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Nonalcoholic fatty liver disease and diabetes

Maria Irene Bellini, Irene Urciuoli, Giovanni Del Gaudio, Giorgia Polti, Giovanni Iannetti, Elena Gangitano, Eleonora Lori, Carla Lubrano, Vito Cantisani, Salvatore Sorrenti, Vito D'Andrea

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease in the world and represents a clinical-histopathologic entity where the steatosis component may vary in degree and may or may not have fibrotic progression. The key concept of NAFLD pathogenesis is excessive triglyceride hepatic accumulation because of an imbalance between free fatty acid influx and efflux. Strong epidemiological, biochemical, and therapeutic evidence supports the premise that the primary pathophysiological derangement in most patients with NAFLD is insulin resistance; thus the association between diabetes and NAFLD is widely recognized in the literature. Since NAFLD is the hepatic manifestation of a metabolic disease, it is also associated with a higher cardiovascular risk. Conventional B-mode ultrasound is widely adopted as a first-line imaging modality for hepatic steatosis, although magnetic resonance imaging represents the gold standard noninvasive modality for quantifying the amount of fat in these patients. Treatment of NAFLD patients depends on the disease severity, ranging from a more benign condition of nonalcoholic fatty liver to nonalcoholic steatohepatitis. Abstinence from alcohol, a Mediterranean diet, and modification of risk factors are recommended for patients suffering from NAFLD to avoid major cardiovascular events, as per all diabetic patients. In addition, weight loss induced by bariatric surgery seems to also be effective in improving liver features, together with the benefits for diabetes control or resolution, dyslipidemia, and hypertension. Finally, liver transplantation represents the ultimate treatment for severe nonalcoholic fatty liver disease and is growing rapidly as a main indication in Western countries. This review offers a comprehensive multidisciplinary approach to NAFLD, highlighting its connection with diabetes.

Key Words: Bariatric surgery; Diabetes; Hepatic steatosis; Liver fibrosis; Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis

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Core Tip: Nonalcoholic fatty liver disease is the most common liver disease worldwide, characterized by fat accumulation in the hepatic parenchyma, with a range of different stages from mild inflammation to severe fibrosis. There is a biunivocal relationship with type 2 diabetes, with important consequences in terms of cardiovascular risk, which seems to also have occurred during the coronavirus disease 2019 pandemic. This review focuses on the pathogenesis, clinical aspects, and treatment, providing guidance for a non-invasive diagnosis and preferred therapy, medical and/or surgical.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease worldwide[1] and represents a clinico-histopathologic entity with features mimicking alcohol-induced liver injury, but occurring, by definition, in patients with little or no history of alcohol consumption. Its prevalence reaches up to 25%-30%[2,3] of the worldwide population, with approximately 2 billion of individuals being affected[4].

NAFLD includes a different variety of findings, ranging from hepatocyte fat accumulation without concomitant inflammation or fibrosis (simple hepatic steatosis), to hepatic steatosis with a necro-inflammatory component (steatohepatitis), which may or may not have associated fibrosis. Nonalcoholic steatohepatitis (NASH) may progress to cirrhosis in up to 20% of patients[5,6], and it is a leading cause of cryptogenic cirrhosis[7].

The cause of NAFLD has not been fully elucidated and is considered multifactorial. A two-hit model of NAFLD development was originally proposed. The first consists of hepatic steatosis, which then sensitizes the liver to a progressive injury and is mediated by "second hits" as inflammatory cytokines, adipokines, and oxidative stress. Together they lead to steatohepatitis and fibrosis[8]. Currently, the two-hit hypothesis has been replaced by the "multiple hit" theory, which recognizes the following components in NAFLD pathophysiology: insulin resistance, obesity, gut microbiota, and environmental and genetic factors[9].

The aim of this review is to report, from a comprehensive multidisciplinary perspective, the pathogenesis, diagnosis, and treatment of NAFLD, highlighting its relationship with diabetes.

PATHOGENESIS

The key concept of NAFLD pathogenesis is excessive triglyceride hepatic accumulation as a result of an imbalance between free fatty acid (FFA) influx and efflux[10]. This can occur from the excessive importation of FFAs from the adipose tissue; diminished hepatic export of FFA, possibly secondary to reduced synthesis or secretion of very low-density lipoprotein; or the impaired beta-oxidation of FFA. The pathogenesis and evolution of NAFLD are depicted in **Figure 1**.

Strong epidemiological, biochemical, and therapeutic evidence supports the premise that the primary pathophysiological derangement in most patients with NAFLD is insulin resistance. Resistance to the action of insulin results in important changes in lipid metabolism. These include enhanced peripheral lipolysis, increased triglyceride synthesis, and increased hepatic uptake of fatty acids. Each of these may contribute to the accumulation of hepatocellular triglycerides, which in turn results in a preferential shift from carbohydrate to FFA beta-oxidation, an occurrence that has been demonstrated in patients with insulin resistance[11]. The association of liver steatosis and metabolic dysfunction is so strict that a new definition was recently proposed to define this entity, namely "metabolic (dysfunction)-associated fatty liver disease" (MAFLD)[12].

The excessive inflow of triglycerides to the liver leads to inflammation, reactive oxygen species (ROS) formation, hepatocyte impaired function, and lipotoxicity. Hepatocellular cells injury activates apoptotic pathways, ultimately causing cellular death. This results in the progression from noninflammatory

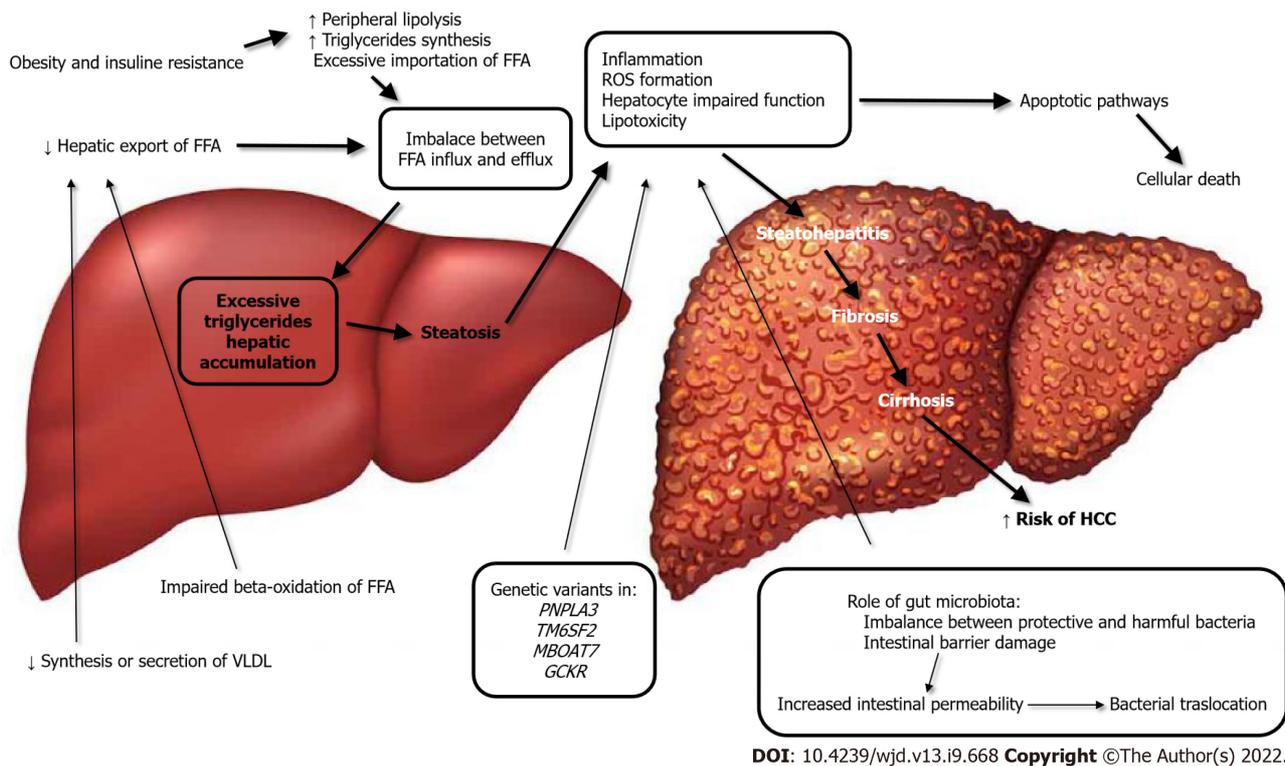


Figure 1 Pathogenesis and evolution of nonalcoholic fatty liver disease. FFA: Fatty free acids; HCC: Hepatocellular carcinoma; ROS: Reactive oxygen species; VLDL: Very low-density lipoprotein.

isolated steatosis to the development of nonalcoholic steatohepatitis, with a risk of further evolution to fibrosis, cirrhosis and, worst-case scenario, to the development of hepatocellular carcinoma[9,13]. In this regard, the major role of mitochondrial dysfunction in the genesis of NAFLD has emerged in recent years; in fact mitochondria are responsible for the β -oxidation of FFAs and controlling the tricarboxylic acid cycle. Furthermore, mitochondria favor cell adaption to oxidative stress, mitigating the effects of ROS production[14].

Intestinal microbes have also been implicated as a potential source of hepatotoxic oxidative injury, and changes in the microbiome play a role in the lipotoxicity and pathogenesis of NAFLD[15,16].

The specific composition of gut microbiota may play a role in both the inflammatory and fibrosis responses in patients with NAFLD. The imbalance between protective and harmful bacteria, such as altered *Firmicutes/Bacteroidetes* ratio, relative abundance of alcohol-producing bacteria, growth of harmful genera, and lack of protective genera, together predispose[17] to damage of the intestinal barrier. The consequent epithelial disruption leads to an altered immune reaction and activation of inflammatory pathways, as a response to the bacterial products, namely short-chain fatty acids, trimethylamine N-oxide, and secondary bile acids[18]. Damage of the intestinal membrane finally results in impaired transport across the mucosa, increasing the filtration of bacterial lipopolysaccharides and thus further contributing to NAFLD development[17,19].

In terms of genetic risk factors, there is also a role in the development of NAFLD. Studies on twins have demonstrated a strong hereditary correlation, estimated to be approximately 50%, to both hepatic fat content and hepatic fibrosis[4]. It is recognized that at least four genetic variants in four different genes (*PNPLA3*, *TM6SF2*, *MBOAT7*, and *GCKR*) are responsible for the encoding of hepatic lipid metabolism regulatory proteins and are therefore involved in the development and progression of NAFLD[12,20].

DIABETES AND NAFLD: A WELL-ESTABLISHED RELATIONSHIP

Among type 2 diabetes (T2D) patients, the prevalence of NAFLD is more than double compared to the general population, and is estimated to be over 55%. The global prevalence of NASH in T2D patients is 37%[1]. The prevalence of NAFLD in T1D is reportedly between 10% and 20%[21,22].

The association between T2D and NAFLD is widely recognized in the literature[23-26]. T2D is itself a risk factor for the development of NAFLD, and seems to accelerate the progression of liver disease[1, 27]. On the other hand, NAFLD is a risk factor for the development of T2D and its complications[22,23, 27-29]. In fact, NAFLD gives a two-fold increased risk of incident diabetes over a course of about 5 years

[23,30], and the risk of patients affected by liver steatosis to develop diabetes increases in parallel to the extent of steatosis severity[30], becoming even higher when the fibrosis is advanced[23,30].

A study on 2020 participants, with a 10-year follow-up, observed that the fatty liver index (FLI), an indirect assessment used to quantify the amount of hepatic fat with a mathematical formula, predicts incident risk of developing T2D and glycemic alterations preceding diabetes. Individuals with a high FLI had an increased risk of developing diabetes, and among these high FLI patients, overweight and obese people had a risk that increased by more than 10- and 15-fold compared to similar body mass index-matched people but lower FLI[31]. Similarly, another study on 28991 pre-diabetic patients with a 3-year follow-up found that high FLI is a risk factor for developing diabetes, even in nonobese patients [32]. Of note, NAFLD predicts the development of metabolic syndrome over a period of less than 5 years[33], and metabolic syndrome is considered a risk factor for T2D.

NAFLD is associated with the development of macrovascular and microvascular complications in T2D patients, including chronic kidney disease (CKD)[29], retinopathy and autonomic neuropathy, although the results across studies are not completely concordant[34,35]. Liver fibrosis is also independently associated with macrovascular and microvascular complications in diabetic patients[36], and although T2D is a well-known risk factor to CKD, NAFLD predicts deterioration of renal function even in healthy subjects.

As per dietary advice, adherence to a Mediterranean diet is inversely associated with NAFLD and prevents the development of T2D and cardiovascular disease (CVD) in patients with NAFLD over a 10-year span[37], whereas the low adherence to these food habits is associated with diabetes and CVD onset in NAFLD patients[38]. Virtually, most studies assessing liver fat content have reported positive results after very low-calorie diets and ketogenic diets. While it is acknowledged that weight loss is associated with amelioration of NAFLD, less is known about the effect of macronutrient distribution on such outcomes. Carbohydrate restriction, with its well-established role in modulating insulin levels, and the newly proposed pathway involving the microbiome shift with increased folate production, likely plays a primary role in the reported effectiveness of ketogenic diets towards NAFLD[39].

Figure 2 summarizes the pathophysiological link between NAFLD and T2D.

DIABETES, NAFLD, AND CARDIOVASCULAR RISK

CVD is among the leading causes of death worldwide[40], and the prevention of cardiovascular events is crucial from a global health perspective.

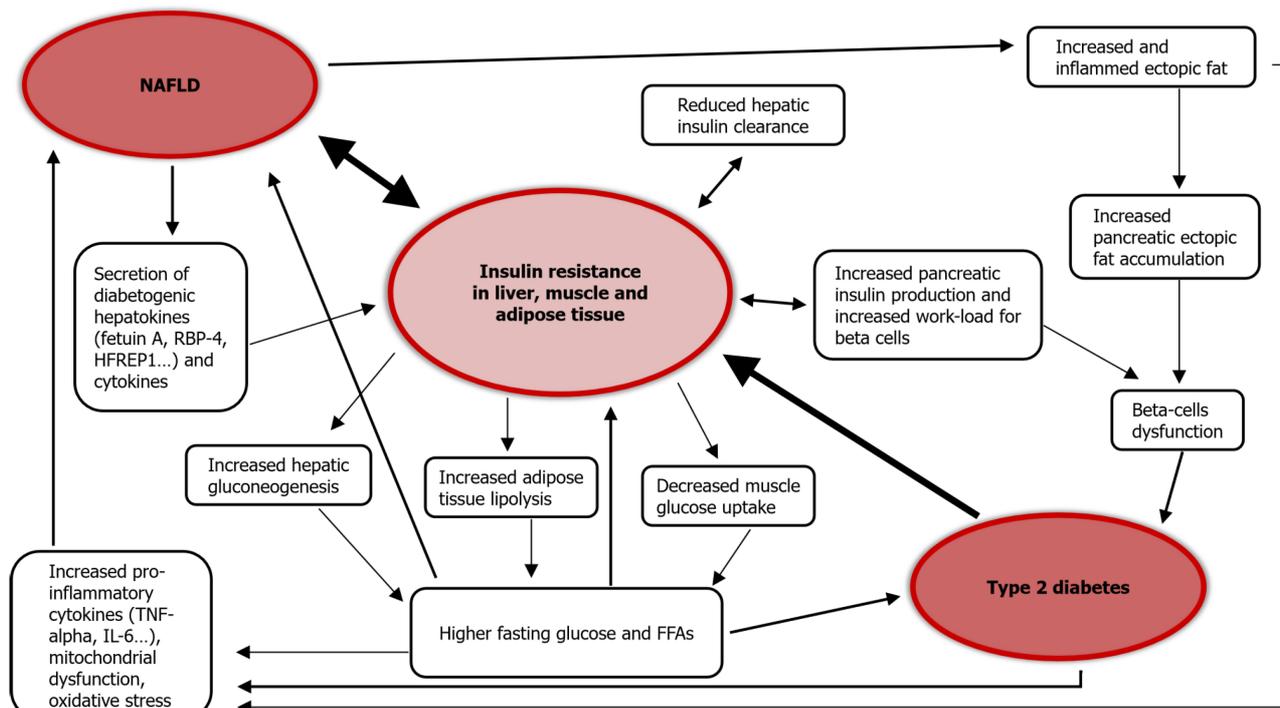
Atherosclerotic CVD is the major cause of morbidity and mortality in diabetic patients[41]. CVD comorbidities often present in diabetic patients as hypertension and dyslipidemia, are additive risk factors for cardiovascular events. T2D is a recognized cardiovascular risk factor as well, and NAFLD contributes independently to CVD[42].

Since NAFLD is the hepatic manifestation of a metabolic disease, it is also associated with a higher cardiovascular risk[43]. A recent meta-analysis assessed the long-term higher risk of fatal and nonfatal CVD events, observing an increase across steatosis stages, reaching the maximum when fibrosis was present[44]. NAFLD is also significantly associated with hypertension[45] and heart failure[46], thus significantly increasing the overall mortality risk[46]. In a retrospective study comparing more than 900 subjects affected either by NAFLD or AFLD or with normal liver appearance on computed tomography, fatty liver independently from the cause of the steatosis was associated with a higher cardiovascular risk [47]. Since NAFLD is a dynamic entity, it is, by definition, subject to variation over time. In the same study, Lee *et al*[47] evaluated 3 million subjects for NAFLD with FLI for a minimum of four times, between 2009 and 2013, concluding that higher persistent FLI led to a higher mortality rate for all causes, myocardial infarction, and stroke. These results were confirmed after correcting for many possible confounders such as age, sex, smoking, alcohol consumption, income, dyslipidemia, body mass index, diabetes, hypertension, and physical activity[47].

As already discussed, diabetes and NAFLD are often associated; thus they may act synergistically to maximally increase cardiovascular risk[48]; the higher incidence of CVD in diabetic patients with steatosis compared to diabetic patients without steatosis[48] seems to confirm this detrimental association.

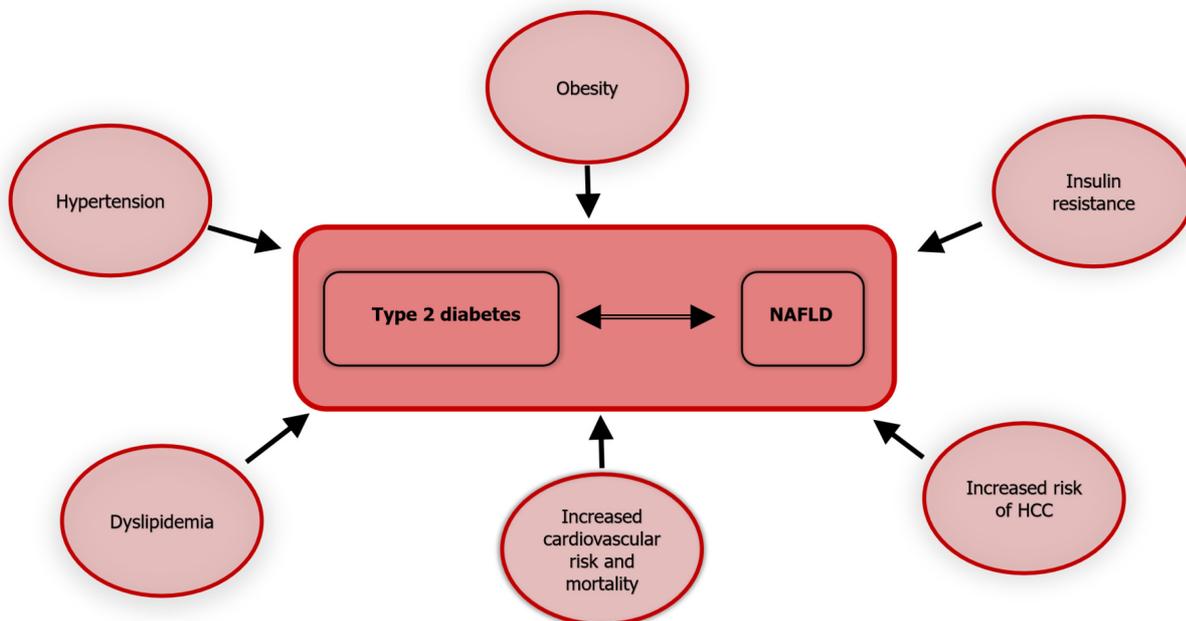
A study on > 130000 T2D patients with a hospital record of NAFLD or AFLD, and no record of any other liver disease, showed an increased risk for recurrent CVD, cancer, and mortality for all causes[49]. Patients with a history of hospital admission and fatty liver were younger than those without liver disease[50]. Of note, similar to what happens in healthy subjects and T2D patients, even in T1D patients, NAFLD increases the cardiovascular risk[51].

Figure 3 illustrates the association of T2D and NAFLD with multiple morbid conditions; thus the coexistence and interaction of the two, further exacerbates the prognosis of each.



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Figure 2 The link between nonalcoholic fatty liver disease and diabetes pathogenesis. Nonalcoholic fatty liver disease increases the risk of developing type 2 diabetes mainly through worsening insulin resistance and increasing gluconeogenesis. By contrast, type 2 diabetes increases the risk of developing liver steatosis and fibrosis through insulin resistance, oxidative stress, and inflammatory cytokines.



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Figure 3 Type 2 diabetes and nonalcoholic fatty liver disease are both associated with multiple metabolic and cardiovascular morbidities. Furthermore, the presence of one increases the risk to develop the other and thus exacerbating the overall prognosis. HCC: Hepatocellular carcinoma; NAFLD: Nonalcoholic fatty liver disease.

DIABETES, NAFLD, AND CORONAVIRUS DISEASE 2019

From the very beginning of the severe acute respiratory syndrome coronavirus 2 pandemic, diabetes has shown an association to this virus infection. In fact, a study on 5700 patients admitted to 12 hospitals in the New York City area demonstrated that the most common comorbidities in admitted coronavirus

disease 2019 (COVID-19) patients were hypertension (56.6%), obesity (41.7%), and diabetes (33.8%)[52]. Diabetes prevalence in COVID-19 patients is high, varying from 15%, in a pool of more than 23000 patients[53], up to almost 40% in another study on 200 hospitalized patients[54].

Diabetic patients have a higher risk of contracting COVID-19[55], a higher risk of hospitalization[54] and mortality[56].

NAFLD is also associated to COVID-19[57], to its severity progression, risk of intubation, dialysis and use of vasopressors[58], although in contrast, some authors[59-61] did not observe a higher risk of severe COVID-19 and intensive care unit access for NAFLD patients.

A longer viral shedding time[62] and a higher mortality for COVID-19 in NASH patients with advanced fibrosis[63] have also been reported.

NAFLD DIAGNOSIS

NAFLD diagnosis is based on three criteria: (1) Absence of significant alcohol intake; (2) presence of hepatic steatosis; and (3) exclusion of other causes of liver disease.

Some clinical biomarkers are used to screen for or diagnose NAFLD, used in complex algorithms for risk stratification. They aim to combine various conditions, such as arterial hypertension with laboratory exams, like transaminases, to predict outcomes of the liver disease, but as single markers, they only provide poor sensitivity and specificity. Yet, their overall performance is limited, with further studies needed to transfer the initial thought cut-off values into the real clinical scenario[64].

It can therefore be asserted that due to the lack of available noninvasive methods to confirm the diagnosis of NAFLD, liver biopsy remains the gold standard to classify steatosis, and NASH. However, biopsy has limitations[65]; namely it is invasive, subject to sampling variability and observer-dependence, and most importantly, carries risks. Therefore, it is not offered to routinely assess the amount of fatty liver in NAFLD patients who may have simple steatosis, as reported in the majority of cases[6].

As previously mentioned, since NAFLD is a dynamic entity[47], varying through lifetime, imaging methods remain the most widely utilized tools to assess NAFLD patients and quantify the relative hepatic steatosis.

NAFLD IMAGING

To date, various imaging methods have been utilized: ultrasonography, CT, magnetic resonance imaging (MRI), and magnetic resonance spectroscopy (MRS). More recently, other diagnostic tools measuring liver stiffness have entered clinical practice, in view of their practical utility, as reported in Table 1.

Ultrasound

Conventional B-mode ultrasound (US) is the most widely used imaging modality for the noninvasive evaluation of hepatic steatosis, as first-line diagnostic imaging procedure, according to clinical practice guidelines[66]. Fatty liver infiltration is characterized by hyperechogenicity of the parenchyma and increasing attenuation of US waves in deeper parts, specifically where there is increasing steatosis[67]. However, US evaluation of fatty livers is based on the operator's experience; in comparison to histology as reference standard, the overall sensitivity and specificity of B-mode US are, respectively, 84.8% and 93.6%, with 0.93 accuracy[68].

US elastography quantitatively evaluates liver stiffness. Two broad categories of imaging-based sonoelastography are currently in clinical use: strain elastography, which is influenced by the operator or physiologic forces that produce tissue deformation; and shear wave elastography (SWE), which instead results from the acoustic radiation force of the tissue displacement[69,70].

Fibroscan uses transient US elastography (TE) to measure hepatic elasticity by quantifying the shear wave velocity with ultrasonic echo pulses from low-frequency vibrations that are transmitted into the liver[71,72]. Since patients with > 66% steatosis at liver biopsy have a false-positive higher rate, *via* the Fibroscan XL probe it is also possible to investigate obese patients, given that during TE the transmission of a mechanical wave through the skin and subcutis could cause technical failure and unreliable measurements[73].

Controlled attenuation parameter (CAP) is another technique implemented on the Fibroscan device. The principle of CAP is to measure the acoustic attenuation in liver of shear waves generated by the probe. The amount of fat deposited in the liver can be inferred from the degree of attenuation[74]. In a multimodality study in patients with biopsy-proven NAFLD, it was shown that using a threshold of 261 dB/m CAP the methodic accuracy was 0.85 (95% confidence interval of 0.75–0.96) for steatosis diagnosis [75].

Table 1 Pros and cons of imaging modalities to assess hepatic steatosis

Modality	Pros	Cons
US B-Mode	Lack of ionizing radiation	No panoramic view
	Less expensive	Operator dependency
	Repeatable	Limited accuracy diagnosing mild hepatic steatosis
	Fast	Rather qualitative nature
	Can be performed at the bedside (no need to transport the patient)	Non simple steatosis/NASH differentiation
	Useful also for identification of other pathology such as liver lesions	
QUS	Same as US B-Mode	Not always available
	Quantitative and semiquantitative fat evaluation (less operator sensitive)	Need to buy newer machines and software
Fibroscan	Quantitative evaluation (less operator sensitive)	Expensive equipment that doesn't supply imaging evaluation
	Lack of ionizing radiation	
	Fast	
	Can be performed at the bedside (no need to transport the patient)	
CT	Fast	Ionizing radiation
	Panoramic view	Limited accuracy diagnosing mild hepatic steatosis
	Volumetric rendering	Non simple steatosis/NASH differentiation
	High spatial resolution	
	Quantitative density evaluation	
MRI	Highly accurate and reproducible for measuring hepatic fat	Expensive
	Panoramic view	Examination time
	Lack of ionizing radiation	Software not always available
	Quantitative fat evaluation	
MRS	Highly accurate and reproducible for measuring hepatic fat	Expensive
	Panoramic view	Examination time
	Lack of ionizing radiation	Software not always available
	Quantitative fat evaluation	Evaluation of small portion of the liver Expertise required for data acquisition and analysis

CT: Computed tomography; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; NASH: Nonalcoholic steatohepatitis; QUS: Quantitative ultrasound; US: Ultrasound.

Two-dimensional SWE is an US technique providing visualization of viscoelastic properties of soft tissues in real time[76]. These techniques employ acoustic radiation force impulses that induce tissue motion at a microscopic level, which in turn produces tissue shear waves. The shear waves are related to tissue stiffness under simple assumptions, expressed as Young's module[77].

In the last several years, quantitative US measures, such as the ultrasonic attenuation coefficient and backscatter coefficient, derived from the raw radiofrequency echo data, have been considered a noninvasive tool for the objective assessment of hepatic steatosis[78].

A general limitation of all US-based methods evaluating liver fat content, including CAP, is that sonography exploits the attenuation of the propagated and reflected waves. While liver fat attenuates sound waves, many other liver pathologies such as hepatitis, hemochromatosis or fibrosis can also affect sound waves in the same manner[79].

CT

CT evaluation of hepatic steatosis is based on the attenuation values of the liver parenchyma, assessed as Hounsfield units (HU), in association with tissue composition. The attenuation value of fat (approximately -100 HU) is much lower than that of soft tissue, so hepatic steatosis lowers the attenuation of liver parenchyma. Some studies have reported that contrast-enhanced venous CT and nonenhanced CT

have comparable diagnostic accuracy for hepatic steatosis[80]; however, nonenhanced CT is usually preferred to avoid the potential errors of contrast-enhanced CT caused by variations in hepatic attenuation related to contrast injection methods and scan times. The two CT indexes most frequently used to assess steatosis are the absolute liver attenuation value (*i.e.* HU-liver) and the attenuation difference between the liver and spleen.

CT is accurate for the diagnosis of moderate-to-severe steatosis but is not as accurate for detecting mild steatosis. The threshold values of CT indices for the diagnosis of hepatic steatosis are quite variable, depending on the methods and populations used[81-83]. Furthermore, some factors may affect hepatic attenuation on CT, such as the presence of excess iron in the liver and ingestion of certain drugs such as amiodarone[84].

Magnetic resonance

While CT and US assess hepatic steatosis through proxy parameters (echogenicity and attenuation, respectively), MRI can more directly measure the amount of hepatic fat, in fact it is an imaging modality with a rich range of contrast mechanisms detecting and quantifying hepatic fat content through the measurement of proton signals present in water and fat[85].

There are conventional MRI methods providing qualitative estimates of hepatic steatosis and fully quantitative MRS and MRI methods that allow for an accurate and precise measurement of hepatic fat content[86-88].

MRS and chemical shift-encoded MRI, when performed in expert hands, can serve as confounder-corrected methods able to discern the number of fat-bound protons divided by the amount of all protons in the liver, including fat- and water-bound protons[89].

To date, MRI especially with the techniques reported above, represent the noninvasive gold standard evaluation of these patients; however, US is broadly gaining popularity.

PREVENTION AND TREATMENT

NAFLD treatment depends on the severity of the disease, ranging from a more benign condition of nonalcoholic fatty liver to nonalcoholic steatohepatitis, which is at the more severe end of the spectrum. However, there are some measures that can be applied to all patients. These include the following. (1) Abstinence from alcohol: evidence shows that in NAFLD patients, there is no liver-safe limit of alcohol intake[90]. Heavy alcohol use is well-known to be associated with hepatic steatosis, hepatic injury, and progression of parenchymal fibrosis[91], but even low alcohol consumption in individuals with metabolic abnormalities could be harmful, thus abstinence from alcohol for patients with NAFLD is always recommended. (2) Immunizations: for patients without serologic evidence of immunity, vaccination for hepatitis A virus and hepatitis B virus is recommended, and, in general, standard, age-appropriate immunizations for all patients[7]. (3) Modification of risk factors for CVD: For patients with hyperlipidemia, lipid-lowering therapy; for patients with diabetes, optimizing blood glucose control[9].

For patients with NASH and T2D, the presence of the liver disease can inform the choice of glucose lowering therapy, and although this is typically with metformin, the beneficial impact on liver histology with certain other insulin-sensitizing agents could be of note when choosing a second-line agent in NASH patients, if metformin is contraindicated or in need of additional glucose-lowering therapy[33, 35]. In this setting, pioglitazone and GLP-1 receptor agonists (*e.g.*, liraglutide, semaglutide) are reasonable options[92] and the apparent benefit of certain insulin-sensitizing agents for NAFLD is likely related to the role that insulin resistance plays in the development of NAFLD[9].

For patients with biopsy-proven NASH and fibrosis stage 2 but without diabetes, the use of vitamin E (800 international units per day) is suggested. The antioxidant, anti-inflammatory, and anti-apoptotic properties of vitamin E accompanied by the ease-of-use and exceptional tolerability have made vitamin E a pragmatic therapeutic choice in nondiabetic patients with histologic evidence of NASH[93].

In every case, weight loss is the primary therapy for most patients with NAFLD. It can lead to improvement in liver biochemical tests, liver histology, serum insulin levels, and quality of life[94-96].

Several studies have suggested that weight loss of at least 5% of body weight is necessary to improve hepatic steatosis, although the long-term benefits of such weight loss are unknown. In a meta-analysis of eight trials including 373 patients, losing 5% of body weight resulted in improvement in hepatic steatosis, while losing of 7% of body weight was associated with improvement in NALFD activity score, which is used to grade disease activity[97].

Unfortunately, only less than 10% of patients that try to lose weight with lifestyle modifications, including diet and physical activity, achieve this target at 1-year, and fewer maintain the weight loss at 5 years[98]. Bariatric surgery is an option that may be considered in those who fail to lose weight by lifestyle changes.

Although weight loss seems to be the main mechanism, bariatric surgery has been shown to improve also liver histology and fibrosis secondary to NASH, in addition to other benefits including an improvement or resolution of T2D mellitus, dyslipidemia, and hypertension, and a reduction of cardiovascular morbidity or mortality[99-101].

A meta-analysis of 10 studies showed that the bariatric surgery group had significantly lower odds of major adverse cardiovascular events as compared to no surgery (odds ratio = 0.49; 95% confidence interval: 0.40-0.60; $P < 0.00001$; $I^2 = 93\%$) suggesting the benefit of bariatric surgery in reducing the occurrence of serious events in patients with obesity and CVDs[102].

In the SPLENDOR study of 1158 patients with histologically confirmed NASH and obesity, bariatric surgery (gastric bypass or sleeve gastrectomy) was associated with a much lower 10-year cumulative incidence of major adverse liver outcomes (2.3% *vs* 9.6%) and major cardiovascular events (8.5% *vs* 15.7%) compared with nonsurgical management[103].

Weight reduction due to bariatric surgery causes inflammatory changes in patients with obesity. After gastric bypass there is a proven reduction of hepatic expression of factors involved in the progression of liver inflammation (macrophage chemoattractant protein 1, and interleukin-8) and fibrogenesis [transforming growth factor- β 1, tissue inhibitor of metalloproteinase 1, α -smooth muscle actin, and collagen- α 1(I)][104], a significant decrease in mean NAFLD fibrosis score after Roux-en-Y gastric bypass (RYGB) and resolution rate of 55% of severe fibrosis in 12-mo observation[105], and, moreover, RYGB contributes to significant reduction in NAFLD activity score, steatosis, inflammation and liver ballooning during 1-year observation[106].

In a long-term follow-up of patients with NASH who underwent bariatric surgery, Lassailly *et al*[107] observed resolution of NASH in liver biopsies from 84% of patients 5 years later. The reduction of fibrosis is progressive, beginning during the 1st year and continuing through 5 years[107].

Among recently available surgical methods, RYGB and laparoscopic sleeve gastrectomy (LSG) are the most performed worldwide. The remaining question is whether RYGB or LSG is more effective[108].

A systematic review and meta-analysis performed by Baldwin *et al*[109] compared RYGB and LSG using separate criteria: transaminases concentration, NAFLD activity score and NAFLD fibrosis score. Overall, both RYGB and LSG significantly improved liver enzymes, NAFLD activity score, and NAFLD fibrosis score postoperatively. Direct comparisons of RYGB to LSG in any of the criteria failed to demonstrate superiority[109]. These findings, without any significant difference between the two groups, are confirmed in other studies[110,111].

Even if the role of bariatric surgery in the treatment of NAFLD is significant, there are some patients that will develop new or worsened features of NAFLD after a bariatric procedure[112]. A 5-year prospective study performed by Mathurin *et al*[113] showed that 19.8% of patients experienced fibrosis progression at 5 years follow up for unknown reason.

Aggravation of NAFLD after surgery should be kept in mind when qualifying patients for a bariatric procedure. At the extreme consequences, and when the progression of liver fibrosis is irreversible, also liver transplantation becomes an option, and indeed NASH is nowadays representing the fastest growing indication in Western countries to this kind of surgery. Yet, lifestyle modifications, as well as pharmacological strategies and tailored immunosuppression *via* a strategic multidisciplinary approach are still key to control diabetes and CVD risk in this setting, too[114].

CONCLUSION

NAFLD is intimately related to T2D and both diseases are highly prevalent worldwide, representing a public health alarm. The diagnosis and management of NAFLD in T2D is challenging, given the inherent cardiovascular risk and the underlying liver parenchymal degeneration. As well as to insulin resistance, NAFLD may be related to other hormonal alterations, quite common in patients with obesity, and potentially contributing to the onset and the worsening of steatohepatitis. A complete hormonal workout, in patients with severe NAFLD, and conversely investigation of NAFLD in patients with T2D, severe obesity or other metabolic disorders is recommended to prevent and monitor NAFLD risk.

Current medical treatments aim to mitigate insulin resistance, optimizing metabolic control and halting hepatic disease progression; yet they are still under debate for their efficacy, and new classes of drugs targeting different pathways need experimentation in the forms of randomized controlled trials, to pursue a tailor-made approach, for example assessing gut permeability and modification of individual human microbiota.

Identification of simple, inexpensive biomarkers would be also of help as an additional diagnostic tool, or to predict disease progression and response to treatment.

Surgery is considered a more advanced therapeutic option, either to improve obesity and control of the associated metabolic conditions, *via* bariatric interventions, either by substituting the cirrhotic liver *via* organ transplantation.

Future research should focus on the treatment of NAFLD, as a risk factor for developing T2D and in how to prevent and detect NAFLD progression in patients with T2D, obesity or other severe metabolic conditions.

FOOTNOTES

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

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