

Nonalcoholic fatty liver disease in patients with type 2 diabetes: a review article

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is caused by a build-up of triglyceride macrovesicles in the liver not related to other etiologies such as alcoholism, medications or genetic disorders. The spectrum of this condition includes nonalcoholic steatohepatitis (NASH) and simple fatty liver.

In 2020, an international panel of experts proposed a new name for this entity and considered that the term “metabolic associated fatty liver disease” (MAFLD) would be the most appropriate to refer to a comprehensive but simple set of criteria for the diagnosis of MAFLD, which is not related to the amount of alcohol consumption and can occur in patients in any clinical setting.

NAFLD is a manifestation of metabolic syndrome and shows high prevalence and risk of rapid progression in patients with type 2 diabetes (T2DM). The current model considers that this process occurs as a consequence of “multiple hits” that could precede the fatty liver disease, this being the most appropriate explanation for the progression of NAFLD in an inflammatory state.

T2DM worsens NAFLD, leading to hyperglycemia and thus building a vicious circle. As for patients with diabetes, the risk of fibrosis must be assessed due to its impact on increased cardiovascular risk and progression of liver disease. This task may be accomplished through non-invasive tests such as hepatic fibrosis biomarkers, elastography or liver biopsy. As more effective treatment alternatives become available, determining the degree of fibrosis will be even more important.

To date, lifestyle changes are one of the most effective treatments for managing NAFLD. Regarding pharmacotherapy, thiazolidinediones are the most effective intervention for this disease in diabetic patients. Treatment with glucagon-like peptide 1 (GLP-1) agonists, such as liraglutide, or with sodium-glucose cotransporter-2 inhibitors have also shown promising results in preliminary studies.

Keywords: Diabetes Mellitus, Type 2; Fibrosis; Fatty Liver (Source: MeSH NLM).

Enfermedad por esteatohepatitis no alcohólica en pacientes diabéticos tipo 2: artículo de revisión

RESUMEN

La enfermedad por esteatohepatitis no alcohólica (EHGNA) se genera por el depósito de macrovesículas de triglicéridos en el hígado, y se excluye de otras etiologías como alcohólica, medicamentosa o secundaria a trastornos genéticos. El espectro de este trastorno considera la esteatohepatitis no alcohólica y esteatosis hepática simple.

En 2020, un panel internacional de expertos propuso una nueva denominación para esta entidad, y se consideró que el término “enfermedad del hígado graso asociado a disfunción metabólica” (MAFLD, por sus siglas en inglés) sería el más apropiado para referirse a un conjunto completo, pero sencillo, de criterios para el diagnóstico de MAFLD, los cuales son independientes de la cantidad de alcohol consumido y pueden aplicarse a los pacientes en cualquier entorno clínico.

La EHGNA es una manifestación del síndrome metabólico, y uno de los grupos de riesgo de prevalencia y progresión rápida son los pacientes con diabetes tipo 2 (DM2). El modelo vigente considera que este proceso ocurre como consecuencia de “múltiples hits” que podrían anteceder a la esteatosis hepática como una explicación más apropiada para considerar la evolución de la EHGNA en un contexto de estado de inflamación.

La DM2 agudiza el EHGNA, lo que conduce a la hiperglicemia, por ende, a la creación de un círculo vicioso. Es importante valorar, para el caso de los pacientes diabéticos, el riesgo de fibrosis debido a su impacto en un mayor riesgo cardiovascular y progresión de la enfermedad hepática, para lo cual podrían emplearse pruebas no invasivas, tales como los biomarcadores de fibrosis, elastografía o una biopsia hepática. A medida que se disponga de alternativas de tratamiento más efectivas,

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será aún más relevante determinar el grado de fibrosis.

Actualmente, el manejo de esta entidad incluye cambios en el estilo de vida como una de las medidas terapéuticas más efectivas. Dentro del tratamiento farmacológico, se considera que la intervención más eficaz para esta enfermedad en pacientes diabéticos es el uso de tiazolidinedionas. El tratamiento con agonistas de péptido similar al glucagón tipo 1 (GLP-1), como liraglutida, o con inhibidores del cotransportador 2 de sodio-glucosa también han mostrado resultados prometedores en estudios preliminares.

Palabras clave: Diabetes Mellitus Tipo 2; Fibrosis; Hígado Graso (Fuente: DeCS BIREME).

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is caused by a build-up of triglyceride macrovesicles in the liver not related to other etiologies such as alcoholism, medications or genetic disorders.

This disorder affects one-fourth of the adults worldwide and represents an important healthcare and economic burden to all societies. However, it does not have an optimal pharmacological treatment. The prevalence of this disease has increased due to the sedentary lifestyle, insufficient physical activity and excessive calorie intake related to a nutritionally unbalanced and unhealthy diet ⁽¹⁾.

NAFLD leads to cardiovascular risks and increased mortality. A research study comprising 2,839 patients with type 2 diabetes mellitus (T2DM) revealed that NAFLD was associated with a significantly higher prevalence of cardiovascular disease than that found in patients without NAFLD, even after adjusting several risk factors ⁽²⁾. Likewise, nonalcoholic steatofibrosis (NASF) could independently predict mortality in patients with NAFLD in that group of evaluated patients ⁽³⁾.

In 2020, an international panel of experts proposed a new name for this entity and considered that the term “metabolic associated fatty liver disease” (MAFLD) would be the most appropriate to refer to a comprehensive but simple set of criteria for the diagnosis of MAFLD, which is not related to the amount of alcohol consumption and can occur in patients in any clinical setting. This definition is based on recognizing that underlying anomalies such as chronic alcohol consumption may coexist with metabolic disorders related to NAFLD pathogenesis. Thus, MAFLD would be the most appropriate term taking into account that said disorders can coexist with other conditions. The criterion to diagnose MAFLD would be the evidence of fatty liver disease (detected by imaging tests, blood biomarkers or liver histology), associated with one or more of the following factors: overweight/obesity, T2DM and evidence of metabolic dysregulation ⁽⁴⁾.

This review article describes NAFLD pathophysiology in patients with T2DM, as well as the clinical signs and

symptoms, diagnosis and treatment of this condition in subjects at high risk.

SEARCH STRATEGY

A literature review was carried out using PubMed based on noteworthy articles in English published until May 30, 2022. Also, the search included the terms “nonalcoholic fatty liver disease” and “type 2 diabetes mellitus” in combination with “histology,” “epidemiology,” “diagnosis,” “cirrhosis,” “mortality,” “treatment,” “risk factors,” “hepatocellular carcinoma or cancer,” “bariatric surgery” and “fibrosis.” Additional noteworthy articles were identified from other articles’ bibliographic references.

PATHOPHYSIOLOGY

Fatty liver disease is caused by the build-up of intracellular triglyceride due to increased de novo synthesis uptake in hepatocytes and free fatty acids as an effect of cellular lipotoxicity.

Liver damage includes inflammation and necrosis caused by high levels of triglycerides and mitochondrial oxidative stress with the subsequent production of free radicals and peroxisomes.

Increased mitochondrial oxidative activity occurs, for example, due to the release of adiponectin, interleukin-6 (IL-6), leptin and tumor necrosis factor alpha (TNF-alpha), overproduced because of the inflammatory state of visceral and subcutaneous tissues.

Chemical mediators, produced by cellular necrosis and inflammation, and adipokines activate stellate cells that lead to the production of collagen, which increases the production of connective tissue growth factor and the build-up of extracellular matrix that stimulates fibrosis (Figure 1). Likewise, the endocannabinoid system and the use of peroxisome proliferator-activated receptors gamma (PPARs gamma) may be very important in fibrogenesis and, in turn, may be potential therapeutic targets ⁽⁵⁾.

Recently, it has even been suggested that dysbiosis in the intestine may play a very important role in NAFLD

pathogenesis and its progression to nonalcoholic steatohepatitis (NASH) ⁽⁶⁾.

Pathogenesis of the relationship between NAFLD and T2DM

This disorder is closely related to insulin resistance. Hence, it is considered as a liver manifestation caused by metabolic syndrome. NAFLD is a manifestation of metabolic syndrome. This complication most often affects patients with T2DM. Compared with nondiabetic patients with NAFLD, the prevalence of fatty liver disease is approximately 80 % higher in patients with T2DM, according to sex and age ⁽¹⁾. Likewise, in patients with T2DM, the frequency of cirrhosis is near 30 %. Furthermore, T2DM worsens NAFLD since uncontrolled diabetes may cause or exacerbate fatty liver disease. On the other hand, NAFLD leads to hyperglycemia, which creates a vicious circle ⁽²⁾.

The "two-hit hypothesis" has become outdated in the last reviews. This classic theory considered that fatty liver disease occurred as a consequence of a second damage after a first attack because of the initial fatty infiltration.

There are four basic histological changes than condition the development of NAFLD, including fatty liver disease, oxidative stress, inflammation and fibrosis (Figure 1).

The current model considers that this process occurs as a consequence of "multiple hits" that could precede the fatty liver disease, this being the most appropriate explanation for the progression of NAFLD toward an inflammatory state ^(5,7).

FOUR BASIC HISTOLOGICAL CHANGES

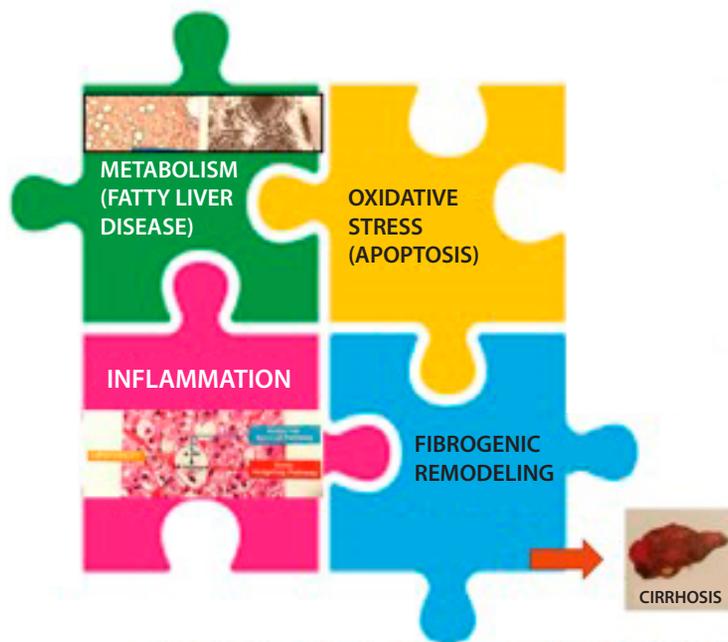


Figure 1. Basic histological changes of NAFLD in patients with T2DM

Source: Adapted from Williams KH, Shackel NA, Gorrell MD, McLennan SV, Twigg SM. Diabetes and nonalcoholic fatty liver disease: a pathogenic duo. *Endocrine Reviews*, February 2013, 34(1):84-129.

Subsequently, according to Figure 2, the currently proposed model includes the following guidelines:

1. In patients with obesity, diabetes causes an increased adipocyte lipolytic activity and the subsequent progression of fatty liver disease.
2. Likewise, it persistently elevates glycemia values in diabetes and produces hepatic insulin resistance, which leads to increased early lipolysis and late fibrotic activity.
3. Furthermore, high blood glucose or hyperglycemia and high levels of advanced glycation end products favor apoptosis and more fibrosis ^(5,8).

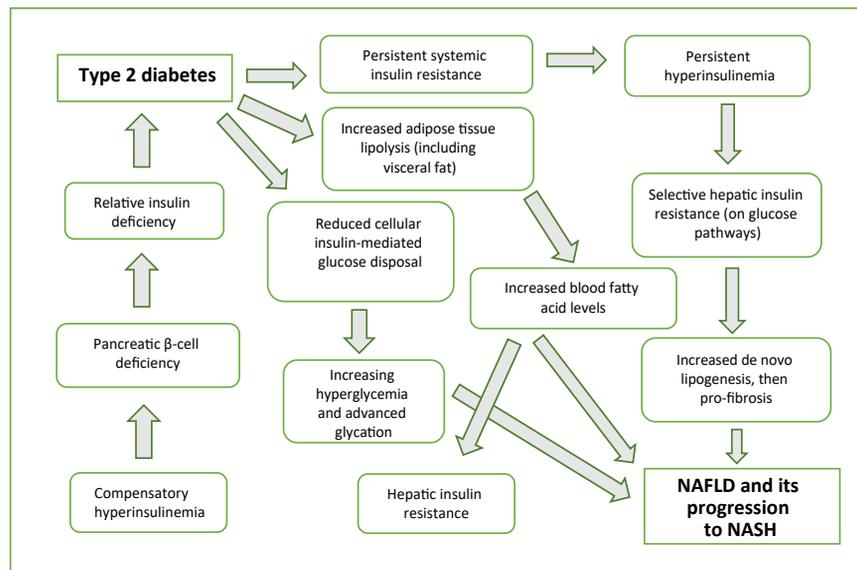


Figure 2. Multiple hit model

Source: Adapted from Williams KH, Shackel NA, Gorrell MD, McLennan SV, Twigg SM. Diabetes and nonalcoholic fatty liver disease: a pathogenic duo. *Endocrine Reviews*, February 2013, 34(1):84-129.

Hepatic insulin resistance associated with NAFLD may cause compensatory hyperinsulinemia and, in addition to a failure in pancreatic cells, may lead to increased glucose levels and even the onset of diabetes^(5,7).

SIGNS & SYMPTOMS AND DIAGNOSIS

Most subjects with NAFLD do not have symptoms, but some patients who suffer from this disease may complain of weakening, tiredness and discomfort in their right upper quadrant. Patients are more likely to be diagnosed by laboratory tests revealing elevated aminotransferase levels or by abdominal imaging tests showing fatty liver disease.

Imaging and/or serologic tests are needed to diagnose fatty liver disease when there are no other etiologies or excessive alcohol consumption. Liver biopsy is the golden standard to diagnose NAFLD and determine the prognosis.

Besides liver biopsy, which is an invasive method, there are currently other tests to detect fatty liver and specific techniques to rate NAFLD^(9,10).

It should be considered that the adverse consequences associated with NASH seem to be strongly related to the level of inflammatory activity and/or hepatic fibrosis, and do not simply determine fatty liver disease. In fact, as more effective treatment alternatives become available, it will be even more important to determine the degree of fibrosis⁽¹¹⁻¹³⁾.

Recommendations for the diagnosis of NASH in patients with diabetes mellitus

Patients with prediabetes or T2DM presenting elevated liver enzymes (aspartate or alanine aminotransferase) or fatty liver diagnosed by ultrasound should be examined for cirrhosis of the liver and NASH.

Diabetes is associated with the progression of NAFLD, including its most serious manifestations such as liver fibrosis, cirrhosis, NASH and hepatocellular carcinoma, as well as an impact on mortality caused by cardiovascular diseases. Elevated concentrations of liver alanine aminotransferase are associated with high body mass index (BMI) and waist perimeter, low levels of high-density lipoprotein (HDL) cholesterol and high triglycerides. It is possible to use non-invasive tests, such as fibrosis biomarkers or elastography, to assess fibrosis risk and, in certain cases, it may be necessary to refer the patient to a hepatologist and perform a liver biopsy for a definite diagnosis^(10,14,15).

Fibrosis risk assessment

The diagnosis of NAFLD is not only limited to detect fatty liver disease, as mentioned before, but includes the diagnosis of fibrosis or clinically significant risk of developing fibrosis, a stage which poses the real challenge.

Patients at high risk for NAFLD, including patients with T2DM, prediabetes, obesity and/or two or more cardiometabolic risks, or patients with persistently elevated plasma aminotransferase and/or fatty liver

disease found in imaging tests for a minimum of six months, should undergo fibrosis screening tests ^(10,16,17).

Clinical panels and biomarkers for predicting fibrosis

Clinical panels that predict significant fibrosis are described below ⁽²⁰⁾.

NAFLD fibrosis score

Angulo et al. used a logistic regression formula to validate an index referred to as “Non-Alcoholic Fatty Liver Disease (NAFLD) Fibrosis Score,” which includes age, platelets, BMI, hyperglycemia, albumin and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio.

The formula for the NAFLD Fibrosis Score is $-1.675 \pm 0.037 \times \text{age (years)} \pm 0.094 \times \text{BMI (kg/m}^2) \pm 1.13 \times \text{high fasting blood glucose level/diabetes (yes = 1, no = 0)} \pm 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelets} \times 10^9/\text{l} - 0.66 \times \text{albumin (g/dl)}$.

Low levels were observed in 61 % of the cases: significant fibrosis was ruled out in 93 %, with a sensitivity and specificity of 82 % and 77 %, respectively. Scores below -1.4 (F0-F2) were considered predictors of no significant fibrosis, with 97 %, while indeterminate scores between -1.4 and 0.675 (F3-F4) were considered predictors of significant fibrosis ⁽¹¹⁾.

This formula shows a histological correlation under the following categories: F0 = no fibrosis, F1 = mild fibrosis, F2 = moderate fibrosis, F3 = severe fibrosis and, finally, F4 = cirrhosis ⁽¹⁴⁾.

APRI (AST to Platelet Ratio Index)

It is calculated as follows: $\text{APRI} = [\text{AST level/AST upper limit of normal/platelet count (109/l)}] \times 100$. Therefore, it comprises one of the simplest and most used biomarker formulations because it can diagnose significant cirrhosis and fibrosis with an acceptable level of accuracy ⁽¹¹⁾.

Fibrosis-4 (FIB-4)

It consists of a combination of four simple variables: age, ALT, AST and platelet count. It is obtained by the following formula: $\text{FIB-4 Index} = [\text{age (years)} \times \text{AST (IU/l)}] / [\text{platelet count (109/l)} \times \text{ALT (IU/l)}]^{1/2}$.

At the beginning, this test was performed in patients coinfecting with HIV, hepatitis C virus (HCV) and hepatitis B virus (HBV). Similarly to FibroTest, FIB-4 demonstrated to be useful to diagnose cirrhosis and/or advanced fibrosis in patients infected with HCV and also in research studies conducted in patients infected with HCV and HBV ⁽¹⁴⁾.

Imaging tests

In general, magnetic resonance imaging (MRI) and computed tomography (CT) scan can detect fatty liver disease, but they do not have the required sensitivity to detect fibrosis

or inflammation. One of the conflicts to determine the specificity and sensitivity of MRI and CT scan to diagnose fatty liver disease is that most patients undergo a liver biopsy for confirmation.

Elastography

Elastography estimates liver stiffness by applying mechanical waves and measuring with imaging their spreading speed through the tissue. The options for this diagnostic modality include ultrasound and magnetic resonance (magnetic resonance elastography associated with MRI) ⁽¹⁴⁾.

The use of multiple serologic panels or the combination of serologic panels and imaging tests can improve the proper evaluation of the degree of fibrosis in a patient ⁽¹⁰⁾.

Liver biopsy

It is considered the gold standard test for diagnosis and can be prescribed in the following situations ^(10,17,18):

- Diagnostic uncertainty after imaging and/or serologic tests.
- Patient’s history suggesting cirrhosis, evidence of inflammatory process or high risk of fibrosis.
- High probability of developing severe fibrosis or cirrhosis.
- Clinical findings of cirrhosis.
- Splenomegaly.
- Cytopenia.
- Ferritin level over 1.5 times the usual maximum limit.
- Age over 45 years and history of obesity or diabetes (higher probability of fibrosis).

TREATMENT

The most outstanding benefits are obtained by treating the related diseases when a specific pharmacological approach has not been determined.

Healthy diet, weight loss as well as exercise provide a significant clinical benefit and should be considered as a first-line treatment for NAFLD ⁽¹⁹⁾ (Figure 3).

Multiple studies have demonstrated that a 5 % body weight loss is required to improve fatty liver disease. In a meta-analysis of eight trials consisting of 373 patients, a body weight loss $\geq 5\%$ resulted in an improvement of fatty liver disease; on the other hand, a body weight loss $\geq 7\%$ was associated with an improvement in the NAFLD activity score (NAS), used to rate the activity of the disease ⁽¹⁹⁻²¹⁾.

As to the pharmacological treatment, there are many therapeutic targets for which studies related to the pathogenicity of this condition have been conducted (Figure 3). Among them, treatment with pioglitazone is

recommended for patients with diabetes and vitamin E for subjects with biopsy-proven NAFLD who do not suffer from

diabetes, since it has been observed that it can improve the liver histology ⁽²²⁾.

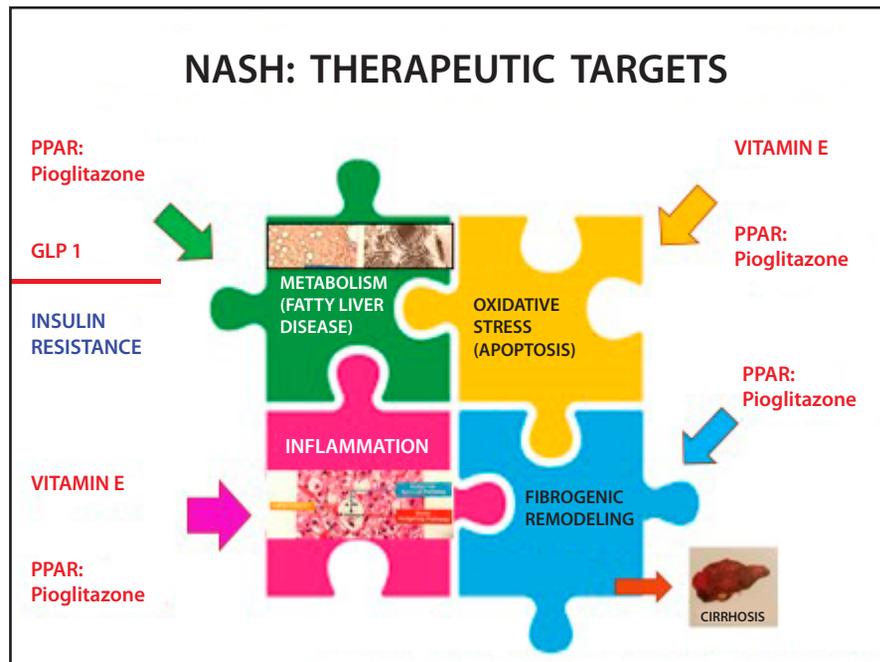


Figure 3. Therapeutic targets in NASH

Source: Adapted from Konerman MA, Jones JC, Harrison SA. Pharmacotherapy for NASH: Current and emerging. *J Hepatol.* 2018;68(2):362-375.

Agents of the thiazolidinedione class (pioglitazone) are efficient interventions for the treatment of this disease in patients with diabetes. These medications increased liver triglyceride levels from 39 % to 51 % and 54 % after three and six months of treatment, respectively. A meta-analysis of four trials that compared thiazolidinediones with placebo in 344 subjects diagnosed with NAFLD revealed that, compared with placebo, thiazolidinediones were more likely to improve liver histological parameters such as ballooning degeneration (*OR* 2.1, 95 % *CI*: 1.3 to 3.4), lobular inflammation (*OR* 2.6, 95 % *CI*: 1.7 to 4.0) and fatty liver disease (*OR* 3.4, 95 % *CI*: 2.2 to 5.3). There was no evidence of fibrosis improvement when each thiazolidinedione was analyzed; however, when the evaluation of the research studies using pioglitazone were limited to three, a significant fibrosis improvement was found in patients treated with pioglitazone, in contrast to patients treated with placebo ⁽²¹⁻²⁴⁾.

On the other hand, the use of biguanides or insulin has not provided proven benefits for fibrosis reversion or regression in patients with T2DM ^(23,25-27).

The treatment with GLP-1 agonists (liraglutide) or

with sodium-glucose cotransporter 2 (SGLT2) inhibitors (empagliflozin and dapagliflozin) have shown promising results in preliminary research studies; however, said results may be mediated by the weight loss caused by these agents ⁽²⁸⁻²⁹⁾. In the case of GLP-1 receptor agonists such as liraglutide, a trial including 52 patients with NASH who received liraglutide or placebo during 48 weeks and underwent a biopsy at the end of the treatment revealed that the disease remitted in 9 (39 %) out of 23 patients of the liraglutide group vs. 2 (9 %) of the placebo group (*RR* 4.3; 95 % *CI*: 1.0 to 17) ⁽³¹⁻³⁴⁾.

In the case of another GLP-1 agonist (semaglutide) tested in a phase 2 trial that included 320 subjects with biopsy-proven NAFLD and F1, F2 or F3 liver fibrosis, this drug (0.4 mg a day) resulted in high rates of histological resolution of NAFLD, in contrast to the use of placebo, after 72 weeks (59 % vs. 17 %; *OR* 6.87, 95 % *CI*: 2.60-17.63). Low doses of semaglutide (0.1 mg or 0.2 mg a day) were ineffective but improved the histological score compared to placebo (40 %; *OR* 3.36, 95 % *CI*: 1.29-8.86 and 36 %; *OR* 2.71, 95 % *CI*: 1.06-7.56, respectively) ⁽³⁵⁻³⁸⁾.

In the future, the development of treatments—mostly in clinical trials—for fatty liver disease and liver fibrosis as

well as cardiometabolic risk factors may be extremely beneficial⁽³⁹⁻⁴¹⁾.

Bariatric surgery

Bariatric surgery significantly reduces the risk of serious liver outcomes as well as serious cardiovascular events in subjects with biopsy-proven NAFLD^(42,43). In patients with T2DM, it allowed improving metabolic outcomes such as diabetes remission and better scores of the activity and regression of hepatic fibrosis^(44,45).

A recent study called “Surgical Procedures and Long-Term Effectiveness in NASH Disease and Obesity Risk” (SPLENDOR) included 1,158 patients with biopsy-proven NASH and without cirrhosis, with a median follow-up of seven years, where only five patients were part of the group that underwent a bariatric surgery and, instead, 40 patients of the control group experienced serious liver adverse events in the follow-up period. The cumulative incidence of major unfavorable liver findings was reduced in 88% in the bariatric surgery group, compared with 2.3% and 9.6% of the surgery group and non-surgery group, respectively (hazard ratio [HR]: 0.12, $p = 0.01$)⁽⁴⁶⁾.

Furthermore, in a study comparing bariatric surgery—laparoscopic gastric banding, gastric bypass or sleeve gastrectomy—and non-surgical management of obesity with usual care conducted in Israel, it was associated with a lower all-cause mortality during a median follow-up of approximately 4.5 years⁽⁴⁷⁻⁴⁹⁾.

CONCLUSIONS

The high prevalence of T2DM and NAFLD can lead to a serious public health problem in the future because of the related mortality and morbidity. The reciprocal influence between the two diseases may alter the natural evolution of both conditions.

Viral, autoimmune or deposit diseases, medications and chronic alcohol consumption should be ruled out in all patients with suspected NAFLD. The degree of fibrosis for its relationship with increased cardiovascular risk and worse liver complication prognosis should be assessed using a predictive marker of fibrosis in all patients at risk of advanced fibrosis. The use of multiple serologic panels or the combination of serologic panels with imaging tests may improve the ability to properly determine the degree of fibrosis in patients.

So far, the treatment of NAFLD through lifestyle interventions is the unique most effective therapeutic measure in the absence of an optimal pharmacological treatment. Among the pharmaceutical strategies, the use of oral antidiabetics such as pioglitazone has proved efficiency in reducing the severity of fibrosis in patients with

diabetes and NAFLD. There is an ample room for further research with prospective studies based on histological findings and a larger sample size in patients with T2DM and NAFLD on different areas such as the pathophysiology, risk factors and treatment of the disease.

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