# Non-alcoholic fatty liver disease: A major challenge in type 2 diabetes mellitus (Review)

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**Abstract.** Non-alcoholic fatty liver disease (NAFLD) has a high prevalence in type 2 diabetes mellitus (T2DM) patients, being one of the disorders with a relevant global burden. Cross-sectional studies have shown that patients with T2DM and NAFLD have a higher prevalence of liver fibrosis, compared with the general population. Patients with non-alcoholic steatohepatitis (NASH) and T2DM have an increased mortality and morbidity, therefore they generate substantial health care costs. NASH worsens chronic diabetes complications, and T2DM aggravate the NASH progression to fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC). The objectives in NAFLD and NASH therapy are to reduce disease activity, to slow down progression of fibrosis, and to lower the risk factors. Unfortunately, there are no specific validated pharmacological therapies. Several trials have demonstrated that anti-diabetic agents such as thiazolidindiones, sodium-glucose co-transporter inhibitors, glucagon like peptide-1 receptor analogs, or dipeptidyl peptidase-4 inhibitors might have complimentary benefits for patients with NAFLD. Some of the effect on reducing steatosis and fibrosis is explained by the weight loss these treatments produce. A goal in standard care is developing screening tools, early and non-invasive diagnosis methods, studying the pleiotropic effects of drugs, together with newer therapeutic agents, which can target mutual pathogenic mechanisms for diabetes and liver disease.

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**Contents**



## 1. Introduction

The annual prevalence of type 2 diabetes mellitus (T2DM) in 2019 was 463 million adults globally, and is estimated to increase to over 700 million by 2045. Half of the people diagnosed with diabetes are unaware of the disease, making this condition a significant subject of interest for physicians (1). In time, diabetes affects the vessels of major organs such as the heart, kidneys, bladder, eyes, nerves and the liver (2-4). A poor glycemic control in T2DM patients is associated with a higher risk for non-alcoholic fatty liver disease (NAFLD), and the magnified insulin resistance (IR) in NAFLD, usually in the presence of metabolic syndrome (MetS), increases diabetes and cardiovascular risk (2,4).

Obesity is a multifactorial disease with a significant health burden that influences the epidemiology of T2DM and NAFLD (5). Its prevalence has tripled in the last 40-50 years, reaching a pandemic level with over 650 million people worldwide in 2016, and still with an ascending trend (6).

NAFLD is the most frequent hepatic disease, with a prevalence of 47.5% (11.7 millions) in people with T2DM, as showed in

a large American cohort in 2017 (7). NAFLD affects 17-46% of adults in Western countries, with its prevalence vary depending on age, sex, diagnostic method or ethnicity (8). NAFLD incidence depends on the diagnostic process which has been used, from 20-86 per 1,000 people-years based on liver enzymes and ultrasound (US) to 34 per 1,000 people-years based on proton magnetic resonance spectroscopy ($^1$H-MRS) (9).

Observational studies published in 2018 estimated a non-alcoholic steatohepatitis (NASH) prevalence of 1.5-6.45% worldwide, with a much higher value of up to 12% in the USA (10). NASH prevalence is expected to increase by more than half by 2030, with the possibility to become the first cause of liver transplant in the USA (10).

NAFLD is defined by excessive hepatic fat accumulation (presence of steatosis) in >5% of hepatocytes according to histological examination or >5.6% of hepatocytes assessed by magnetic resonance imaging (MRI). NAFLD consists of two distinct conditions: NAFL and NASH with a different prognosis, which can lead to fibrosis, cirrhosis and hepatocellular carcinoma (HCC) (11). The diagnosis of NAFLD can be made after excluding a daily alcohol consumption of >30 g for men (>21 drinks/week) or >20 g for women (>14 drinks/week), and other possible etiologies for hepatic steatosis (12).

HCC is the fifth most common cancer in men and the seventh most common in women. After lung cancer, it is the second cause of cancer mortality, being responsible for 11% of cancer-related deaths (13).

The reciprocal relationship between T2DM and NAFLD is probably one of the biggest challenges for physicians who treat these patients (12). In the development of NAFLD, several pathophysiological processes are involved, such as alteration in glucose and lipids metabolism, insulin resistance (IR), all common in T2DM. Also, patients with T2DM and NAFLD associate with the same comorbidities, including metabolic syndrome (MetS), hypertension, hypertriglyceridemia, low high-density-lipoprotein-cholesterol and abdominal fat accumulation (14).

NAFLD is strongly associated with obesity, with a prevalence of 80% in obese individuals, compared with 16% of the population with a body mass index (BMI) <25 kg/m$^2$, and without metabolic risk factors. Hepatic steatosis is more closely correlated with visceral adiposity (measured as abdominal circumference), than it is associated with BMI because visceral adipose tissue (VAT) is more metabolically active (15,16).

## 2. NAFLD and insulin resistance - lipotoxicity and glucotoxicity

In NAFLD, insulin resistance (IR), a well-known state of T2DM, affects the muscle, the liver and the adipose tissue (13). Glucotoxicity and lipotoxicity are in strong association, and they contribute together to exacerbate IR and alteration of insulin secretion (14).

Increased adiposity, especially VAT, is often present in NAFLD and T2DM, and is associated with adipocyte insulin resistance and dysfunction (14). This leads to excess free fatty acids (FFA) released into the circulation, and in the end, to an excess fat uptake by the liver, pancreas and skeletal muscles, becoming a vicious cycle. FFAs can be oxidized through mitochondrial β-oxidation or esterified to triglycerides. Lipotoxicity is strongly correlated to peripheral IR, hepatic gluconeogenesis and glycogenolysis, which lead to hyperglycemia, pancreatic beta-cell dysfunction and alterations in insulin secretion (13).

The hepatocytes and adipocytes from VAT are in close juxtaposition with immune cells, hepatic stellate cells, Kupffer cells, endothelial cells and macrophages where biochemical signalling pathways take place, activated by obesity and a high-fat diet (HFD). This pathway underlies the low-grade chronic inflammation present in hepatic steatosis, also sustained by a high level of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1 beta (IL-1β) found in mice with high-fat diet (15).

VAT secrete considerable amounts of adipocyte-derived cytokines called adipokines, of which the most well-described are adiponectin and leptin. Leptin controls energy intake and energy spending, metabolism, reproduction and stops lipid accumulation in non-adipose tissues, such as the liver. Obesity is a state of leptin resistance, both central and peripheral, associated with low levels of adiponectin, a cytokine responsible for the modulation of the inflammatory response, intensification of liver fat oxidation and decrease in the activity of fatty acid synthase (14).

Glucotoxicity, a chronic condition in T2DM, causes glucose-induced insulin resistance, cellular dysfunction and a series of metabolic alterations. Individually, fructose and sucrose are considered lipotoxic to hepatocyte activity, because they have been proven to enhance *de novo* lipogenesis and ectopic fat accumulation. Persistent high levels of glycaemia cause both functional and structural harm to beta cells, which develop oxidative stress, increase the production of reactive oxygen species, DNA alteration and pro-apoptotic pathways (13).

Research has been conducted on intestinal microbiota, which determines nutrient consumption, caloric intake, influencing weight and insulin sensitivity (16). The favourable effects of antibiotics on bowel decontamination in patients with cirrhosis that permit bacterial translocation and inactivation are well-known. Still, the effect of microbiota on the progression of liver fibrosis needs to be further studied (16).

## 3. NAFLD evaluation and progression

Usually, NAFLD is a slowly progressive condition, with fibrosis advancing in a fifth of individuals (11). Comparing to chronic liver diseases, such as hepatitis B or hepatitis C, the natural history of NASH is much more unpredictable (16). The progression of fibrosis in NAFLD depends on genetic factors, extrinsic environmental and intrinsic microbial factors (17). The natural history of NAFLD can be modified, even reverted, through diet and lifestyle changes (18). While some studies support age and diabetes as significant drivers in fibrosis evolution (19), others consider hypertension and AST/ALT ratio more relevant in the prognosis of liver fibrosis (17). Among patients who develop progressive hepatic fibrosis, there are two categories of individuals: rapid progressors (advance from stage 0 to bridging fibrosis or cirrhosis), who are 20% of patients, and slow progressors (progression from stage 0 to stage 1 or 2 of fibrosis) (17). Liver-related morbidity and

mortality increase remarkably with stage 2 of fibrosis and in particular with cirrhosis (16). A study by Ciupińska-Kajor *et al* showed that severe fibrosis and cirrhosis are more frequent in morbidly obese patients (20).

Patients with T2DM have more than a 2-fold increase in the prevalence of NAFLD/NASH, regardless of the diagnostic method, with an ~70% prevalence when sensitive methods are used (21). The prevalence of NAFLD depends on the diagnostic tool used and on different cut-off points selected as usual (e.g., alanine aminosferase). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are considered poor markers for NAFLD. Liver ultrasound is available, has a low cost, making it suitable for screening routine (22). Hernaez *et al* (23) reported a meta-analysis of the studies which evaluate the accuracy of liver ultrasound in detecting steatosis. This method has 84.8% sensibility (95% confidence interval between 79.5 and 88.9), and 93.6% specificity (95% CI between 87.2 and 97.0) for moderate-severe NAFLD. However, liver ultrasound does not discriminate mild steatosis. Fatty liver index (FLI), a non-invasive algorithm using anthropometric and biological parameters (BMI, waist circumference, plasma triglycerides level, γ-glutamyl transferase), are accepted and validated, in comparison with liver ultrasound, but fibrosis may alter the result. Novel techniques, i.e. controlled attenuation parameter (CAP), $^{1}$H-MRS and MRI-proton density fat fraction are more accurate and are quantifiable, which can be helpful in the follow-up. Techniques that measure hepatic triglyceride accumulation are becoming more widely available. They may become the gold standard for steatosis screening in high-risk patients (22).

Evaluating inflammation and fibrosis are the next important steps after diagnosing NAFLD. Although the gold standard is liver biopsy, some non-invasive scores i.e. FibroTest, NAFLD fibrosis score, BARD score, FIB-4, NAFIC score based on clinical parameters (plasmatic levels for ALT, AST, albumin, BMI, diagnosed diabetes) are also used (24). There are new promising biomarkers (i.e., metabolomics), and genetic tests studied for future implementation. The polymorphism patatin-like phospholipase 3 (PNPLA3; rs 738409) has been associated with more significant accumulation of liver lipids (25). Vibration-controlled transient elastography (FibroScan) and magnetic resonance elastography (MRE) determine the stage of fibrosis, replacing biopsies in some cases. Although MRE is more expensive and not always available, its result does not interfere with BMI, considering patients with T2DM have quite often a higher BMI than the general population (1).

## 4. Therapeutic management

The aims in NAFLD and NASH therapy are to reduce disease activity, to slow down progression of the fibrosis, and to lower the risk factors. Unfortunately, there are no specific pharmacological therapies validated; consequently, the lifestyle interventions are considered standard of care (13,20). The management of NASH should also include pharmacological treatment of comorbidities such as therapy for hyperglycemia, or dyslipidemia and control of other cardiovascular risk factors (24).

Studies showed an improvement in NAFLD and NASH correlated with the percentage of weight loss following dedicated programs, such as a hypocaloric diet and 200 min exercises per week (26,27), or after metabolic surgery (28). Some studies found that >7% of weight loss is associated with a decrease in steatosis (26). A more significant weight loss (8-10%) can reverse steatohepatitis, and if >10% is achieved it can lead to considerable regression of fibrosis (29). Patients who undertook bariatric surgery had even more surprising results, so the decrease in steatosis was observed in 90% of patients, decrease in steatohepatitis in ~80% of them, and a reduction in fibrosis was observed in 65% of patients (28).

In a ten-week randomized-controlled trial, patients were given either an omega-3 polyunsaturated fatty acid (PUFA) rich diet or a saturated fat diet. Patients included in the first group had a significantly reduced steatosis assessed with $^{1}$H-MRS (-26% after intervention), in comparison with patients from the saturated fat diet, in whom steatosis had even progressed (+8% after intervention) (29). A series of studies are needed to assess the role of lifestyle intervention as a therapy for patients with NASH (24). The Mediterranean Diet and the Dietary Approach to Stop Hypertension (DASH) are considered effective (30).

The recommendation of caloric intake is 30-35 kcal/kg/day, with adjustment depending on the level of physical activity the patient would reach. Regarding the macronutrients, carbohydrates should make up 45-55% of the daily caloric intake, obtained from whole grains, fruits and vegetables; 20-30% of caloric intake should come from 'healthy' fats, monounsaturated fatty acids (MUFA) and PUFA, found in seeds, nuts, olive oil and fatty fish 'as little thermally processed as possible'. Proteins represent 10-15 to 20% of the total daily caloric requirements, obtained from both animal and vegetable sources. The diet is more beneficial if it includes fiber, antioxidants, probiotics and prebiotics along with 33 ml/kg/day liquids and a moderate sodium restriction (31,32).

## 5. Anti-diabetic agents targeting NAFLD

Some studies showed an efficacy in reducing steatosis for pioglitazone, liraglutide, vitamin E, obeticholic acid, but cross-comparisons between studies cannot be considered, because of the heterogeneity regarding materials and methods (24). Thiazolidinediones (TZDs), especially pioglitazone, through activating the peroxisome activator-proliferator receptor-γ (PPAR-γ), improve steatosis and fibrosis scores, along with insulin sensitivity in adipose tissue, muscle and liver (33). The study of Cusi *et al* (34) suggests that the administration of pioglitazone in patients with T2DM and NAFLD/NASH leads to improvement in liver fibrosis. The PIVENS trial (Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis) showed no benefit regarding the administration of pioglitazone vs. placebo for the primary composite outcome (improvement of the histological lessions), but hepatic steatosis and lobullar inflammation were reduced (35). In contrast, the authors found vitamin E superior to placebo as a therapy for NASH in patients without diabetes (35). These data support the beneficial effect of pioglitazone in NAFLD/NASH, mainly in patients with T2DM, most likely because of the metabolic properties of PPAR-γ.

Glucagon-like peptide-1 receptor agonist (GLP-1 RA) is a new class of glucose-lowering agents, which have additional

benefits in patients with NAFLD/NASH through weight loss, increasing insulin sensitivity and even a direct effect on suppression of lipogenesis in hepatocytes (36). Liraglutide was studied in different doses starting from 0.3 mg to 3 mg/day, and it improved biological and clinical parameters i.e. AST, ALT, BMI, HbA1c, fasting plasma glucose, visceral fat accumulation, along with reducing hepatic steatosis assessed through either ultrasonography or MRI in patients with T2DM and NAFLD/NASH (37,38). Liraglutide Efficacy and Action in NASH (LEAN study), a double blind, randomized control trial evaluated the effect of liraglutide administration in patients with NASH diagnosed by liver biopsy. The study included 52 patients, 17 with T2DM and 35 without, randomly assigned to either placebo or 1.8 mg/day of liraglutide. After 48 weeks, 9 out of 23 patients who received liraglutide had a reduction in primary point (resolution of steatohepatitis without worsening fibrosis), compared with 2 out of 22 in the placebo group. Also, the placebo group had worse results concerning secondary outcomes (progression in fibrosis) as well, 8 out of 22 patients vs 2 out of 23 in the liraglutide group (37).

Dipeptidyl peptidase-4 inhibitors (DPP-4i) are another category novel agents used in T2DM, with promising effects in NAFLD/NASH. Circulating DPP-4 levels were found in patients with NASH, and they were correlated with liver fibrosis and hepatocytes apoptosis (38). Sitagliptin, the most studied DPP-4i agent, showed improvements regarding ALT, AST and hepatocyte ballooning, in one study (38). At the same time, other researchers did not find benefits in the administration of sitagliptin at patients with NAFLD/NASH (39).

Empagliflozin, a sodium-glucose cotransporter two inhibitor (SGLT2i), was studied in the Effect of Empagliflozin on Liver Fat (E-LIFT) trial, which proved that it reduces liver fat and ALT levels in patients with T2DM and NAFLD (40). This class of drug that has cardiovascular benefits (41), seem to have an advantage in NAFLD. Thus, the combination between a GLP-1 RA, and an SGLT2i might have complimentary benefits for patients with T2DM, NAFLD and/or with cardiovascular disease (35).

Treatment of hyperglycemia is important in NAFLD/NASH patients, considering diabetic individuals have worse evolution of microvascular complications like retinopathy (42) and nephropathy (43). Hence, clinicians can use any glucose-lowering agents mentioned above (SGLT-2i, GLP-1 RA, DPP-4i) to achieve T2DM control before debut of complications, and simultaneous treatment of NAFLD (34).

## 6. Conclusions

The research on non-invasive diagnostic tools, effective and safe therapies in NAFLD is interposed with other highly prevalent diseases like T2DM. These two pathologies are interrelated having common risk factors, similar prognosis and significant socioeconomic burden. Thus, an active screening for NAFLD/NASH in patients with diabetes and vice-versa is useful for the prevention of the aggravation of both diseases.

Clinicians should put more emphasis on lifestyle interventions, through empowering patients in taking responsibility and being aware of their essential role in managing NAFLD/NASH.

Although there is no specific treatment for NAFLD/NASH, agents with pleiotropic effects that target multiple pathogenic mechanisms such as thiazolidinediones, GLP-1 RA, SGLT2i or vitamin E proved to be beneficial in some studies. Whether these treatments slow the rate of NAFLD/NASH progression to fibrosis and cirrhosis will be decided by future studies.

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## Authors' contributions

APS, RAS and AIS conceived and designed the study. CB, CS ans SDS aquired the data and performed the literature research. ES, FG, and REB verified and selected the studies for the final analysis. CS, AIS, REB and SDS have equal contributions with first author. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

APS is currently Vice President of the Romanian National Diabetes Committee and has given talks, attended conferences and participated in advisory boards sponsored by various pharmaceutical companies. RAS attended conferences sponsored by Wörwag Pharma. The rest of the authors declare that they have no competing interests.

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