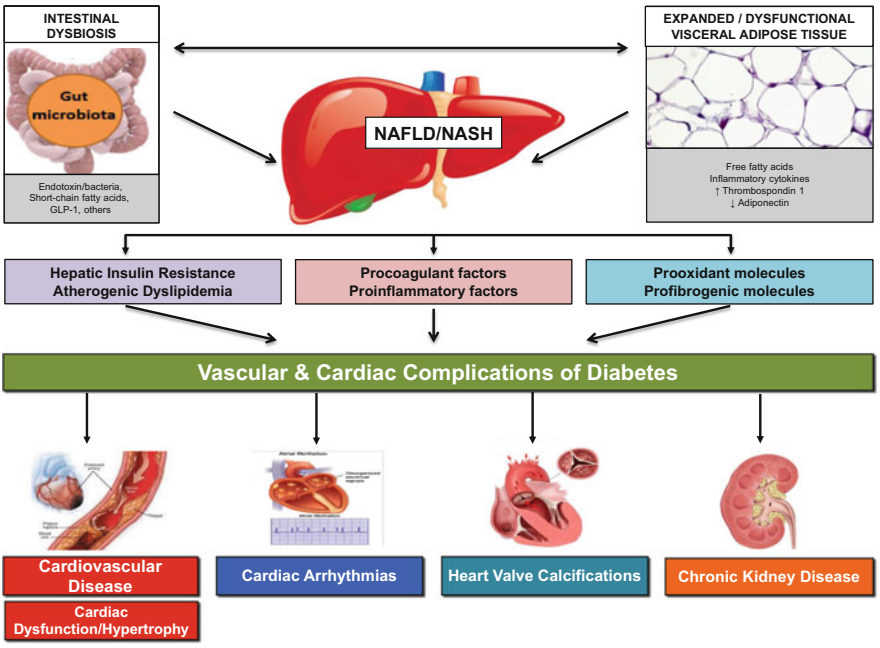

Fig. 3 Schematic representation of putative mechanisms by which NAFLD may contribute to the development and progression of chronic vascular complications of diabetes

atherogenic lipids, and the systemic release of a myriad of proinflammatory, prooxidant, prothrombogenic, and vasoactive mediators. All these NAFLD-related changes can adversely influence the risk of developing CKD, CVD, and other cardiac complications (Targher et al. 2010c; Anstee et al. 2013; Byrne and Targher 2015; Mantovani et al. 2016a; Lonardo et al. 2016).

However, although all these pathophysiological mechanisms plausibly link NAFLD to the development and progression of both CVD and CKD, no studies to date have definitely proven a cause-and-effect relationship, and further research is needed to gain mechanistic insights into the pathophysiology linking NAFLD to CVD and CKD. An improved knowledge of the pathophysiological links between NAFLD, diabetes, and these chronic vascular complications will not only help develop new pharmacological treatments for NAFLD, but may also help decrease the global burden of these very common noncommunicable diseases that we now know share a "common soil" with NAFLD.

Management of NAFLD in Patients with Diabetes

Existing diabetes guidelines do not advocate screening for liver-related complications among patients with T2DM or T1DM, making the liver a potentially neglected target organ for undetected chronic disease progression to cirrhosis. However, given

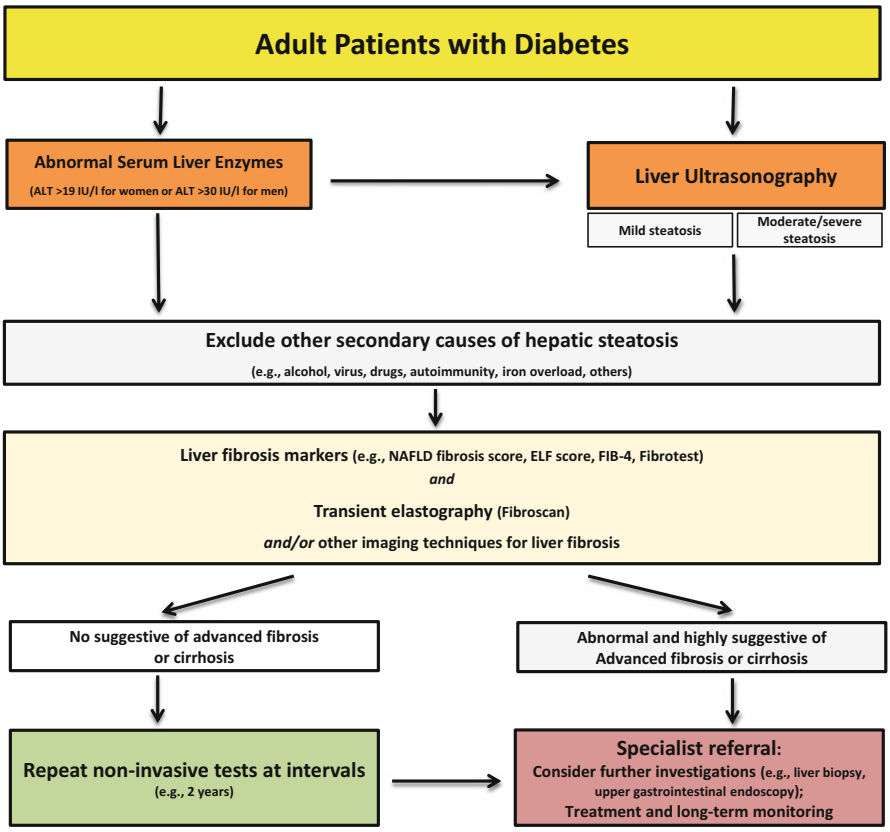

Fig. 4 Proposed pragmatic algorithm for the diagnosis and management of NAFLD in adult patients with diabetes. The algorithm has been developed by the authors using both available evidence and guidelines, as well as personal opinion where uncertainty exists and evidence is not available

the increasingly growing prevalence of NAFLD in people with diabetes and its related hepatic and extrahepatic complications, NAFLD should always be ruled out in all adult individuals with T2DM or T1DM.

Figure 4 shows a possible pragmatic algorithm for the diagnosis and management of NAFLD in people with diabetes. It is important to emphasize that currently, in the literature, there is an intense debate on these aspects, and that a completely validated and shared algorithm for the diagnosis and management of NAFLD in adult patients with T1DM or T2DM does not exist yet. Therefore, this proposed algorithm is based on available evidence and guidelines as well as authors' personal opinions, when uncertainty exists and evidence is unavailable.

For example, to date, whether individuals with T2DM and NAFLD should be treated to a specific HbA1c, LDL-cholesterol, and blood pressure target remains uncertain. NAFLD is a novel and emerging CVD risk factor that often coexists with

features of the metabolic syndrome. Since CVD risk tends to be underestimated in patients with T2DM, it is likely that the available (traditional) CVD risk algorithms will further underestimate the CVD risk in people with coexistent T2DM and NAFLD. Consequently, in the absence of available evidence to the contrary, the authors recommend treatment with a statin in all patients with NAFLD if estimated 10-year CVD risk score is >15% using any of the available CVD risk calculators. Whether clinicians should treat plasma LDL cholesterol to target is also currently unknown. We believe that a pragmatic approach would be to assume that patients are at the same CVD risk as individuals who have already suffered a first atherosclerotic CVD event and adjust their statin dose accordingly, aiming to treat to a target LDL cholesterol of <2.6 mmol/L (a lower LDL cholesterol goal of <1.8 mmol/L is suggested in individuals with overt CVD) (Targher and Byrne 2013). Patients with high triglyceride and/or low HDL cholesterol levels should be also treated with fenofibrate (or high-dose omega 3 polyunsaturated fatty acids).

As previously reported, serum liver enzymes (i.e., serum aminotransferases and gamma-glutamyltransferase levels) are not reliable indicators for the screening and diagnosis of NAFLD in patients with T2DM or T1DM and, therefore, they should not be used alone in clinical practice. As previously discussed, the majority of diabetic patients with NAFLD have normal or only slightly elevated levels of serum liver enzymes (Chalasani et al. 2012; Targher and Byrne 2013). Moreover, patients with normal *versus* elevated serum aminotransferase levels may have similar severity of NASH or liver fibrosis. For these reasons, many authors have proposed to reduce the normal range values of serum aminotransferases (suggesting, for example, a level of serum alanine aminotransferase [ALT] <19 U/l for women and <30 U/l for men, respectively) in order to increase the likelihood of excluding NAFLD (Chalasani et al. 2012; EASL-EASD-EASO clinical practice guidelines 2016).

As previously discussed, it is known that liver ultrasonography has a good diagnostic accuracy to detect the presence of mild and moderate-severe steatosis, demonstrating a sensitivity and specificity, respectively, of 85% and 95% (especially when liver fat infiltration is at least 20–30%). Moreover, ultrasonography is relatively inexpensive and may help clinicians to exclude other causes of liver diseases and identify any early signs of cirrhosis or portal hypertension. Therefore, as suggested by several authors, this imaging technique remains now the recommended first-line imaging modality for the screening and diagnosis of NAFLD in patients with and without diabetes mellitus (Chalasani et al. 2012; Targher and Byrne 2013; EASL-EASD-EASO clinical practice guidelines 2016).

As shown in Fig. 4, our proposed algorithm can be used to identify T2DM/T1DM patients for liver biopsy, or if biopsy is not undertaken (as is occurring more frequently in many centers), a careful assessment of liver fibrosis by the use of nonivasive markers of fibrosis and/or transient elastography (Fibroscan) is mandatory for selecting patients for upper gastrointestinal endoscopy, potential treatment of esophageal varices, and routine surveillance. The NAFLD fibrosis score and fibrosis-4 (FIB4) score are examples of validated nonproprietary, noninvasive clinical scores for estimating the severity of liver fibrosis. The enhanced liver fibrosis (ELF) score

and the Fibrotest are examples of proprietary clinical scores that have also been proposed for the noninvasive assessment of advanced hepatic fibrosis based on clinical biochemical indices and/or panels of specific serum fibrosis biomarkers.

In a cohort study of over 1900 Chinese patients with T2DM, it has been tested the strategy of screening diabetic patients for NAFLD with Fibroscan (Kwok et al. 2016). Hepatic steatosis and fibrosis were assessed by controlled attenuation parameter (CAP) and liver stiffness measurements by Fibroscan at a diabetic center for patients from primary care and hospital clinics. The authors found that diabetic patients had a very high prevalence of hepatic steatosis (72.8%, 95% CI 70.7–74.8%) and advanced hepatic fibrosis (17.7%, 95% CI 16.0–19.5%). Those with obesity and dyslipidemia were at particularly high risk and may be the target for liver assessment (Kwok et al. 2016). These data further support screening for NAFLD and/or advanced fibrosis in patients with T2DM.

Treatment Options for NAFLD in Patients with Diabetes

Currently, there are no approved pharmacological agents for the treatment of NAFLD. Most interventions evaluated for NAFLD treatment are those commonly used for the treatment of T2DM and exert a rather indirect effect through improvement in both insulin resistance and plasma glucose levels. These pharmacological interventions have also been to date the most effective treatments for NAFLD, which is perhaps not surprising, considering the high degree of interplay between these two diseases. Currently, however, no specific data are available regarding the pharmacological agents for the treatment of NAFLD in adult patients with T1DM.

Pharmacotherapy for NAFLD should probably be reserved for patients with NASH, who are at the highest risk for disease progression (Chalasani et al. 2012; EASL-EASD-EASO clinical practice guidelines 2016). However, the major problem in this field of research is the scarcity of definitive, large randomized controlled trials. To date, there are very few high-quality, randomized, blinded, adequately powered, controlled trials of sufficient duration and with adequate histological outcomes.

Currently, the therapeutic approach to diabetic patients with NAFLD is multifactorial, as summarized in Fig. 5. The first approach is the treatment of overweight and obesity (especially through appropriate changes in lifestyles and/or bariatric surgery for properly selected patients with severe obesity), the optimization of glycemic control, and the treatment of all coexisting cardiometabolic risk factors, mainly atherogenic dyslipidemia and hypertension, possibly by the use of drugs with potentially positive hepatic effects. The main goals of treatment are: to improve insulin resistance, to reduce intrahepatic fat infiltration, and to avoid the progression of NAFLD/NASH to more severe histological forms (cirrhosis, liver failure, and HCC) (Table 1).

All patients with NAFLD, irrespective of presence of diabetes, should avoid alcohol consumption, even moderate, as well as the use of potentially hepatotoxic drugs, when possible. Similar recommendations should be given for the use

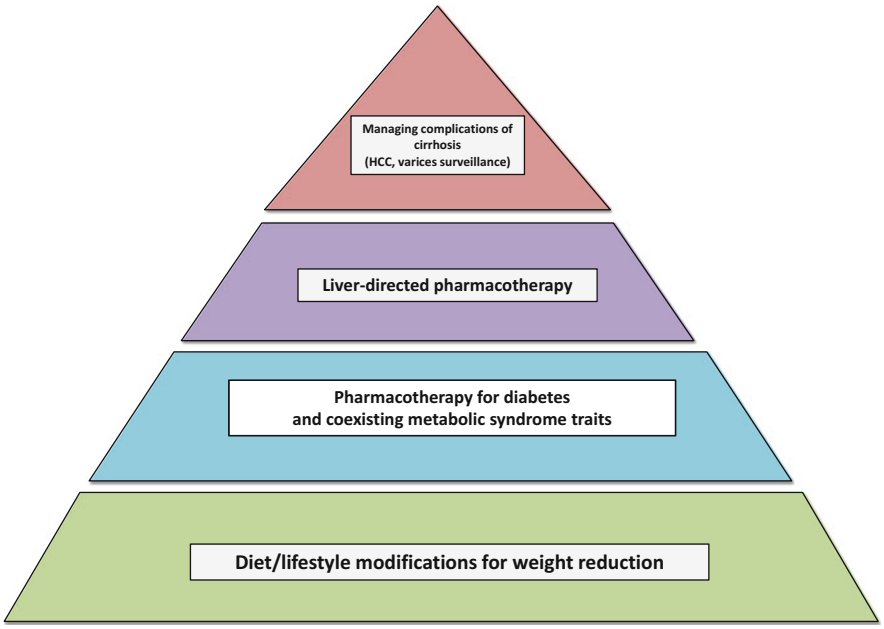

Fig. 5 Management strategies of NAFLD in patients with diabetes

Table 1 Management strategies of NAFLD/NASH in patients with type 2 diabetes

Treatment of NAFLD in patients with T2DM
Weight loss through appropriate diet/lifestyle modifications (need a reduction of 5% to ameliorate hepatic steatosis and about 10% to improve liver necro-inflammation)
Stop cigarette smoking and avoid excessive alcohol consumption
Regular exercise/physical activity: 150 min/week of moderate-intensity aerobic physical activities in 3–5 sessions are generally recommended. Alternatively, resistance training is effective, having effects on metabolic risk factors
Avoid fructose-containing beverages and foods
Achieve a good glycemic control (hemoglobin A1c <7% [<53 mmol/mol] if no contraindications); metformin is the first drug of choice for most patients with T2DM. If the patient has biopsy-proven NASH and there are no contraindications, consider pioglitazone. Consider also GLP-1 agonists if no contraindications
If blood pressure is ≥140/90 mmHg, start an appropriate anti-hypertensive therapy; treatment with ACE-inhibitors or angiotensin receptor blockers as first-line therapy
If dyslipidemia or 10-year cardiovascular risk >15%, start treatment with statins (*plus* fenofibrate if necessary)
If body mass index >35 kg/m^2, consider bariatric (metabolic) surgery
Monitoring for onset hepatic complications (e.g., cirrhosis, portal hypertension, esophageal varices and hepatocellular carcinoma)

Note: Currently, no specific indications for the treatment and management of NAFLD in adult patients with type 1 diabetes are available. However, a careful surveillance for advanced liver disease as well as an early, aggressive treatment of all modifiable cardiovascular risk factors are also needed in this group of patients

of cigarette smoking to avoid the worsening of the NAFLD-related CVD risk. Clinicians should also recommend avoiding fructose-containing beverages and foods, given that an association has been reported between high fructose intake and risk of progressive NAFLD (Chalasani et al. 2012; Rinella 2015; EASL-EASD-EASO clinical practice guidelines 2016).

It is well established that gradual body weight reduction, achieved either by hypocaloric diet alone or in combination with regular physical activity, can be effective in decreasing hepatic steatosis, necroinflammation and fibrosis; the reduction of hepatic steatosis and necroinflammation is proportional to the intensity of the lifestyle intervention and generally requires a weight loss between 5% and 10% (a reduction of hepatic fibrosis is usually less easy to obtain, but it requires a sustained weight loss of at least 10%). However, in real life, an adequate weight loss is very difficult to achieve and maintain, and an appropriate aerobic physical activity is often impractical, especially in older T2DM patients, because of comorbid joint arthritis limiting a full range of joint movements. In such a situation, resistance training might be a valid alternative option to help induce a net negative energy balance and decrease hepatic fat content. Recent research has also shown a benefit of resistance training in ameliorating some of the histological features of NAFLD, independently of weight loss (Chalasani et al. 2012; Rinella 2015; EASL-EASD-EASO clinical practice guidelines 2016).

Many people with T2DM are treated with statins for dyslipidemia. It should be noted that statins can be safely used for dyslipidemia in patients with NAFLD/NASH and some studies, although not all, have also suggested that statins might exert some beneficial effect on NASH histology. To date, however, as randomized controlled trials with histological liver endpoints are not available, statins should not be used to specifically treat NAFLD/NASH (Chalasani et al. 2012; Targher and Byrne 2013; Corey and Rinella 2016; EASL-EASD-EASO clinical practice guidelines 2016).

To date, only limited evidence supports definitive treatment recommendations for specific pharmaceutical therapy in patients with coexistent NAFLD/NASH and diabetes. The available randomized controlled trials studying the histological liver endpoints in this patient population are generally small, with a short duration and have provided inconsistent outcomes. Thus, tailoring an individual treatment strategy to reduce body weight and optimize metabolic control of diabetes with the potential to improve liver phenotype remains the current gold standard.

The most available evidence for the treatment of NAFLD is the use of pioglitazone in patients with biopsy-proven NASH (Chalasani et al. 2012; Rinella 2015; EASL-EASD-EASO clinical practice guidelines 2016; Ratziu 2016). The effect of pioglitazone (an insulin-sensitizing agent that is a selective ligand of the peroxisome-proliferator-activated receptor gamma) is partly mediated by increases in adiponectin, which is known to exert beneficial effects on the liver that include reducing hepatic gluconeogenesis and reducing fatty acid influx. Some randomized controlled trials have documented that pioglitazone treatment significantly improves hepatic steatosis and necroinflammation, but not hepatic fibrosis, in patients with biopsy-proven NASH and that its interruption may determine the reappearance of

the liver damage. To note, the majority of participants of these published clinical trials were nondiabetic. More recently, in a randomized, double-blind, placebo-controlled trial (including 101 patients with prediabetes or T2DM and biopsy-proven NASH who were randomly treated with pioglitazone, 45 mg/day, or placebo for 18 months, and then followed by an 18-month open-label phase with pioglitazone treatment), Cusi et al. have reported that among those randomly assigned to pioglitazone, 58% achieved the primary study outcome (i.e., a reduction of at least 2 points in the NAFLD activity score in 2 histologic categories without worsening of fibrosis) and 51% had resolution of NASH. Pioglitazone treatment was also associated with reduced intrahepatic fat content and improved adipose tissue, hepatic, and muscle insulin sensitivity. All 18-month metabolic and histologic improvements persisted over 36 months of therapy. The overall rate of adverse events did not significantly differ between the two groups, although weight gain was greater with pioglitazone (~2.5 kg vs. placebo) (Cusi et al. 2016). Despite these encouraging data, pioglitazone is currently not licensed for the treatment of NAFLD/NASH, and some concerns regarding fluid retention, weight gain, and, to a lesser extent, increased risk of bone fractures and bladder cancer have meant that the chronic use of pioglitazone in T2DM patients with NAFLD remains limited.

Metformin is currently the first-line therapeutic agent in the management of patients with T2DM. Studies using metformin for the treatment of NAFLD have produced conflicting results. Collectively, these studies suggested that metformin treatment has beneficial effects on serum liver enzymes and insulin resistance, but has no significant effect on NAFLD histology. However, some experimental and observational (case-control or prospective) studies have suggested that treatment with metformin in patients with T2DM may reduce the risk of developing HCC, a serious complication of NAFLD (Zhang et al. 2012; Singh et al. 2013; Chen et al. 2013). In vitro studies showed that metformin is an activator of AMP-activated protein kinase signaling and reduces mTOR pathway (Chen et al. 2013). Further investigation is warranted on this issue. That said, metformin is not currently recommended as a specific treatment for liver disease in patients with NAFLD/NASH (Chalasani et al. 2012; Rinella 2015; EASL-EASD-EASO clinical practice guidelines 2016).

Sulfonylureas are commonly used as second-line agents for glycemic control in patients with T2DM. There are no currently prospective data examining their use in NAFLD with coexistent diabetes. Some retrospective data exist suggesting that the prevalence of hepatic fibrosis in patients with T2DM and NAFLD is slightly higher in those treated with sulfonylureas. However, no adjustment was made for glycemic control or diabetes duration. Given the availability of generic sulfonylureas, it is unlikely that future prospective studies will address the outstanding issues that surround their use in the context of NAFLD; however, as this class of drugs is associated with a gain in weight and is metabolized extensively by the liver, it is unlikely to be an attractive treatment option for T2DM patients with coexistent NAFLD.

The incretin mimetic drugs (i.e., dipeptidyl peptidase [DPP]-4 inhibitors and glucagon-like peptide [GLP]-1 agonists) are now widely prescribed as adjunctive

oral therapy in patients with T2DM. This class of drugs is effective for the treatment of T2DM, determining weight loss, reducing appetite, and improving insulin sensitivity. GLP-1 receptors are present in human hepatocytes, and activation of these receptors may have a direct action to decrease hepatic steatosis by improving insulin signaling. Experimental data in animals support the use of GLP-1 agonists for NAFLD treatment. Human studies investigating the effect of some GLP-1 agonists (exenatide and liraglutide) on liver injury are currently limited to single case reports and large retrospective studies of serum liver enzymes in patients with T2DM. These two drugs significantly improved serum liver enzyme concentrations in a dose-dependent manner, with comparable safety profiles in T2DM patients with and without abnormal liver biochemistry (Targher and Byrne 2013; Rinella 2015; Corey and Rinella 2016; EASL-EASD-EASO clinical practice guidelines 2016). More recently, a double-blind, randomized, placebo-controlled phase 2 study (LEAN) trial (involving 52 obese patients with and without T2DM with biopsy-proven NASH) employing of liraglutide 1.8 mg per day subcutaneously resulted in significant decreases in liver fat content and histological resolution of NASH in more patients compared with placebo (39% vs. 9%) after 48 weeks of treatment (Armstrong et al. 2016). This may suggest that liraglutide exerts effects additional to simple weight loss. Future, longer-term phase 3 trials with liraglutide are needed to confirm its efficacy in patients with NASH. Thus, at present, although GLP-1 agonists have shown promising results in the improvement of hepatic steatosis and necroinflammation, there are no robust data with histological endpoints as a primary outcome to formally comment on the effectiveness of GLP-1 agonists as a treatment for NAFLD/NASH with coexistent diabetes. Currently, no evidence is available regarding the efficacy of DDP-4 inhibitors for the treatment of NAFLD/NASH in diabetes. Prescribing advice remains to use caution in more severe hepatic impairment, although this class of agents is predominantly renally excreted.

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a new class of oral hypoglycemic agents that work by decreasing renal glucose reabsorption. Some animal models of NAFLD with SGLT2 inhibitors have demonstrated a protective effect on hepatic steatosis, inflammation, and fibrosis. This attenuated steatosis–fibrosis progression may well be due to a combination of negative energy balance through glycosuria and substrate switching toward lipids as a source of energy expenditure. To date, there are no human studies of SLGT2 inhibitors and NAFLD; however, given the net weight loss of approximately 1.8 kg seen in a published meta-analysis, it may represent an attractive pharmacological strategy, but this remains to be investigated in dedicated randomized controlled trials.

It is known that chronic insulin treatment increases body fat, but it does not appear to promote or worsen NAFLD in patients with diabetes (EASL-EASD-EASO clinical practice guidelines 2016). While acute insulin infusion dose-dependently increases hepatic fat content in T2DM, chronic insulin treatment improves adipose tissue insulin resistance and therefore reduces free fatty acid flux and hepatic fat content. A pilot randomized clinical trial comparing the 12-week effects of insulin glargine and liraglutide therapy on liver fat content as measured by magnetic resonance in 35 patients with T2DM inadequately controlled with oral agents

therapy found that the administration of insulin glargine therapy significantly reduced the liver fat burden in these patients (Tang et al. 2015).

High doses of omega-3 polyunsaturated fatty acids (PUFAs) are effective in treatment of hypertriglyceridemia that is often observed in patients with T2DM and NAFLD. Nine eligible studies, involving about 350 patients with NAFLD and testing doses of omega-3 PUFA treatments, have documented significant reductions in hepatic fat content without relevant side effects. However, the size of the effect was relatively small. To date, the optimal dose and duration of treatment with omega-3 PUFAs is not known, and well-designed randomized controlled trials are needed to recommend omega-3 PUFA supplementation for the treatment of NAFLD/NASH (Chalasani et al. 2012; Targher and Byrne 2013; EASL-EASD-EASO clinical practice guidelines 2016).

Given that increased oxidative stress occurs in both NAFLD and T2DM, another therapeutic option for NAFLD treatment is to decrease oxidative stress by administration of an antioxidant, such as vitamin E. In the PIVENS trial, involving 247 nondiabetic adults with NASH, the treatment with vitamin E (at a dose of 800 U/day for 96 weeks), as compared with placebo, was associated with significant improvements in serum liver enzymes and some histological features of NASH (steatosis, inflammation, and ballooning). However, before vitamin E can be recommended for the treatment of NAFLD, further evidence is required to support efficacy and, importantly, the safety of this fat-soluble agent. Moreover, insufficient evidence is available to treat patients with diabetes or cirrhosis (Chalasani et al. 2012; Rinella 2015; Corey and Rinella 2016; EASL-EASD-EASO clinical practice guidelines 2016).

Pentoxifylline has been shown to decrease oxidative stress and inhibit lipid oxidation. A meta-analysis of some small randomized controlled trials has examined the use of pentoxifylline in NAFLD, documenting a decrease in serum liver enzymes and an improvement in hepatic steatosis, lobular inflammation, and fibrosis (Chalasani et al. 2012; Rinella 2015; Corey and Rinella 2016). These small studies suggest that this drug may have benefit in NASH and has a very good safety profile. However, until more definitive data are available, its impact on NASH remains elusive.

Vitamin D_3 plays a key role in calcium homeostasis and bone mineralization. Vitamin D_3 deficiency is a highly prevalent condition worldwide. Some small studies have demonstrated that patients with NAFLD had significantly lower 25 (OH)-vitamin D_3 levels than those without liver involvement. Again, emerging experimental evidence suggests that low serum vitamin D_3 levels predispose to intrahepatic lipid accumulation and hepatic inflammation, contributing to the development and progression of NAFLD. However, whether vitamin D_3 supplementation ameliorates NAFLD histology is uncertain, and further randomized controlled trials with adequate histological endpoints are needed before its use can be recommended for the specific treatment of NAFLD or NASH (Targher and Byrne 2013).

An interesting novel agent is the insulin sensitizer farnesoid X receptor (FXR) ligand obeticholic acid (i.e., a synthetic variant of the natural bile acid

henodeoxycholic acid that is a potent activator of the FXR). In a multicenter, randomized, placebo-controlled (FLINT) trial of 283 individuals with noncirrhotic NASH (only about half of whom with established T2DM), obeticholic acid treatment was associated with both resolution of NASH and improvement in fibrosis at 72 week liver biopsy (Neuschwander-Tetri et al. 2015). While these are encouraging data, the efficacy and long-term safety features (e.g., pruritus and increased LDL-cholesterol levels with the use of this drug) need to be addressedf.

Interestingly, a recent Bayesian network meta-analysis combining direct and indirect treatment comparisons has assessed the comparative effectiveness of pharmacological agents for the treatment of NASH. Collectively, nine randomized, controlled trials including nearly 1,000 patients with biopsy-proven NASH, comparing vitamin E, glitazones, pentoxifylline, or obeticholic acid to one another or placebo, were identified. This Bayesian network meta-analysis revealed only moderate-quality evidence for glitazones, pentoxifylline, and obeticholic acid to decrease lobular inflammation and for pentoxifylline and obeticholic acid to improve hepatic fibrosis (Singh et al. 2015). Collectively, the findings of this meta-analysis do not currently allow for straightforward recommendations for drug treatment of this liver disease.

Promising novel agents with antiinflammatory, antifibrotic, or insulin-sensitizing properties (dual PPARα/δ agonists, dual chemokine receptor [CCR]2/CCR5 antagonists, and fatty acid/bile acid conjugates), and antifibrotic agents (anti-lysyl oxidase-like [anti-LOXL2] monoclonal antibodies) are also being tested in late-phase randomized controlled trials in NASH (Ratziu 2016).

Finally, bariatric surgery, as a nonpharmaceutical effective treatment to decrease body weight, insulin resistance, and reverse T2DM, also markedly improves all histological lesions of NASH, including hepatic necroinflammation and fibrosis (Chalasani et al. 2012; Targher and Byrne 2013; Corey and Rinella 2016; EASL-EASD-EASO clinical practice guidelines 2016). Bariatric surgery should be an accepted treatment option in people who have T2DM and severe obesity (body mass index >35 kg/m^2). Bariatric surgery should be also considered as an alternative treatment option in patients with a body mass index between 30 and 35 kg/m^2 when T2DM cannot be adequately controlled by optimal medical regimen, especially in the presence of major CVD risk factors. However, while bariatric surgery is undoubtedly effective, there are limitations including complications, patient's acceptability, service availability, and costs. Of note, the possible side effects and long-term consequences of bariatric surgery need to be also considered and weighed against those of lifestyle intervention and drug treatment.

Summary

The perception of NAFLD as an uncommon and benign condition is rapidly changing. Because of its strong association with insulin resistance, NAFLD immediately requests clinical search for features of metabolic syndrome and T2DM. In addition, established T2DM requires thorough clinical testing whether NAFLD/NASH might also be present.

Specifically, clinicians have to keep in mind that NAFLD is very common in patients with T2DM or T1DM (affecting about 30–50% of adult patients with T1DM and up to 70–75% of those with T2DM), and that these patients are also more likely to develop the more severe forms of NAFLD (NASH, advanced fibrosis, cirrhosis and, in some cases, HCC). In addition, because of the link between diabetes, NAFLD, and adverse cardiovascular outcomes, more careful surveillance of these at-risk patients will be needed with the combined use of serum liver enzymes, liver imaging, transient elastography, and clinical risk score systems for advanced liver fibrosis.

We strongly believe that the possibility of NAFLD should be entertained as a part of the routine evaluation of patients with T2DM, in the same way we search for microvascular complications and CVD. Additionally, a multidisciplinary approach to the treatment of diabetic patients with NAFLD, based on a careful evaluation of related cardiometabolic risk factors and monitoring for cardiovascular, kidney, and liver complications, is warranted.

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