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Nonalcoholic fatty liver disease and diabetes

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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 have or have not a fibrotic progression. The key concept of NAFLD pathogenesis is excessive triglycerides hepatic accumulation because of imbalance between free fatty acids 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 diabetes and NAFLD association is widely recognized in literature. Since NAFLD is the hepatic manifestation of a metabolic disease, it is associated with a higher cardiovascular risk, too. Conventional B-mode ultrasound is broadly adopted as first-line imaging modality for hepatic steatosis, although magnetic resonance represents the gold standard non-invasive modality for quantification of the fat amount in these patients. Treatment of NAFLD patients depends on the severity of the disease, ranging from a more benign condition of nonalcoholic fatty liver to nonalcoholic steatohepatitis. Abstention from alcohol, a Mediterranean diet and modification of risk factors are always recommended for patients suffering from NAFLD to avoid major cardiovascular events, as per all

diabetic patients. In addition, the weight loss induced by bariatric surgery seems to be effective also 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 the one growing most 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, characterised 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 risks, as it seems to have happened also 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.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease in the world[1] and represents a clinical-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 hepatocytes fat accumulation without concomitant inflammation or fibrosis (simple hepatic steatosis), to hepatic steatosis with a necro-inflammatory component (steatohepatitis), that may or may not have associated fibrosis. This one, called nonalcoholic steatohepatitis (NASH), may progress to cirrhosis in up to 20% of patients[5,6] and it is recognized to be a leading cause of cryptogenic cirrhosis[7].

NAFLD cause has not been fully elucidated and is considered multifactorial. A two-hit model of NAFLD development was originally proposed: the first consisting with hepatic steatosis, that then sensitizes the liver to a progressive injury and mediated by "second hits" as inflammatory cytokines, adipokines and oxidative stress. Altogether they lead to steatohepatitis and fibrosis[8]. Nowadays, the two-hit hypothesis has been replaced with 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 triglycerides hepatic accumulation as a result of imbalance between free fatty acids (FFA) influx and efflux[10]. This can occur from the excessive importation of FFAs from the adipose tissue, from diminished hepatic export of FFA, possibly secondary to reduced synthesis or secretion of very low-density lipoprotein, or from impaired beta-oxidation of FFA. Pathogenesis and evolution of NALD is 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 has been recently proposed to define this entity, "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 non-inflammatory isolated steatosis to the development of nonalcoholic steatohepatitis, with a risk of further evolution to fibrosis, cirrhosis and, at worst, to the development of hepatocellular carcinoma[9,13]. To this regard, the major role of mitochondrial dysfunction in the genesis of NAFLD has emerged in recent years, in fact mitochondria are responsible for β-oxidation of FFAs and control the tricarboxylic acid cycle. Furthermore, mitochondria favour cell adaption to oxidative stress, mitigating the effects of ROS production[14].

Intestinal microbes have been implicated as a potential source of hepatotoxic oxidative injury, too, and changes in the microbiome have been demonstrated to play a role in 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, the relative abundance of alcohol-producing bacteria, growth of harmful genera, and lack of protective genera, altogether predispose[17] to the damage of the intestinal barrier. The consequent epithelial

disruption leads to an altered immune reaction and an activation of inflammatory pathways, as a response to the bacterial products, namely short-chain fatty acids, trimethylamine N-oxide, and secondary bile acids[18]. The damage of the intestinal membrane finally results to an 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 recognised 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 with 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 in comparison to the general population, and it is estimated to be over 55%. The global prevalence of NASH in type 2 diabetic patients is 37%[1]. With regards to the prevalence of NAFLD in type 1 diabetes, it is reported between 10% and 20%[21,22].

T2D and NAFLD association is widely recognized in the literature[23-26]: T2D is itself recognized as a risk factor for the development of NAFLD, and seems to accelerate the progression of liver disease[1,27]. On the other hand, more recently it has been proved that 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 around 5 years[23,30], and the risk of patients affected by liver steatosis to develop diabetes increases in parallel to the extent of the steatosis severity[30], becoming even higher when the fibrosis is advanced[23,30].

A study on 2020 participants, with a 10 years' follow-up, observed that 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 glycaemic

alterations preceding diabetes. Individuals with high FLI had an increased risk of developing diabetes, and among these high FLI patients, overweight and obese people had the risk increased by more than 10 and 15-fold in comparison to similar body mass index-matched people, but lower FLI[31]. Similarly, another study on 28991 pre-diabetic patients with a 3-years follow-up observed that high FLI is a risk factor for developing diabetes, even in non-obese patients[32].

It is of note to mention that NAFLD predicts the development of metabolic syndrome over a period of less than five years[33], and metabolic syndrome is considered a risk factor for T2D.

NAFLD has been associated to the development of macro and micro-vascular complications in T2D patients, including chronic kidney disease (CKD)[29], retinopathy and autonomic neuropathy, although results across studies are not completely concordant[34,35]. Liver fibrosis is also independently associated with micro and macrovascular 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, the 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 ten-year time[37], while the low adherence to these food habits is associated to diabetes and CVD onset in NAFLD patients[38]. Virtually, most studies assessing liver fat content report positive results after very low-calorie diets and very low-calorie ketogenic diets. Whether it is acknowledged that weight loss is associated with amelioration of NAFLD, less is known relatively to the effect of macronutrient distribution on such outcome. Carbohydrate restriction, with its well-established role in modulating insulin levels, and the newly proposed pathway involving the microbiome shift with increased folate production, surely plays a primary role in the reported effectiveness of Ketogenic Diets towards NAFLD[39].

Figure 2 summarises the pathophysiological link between NAFLD and type 2 diabetes.

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 for diabetic patients[41]. CVD comorbidities, often present in diabetic patients, as hypertension and dyslipidaemia, are additive risk factors for cardiovascular events. T2D is a recognised cardiovascular risk-factor as well and NAFLD contributes independently to CVD[42].

Since NAFLD is the hepatic manifestation of a metabolic disease, it is associated with a higher cardiovascular risk, too[43]. A recent metanalysis assessed the long-term higher risk of fatal and non-fatal CVD events, observing an increase across steatosis stages, reaching the maximum when fibrosis was present[44]. NAFLD is also significantly associated to 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 (alcoholic fatty liver disease) or with normal liver appearance on computed tomography (CT), fatty liver, independently from the cause of the steatosis, was associated to 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 a higher persistent FLI was led to a higher mortality rate for all causes, myocardial infarction, and stroke. These results were confirmed after correction for many possible confounders, as age, sex, smoking, alcohol consumption, income, dyslipidaemia, 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, in comparison 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 patients without liver disease[50]. Of note, similarly to what happens for healthy subjects and T2D patients, even in type 1 diabetic 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.

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. A study on 5700 patients admitted to 12 hospitals in the New York City Area demonstrated in fact 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 has been also associated to COVID-19[57], to its severity progression, risk of intubation, dialysis and use of vasopressors[58], although in contrast, some other authors[59-61] did not observe a higher risk for 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 the presence of three criteria: (1) absence of significant alcohol intake; (2) presence of hepatic steatosis; and (3) exclusion of other causes of liver disease.

There exist clinical biomarkers 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, as single markers 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 could 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 to classify NASH. However, biopsy has limitations[65]: it is invasive, subject to sampling variability, observer-dependence and most-importantly, it is invasive carrying out 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 life-time course, 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 (US), CT, magnetic resonance imaging (MRI), and magnetic resonance spectroscopy (MRS). More recently, other diagnostic tools measuring liver stiffness 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 non-invasive 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].

Ultrasound 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 SWE (shear wave elastography), which instead results from the acoustic radiation force of the tissue displacement[69,70].

Fibroscan uses transient ultrasound 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 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].

Two-dimensional SWE is an ultrasound 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 years, quantitative ultrasound measures, such as the ultrasonic attenuation coefficient and backscatter coefficient, derived from the raw radiofrequency echo data, have been considered as non-invasive tool in 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 to 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 non-enhanced CT have comparable diagnostic accuracy for hepatic steatosis[80]; however, non-enhanced 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 shifting encoding-MRI, when performed in expert hands, can serve as confounder-corrected methods able to discern the amount of fat-bound protons divided by the amount of all protons in the liver, including fat- and water-bound protons[89].

To now, MRI especially with the techniques reported above represent the non-invasive 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: (1) Abstension 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 fibroisis[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 non-diabetic 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 suggest also 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 ten studies showed that the bariatric surgery group had significantly lower odds of major adverse cardiovascular events as compared to no surgery (OR = 0.49; 95%CI 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 percent) and major cardiovascular events (8.5 *vs* 15.7 percent) 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-β1, tissue inhibitor of metalloproteinase 1, α-smooth muscle actin, and collagen-α1(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 first 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 4 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 4 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].

CONCLUSIONS AND FUTURE PERSPECTIVES

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 randomised 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.

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