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Diabetes and Fatty Liver

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NOTICE OF UPDATE

The DDG clinical practice guidelines are updated regularly during the second half of the calendar year. Please ensure that you read and cite the respective current version.

UPDATES TO CONTENT AND DIFFERENT RECOMMENDATIONS COMPARED TO THE PREVIOUS YEAR'S VERSION

Change 1: For the screening of non-alcoholic fatty liver disease, reference was made to the updated S2k guideline on non-alcoholic fatty liver disease of the German Society for Gastroenterology, Digestive and Metabolic Diseases/Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) [7], the European algorithm of the EASL Clinical Practice Guidelines [8], and a recently proposed procedure for general practitioners and diabetologists [9]
Reason: New recommendation for structured screening for non-alcoholic fatty liver disease for general practitioners and diabetologists
Supporting reference: [7–10]
Change 2: New results from pharmacological phase 2 therapy studies are given.
Reason: This provided important new insights into the possible future pharmacological therapy of non-alcoholic fatty liver disease.
Supporting reference: [22–25]

Introduction

Non-alcoholic fatty liver disease (NAFLD) affects more than 25 % of the adult population worldwide. According to analyses for 2016, Germany ranks third behind Greece (41 %) and Italy (25.4 %) in the prevalence of NAFLD (22.9 % of the total population). An increase in the prevalence of NAFLD to 26.4 % has been calculated for Germany for the year 2030. At around 70 %, the frequency of NAFLD is particularly high in people with obesity and/or type 1 diabetes [1]. However, NAFLD also occurs in about 7 % of thin people and is then primarily of genetic origin [1]. There is also preliminary evidence that therapy with checkpoint inhibitors, which is increasingly used in the context of cancer treatments, may induce NAFLD in lean individuals via subclinical inflammation of subcutaneous adipose tissue, which leads to, among other things, significant weight loss [2]. In Europe and the USA, NAFLD is now regarded as the most frequent cause of chronic liver diseases although most people with NAFLD die from secondary diseases resulting from diabetes or cardiovascular diseases. Therefore, it is particularly important to test patients with type 2 diabetes for the presence, and especially the degree of severity, of NAFLD, and to plan therapy accordingly [3, 4]. New research from the German Diabetes Study (GDS) indicates that especially the severely insulin-resistant diabetes subtype (cluster) has a significantly increased prevalence of NAFLD already in the year of diabetes diagnosis and shows a greater increase in surrogate markers of fibrosis in the first 5 years [5].

Definition and incidence

A fatty liver can have many causes. First, a systematic evaluation is performed, and if suspected, laboratory tests to confirm specific illnesses are carried out and drug therapies are evaluated (▶ **Table 1**). If no evidence is found for these diseases, it is usually because NAFLD is present. NAFLD includes not only non-alcoholic fatty liver (simple non-alcoholic steatosis, NAFL), which is not associated with relevant inflammatory or fibrotic changes in the liver and affects about 70 % of people with NAFLD, but also non-alcoholic steatohepatitis (NASH), liver fibrosis, and cirrhosis without other aetiologies. These represent advanced stages of NAFLD, with NASH present in about 30 % of people with NAFLD. People with fatty liver and diabetes are > 40 % likely to have NASH [4, 6].

Screening

In April 2022, the updated S2k guideline on non-alcoholic fatty liver disease of the German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS) was published with the participation of representatives of various medical societies, including the German Diabetes Society, represented by Michael Roden and Norbert Stefan [7]. It takes the following position for screening for NAFLD, among others: Screening for NAFLD is not recommended in the general population. However, a (non-invasive) assessment should be carried out if risk factors for the development of NASH are present. Screening should therefore be carried out primarily in people with type 2 diabetes, metabolic syndrome, overweight/obesity or arterial hypertension. For this purpose, a screening algorithm has been proposed that includes both steatosis and fibrosis risk, can be modified according to availability and can be carried out in the general practitioner's practice. This algorithm is broadly in line with the European Algorithm of the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines [8, 9] and a recently proposed procedure for general practitioners and diabetologists [10]. In ▶ **Fig. 1**, we have mapped out the essential steps in this process.

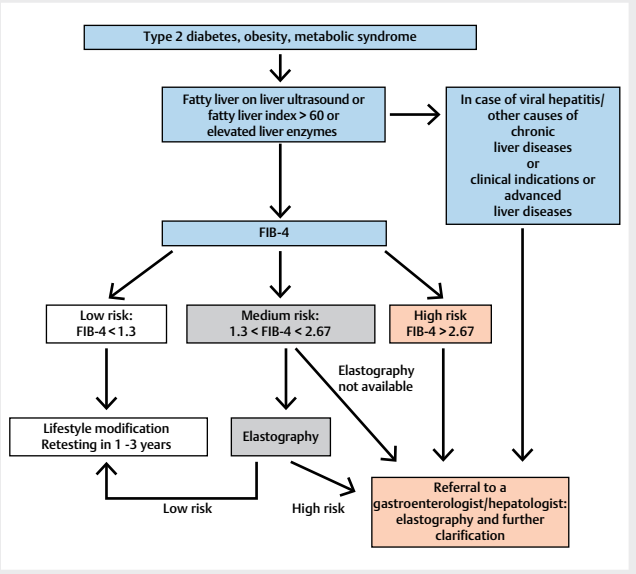
Diagnosis

Currently, ultrasound, proton magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI) are used to diagnose NAFLD. The two non-invasive MR methods allow a precise determination of the lipid content of the liver and are therefore preferred to quantification of the lipid content of the liver using liver biopsy. The liver biopsy is currently the most suitable method for diagnosing inflammatory changes, i. e. NASH, as well as for the diagnosis of liver fibrosis. Ultrasound or MR-based techniques such as FibroScan and MR elastography (MRE) are quite accurate, but also expensive, non-invasive methods for diagnosing fibrosis (▶ **Table 2**). Tests and scores based on anthropometric and laboratory chemical parameters are also available and can be used for risk assessment of NASH and fibrosis. In addition to transaminases (glutamate-pyruvate transaminase (GPT)/alanine aminotransferase (ALT), glutamate oxaloacetate transaminase (GOT)/aspartate aminotransferase (AST)), special tests can also assist in diagnosing fibrosis

▶ **Table 1** Causes of fatty liver.

Causes	Diagnostics
Non-alcoholic fatty liver	Steatosis with none of the causes listed below
Alcohol	> 21 standard drinks [1] per week for men. > 14 standard drinks [1] per week for women
Medication	E.g., glucocorticoids, oestrogens, amiodarone, tamoxifen, tetracycline, methotrexate, valproic acid, antiviral drugs, perhexiline maleate, chloroquine
Viral hepatitis	Virus serology
Autoimmune hepatitis	Autoimmune serology
Hemochromatosis	Elevated ferritin levels and transferrin saturation in serum
Wilson's disease	Lower levels of caeruloplasmin in serum
Alpha-1-antitrypsin deficiency	Lower alpha-1 antitrypsin levels in serum
Celiac disease	Gliadin antibodies, anti-tissue transglutaminase
Other	E.g., severe malnutrition, hypobetalipoproteinaemia, lipodystrophy, pronounced chronic inflammatory bowel diseases

[1] Standard drink contains 14 g alcohol.



▶ **Fig. 1** Screening algorithm. FIB-4: fibrosis-4 index. Data according to [7, 9, 10].

stages 3 and 4 [4, 8, 11, 12] although their accuracy seems to be lower, especially in diabetes mellitus [13].

From NAFLD to MASLD

Since many years there was a discussion among experts as to whether metabolic risk factors should replace alcohol consumption as the focus in defining fatty liver disease [14]. This approach is mainly based on the important finding that the pathogenesis of fatty liver is strongly influenced by changes in glucose and lipid metabolism [15, 16].

In 2023, a multi-society Delphi consensus statement suggested renaming NAFLD to metabolic dysfunction-associated steatotic liver disease (MASLD) [17]. It includes patients with hepatic steatosis and at least one of five cardiometabolic risk factors. In addition, the term fatty has been converted into its synonym steatotic, because it was thought that fatty describes a medical condition that can be stigmatizing for some patients. Thus, the overarching term for fatty liver disease was changed to steatotic liver diseae (SLD). In addition, the term metabolic dysfunction-associated steatohepatitis (MASH) replaced NASH. Furthermore, a new category, outside MASLD, termed metabolic and alcohol related/associated liver disease (MetALD), was selected to refer to subjects with metabolic dysfunction-associated steatotic liver disease, who consume greater amounts of alcohol per week (140-350 g/wk and 210-420 g/wk for females and males, respectively). If no overt cardiometabolic criteria are present, other causes should be ruled out. If none are identified, this condition is referred to as cryptogenic SLD.

Risk for advanced liver diseases and cardiometabolic diseases in NAFLD

In a large meta-analysis of 11 studies, it was shown that in people with NAFLD with fibrosis detected by liver biopsy, over a period of 2145.5 person years, progression was observed in 33 % of people, stabilization in 43 % and regression of fibrosis in 22 % [18]. Interestingly, however, the same percentage of people with NAFL or NASH (about 18 % each) without fibrosis in the first liver biopsy have progressed to advanced fibrosis in the subsequent biopsy [18]. In NAFLD, hepatocellular carcinoma can also develop directly from NAFL without having had NASH [6].

People with NAFLD have a 2–6 times higher risk of type 2 diabetes and/or cardiovascular disease [19]. This risk is particularly high if there is abdominal obesity and especially if there is insulin resistance. As more people with NAFLD die from complications of diabetes, including cardiovascular disease [6], it is of utmost importance to above all diagnose and prevent cardiometabolic diseases as well as advanced liver diseases.

Therapy for NAFLD

First and foremost, in the therapeutic approach and prevention of progression of NAFLD is a lifestyle modification including a balanced, calorie-reduced diet and an increase in physical activity (▶ **Table 3**). The effectiveness of lifestyle intervention fundamentally depends on the achieved reduction in body weight. Weight loss of about 5 % results in a 30 % reduction of the liver lipid content. However, to positively influence hepatic inflammation and fibrosis, weight loss of more than 10 % is likely necessary. For effective NAFLD therapy, revised nutritional meal plans should include a reduction in fast-digesting carbohydrates, especially of products containing fructose, and of saturated fatty acids. Endurance and strength training can also be effective in addition to diet modification [4].

Bariatric surgery for pronounced obesity or moderate obesity and type 2 diabetes causes a large reduction in the liver lipid content as well as weight loss, although effects on inflammation and fibrosis of the liver have not yet been sufficiently investigated [4]. Recently, the results of the SPLENDOR study have been of particular interest. In this study, bariatric surgery significantly reduced the risk of adverse liver damage and major cardiovascular events in patients with NASH and obesity compared to nonsurgical treatment [20].

So far, no pharmacological therapy has been approved to treat NAFLD. If type 2 diabetes is present, however, drugs can be used to specifically treat diabetes in order to also treat NAFLD. The joint guidelines of the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD) and the European Association for the Study of Obesity (EASO) as well as those of the American Association for the Study of Liver Diseases recommend the use of peroxisome proliferator-activated receptor (PPAR)-gamma agonist pioglitazone if there are no associated contraindications (heart failure, history of bladder carcinoma, increased risk of bone fractures) [4, 8]. Recent data from studies with relatively small case numbers indicate that GLP-1 receptor agonists (GLP-1: glucagon-like peptide 1) such as liraglutide and SGLT-2 inhibitors (SGLT-2: sodium-dependent glucose transporter 2) can reduce the liver lipid content and improve NAFLD and type 2 diabetes. In particular, therapy with semaglutide at daily subcutaneous doses of 0.1 mg, 0.2 mg or 0.4 mg showed strong effects on the remission of NASH without progression of fibrosis in a phase 2

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▶ **Table 2** Diagnosis of NAFLD.

Method	Characteristics	Advantages	Disadvantages
Liver biopsy	▪ Lipid droplets in > 5 % of hepatocytes	▪ To date, the reference method for lipid determination ▪ The reference method for the determination of inflammation and fibrosis	▪ Not suitable for screening ▪ Can result in sampling errors ▪ Invasive ▪ Prone to complications
Sonography	▪ Liver and kidney echogenicity ▪ Border to the diaphragm and intrahepatic structures	▪ Widely available ▪ Inexpensive	▪ Low sensitivity and specificity at lipid content < 25 %.
Fatty liver index (FLI)	▪ BMI ▪ Waist circumference ▪ Gamma GT ▪ Fasting triglycerides	▪ Widely available ▪ Inexpensive	▪ Low sensitivity and specificity at lipid content < 25 %.
Indices for fibrosis (non-commercial: NAFLD-FS, FIB-4 score; Commercial: ELF, FibroTest, FibroMeter)	▪ Formulas using the following parameters: ▪ Age, ▪ BMI, ▪ Fasting blood glucose, ▪ Diabetes diagnosis, ▪ GOT (AST), ▪ GPT (ALT), ▪ Gamma GT (GGT), ▪ Thrombocytes, ▪ Albumin and ▪ Specific blood markers	▪ Widely available ▪ Inexpensive	▪ Low sensitivity and specificity at lipid content < 25 %.
Transient elastography	▪ Propagation of the pulse of a low frequency transducer for estimating the lipid content and the degree of fibrosis	▪ Non-invasive ▪ Can better assess lipid content than the fatty liver index or the fibrosis indices	▪ Lower sensitivity and specificity for obesity ▪ Relatively expensive
Computer tomography	▪ Houndsfield units	▪ Can better assess lipid content than fatty liver index or transient elastography	▪ Radiation exposure ▪ Inferior to MR imaging
Magnetic Resonance (MR) imaging and spectroscopy	▪ MR-based measurement of the proton density of triglyceride and water (MR-PDFF) ▪ ^{1}H-MR spectroscopy	▪ Very precise for diagnosis of lipid content ▪ Low sampling error	▪ Extremely expensive
MR elastography	▪ MR-based imaging of tissue excitation by low-frequency sound waves	▪ Relatively well-suited for non-invasive diagnosis of fibrosis ▪ Low sampling error	▪ Extremely expensive

NAFLD: non-alcoholic fatty liver disease; BMI: body mass index; GOT (AST): glutamate oxaloacetate transaminase (aspartate aminotransferase); GPT (ALT): glutamate-pyruvate transaminase (alanine aminotransferase); GGT: gamma-glutamyl transferase; MR: magnetic resonance.

study in people with NASH and liver fibrosis at stage F1-F3, compared to placebo [21]. However, in another phase 2 study, semaglutide at the dose of 2.4 mg once weekly showed no resolution of NASH or improvement in fibrosis compared to placebo in patients with NASH-associated cirrhosis [22]. All other pharmacological therapies for type 2 diabetes have so far shown no clinically-relevant effects on the course of NAFLD [4].

There are other treatment approaches showing positive effects in current placebo-controlled phase 2 trials. The pan-PPAR (PPAR alpha, delta and gamma) agonist lanifibranor showed a marked improvement in NASH and fibrosis in patients with NASH without cirrhosis [23]. The liver-selective thyroid hormone receptor β-agonist resmetirom showed a significant improvement in steatosis and, in a subgroup, also a resolution of NASH in the treatment of patients with NASH and hepatic fibrosis F1-F3 [24]. The fibroblast growth factor 21 (FGF21) analogue pegozafermin also induced NASH resolution and improvement of fibrosis in patients with NASH and liver fibrosis F2-F3 [25].

Outlook

The increasing prevalence of NAFLD in the most common metabolic diseases such as obesity and type 2 diabetes requires targeted screening and careful diagnosis of liver diseases in these patient groups. Early prevention or therapy of NAFLD will reduce both the liver-specific as well as the diabetic consequences and complications. In the future, this will require the full use of all existing diagnostic possibilities including fibrosis screening on the one hand,

▶ **Table 3** Effects of intervention on NAFLD and diabetes.

Intervention	Effects on the liver	Systemic effects
Lifestyle	Steatosis: ↓ ↓ ↓ Inflammation: ↓ ↓ Fibrosis: ↓ or =	Blood glucose: ↓ ↓ Insulin resistance: ↓ ↓ Dyslipidaemia: ↓ Weight: ↓
Bariatric surgery	Steatosis: ↓ ↓ ↓ Inflammation: ↓ ? Fibrosis: ?	Blood glucose: ↓ ↓ ↓ Insulin resistance: ↓ ↓ ↓ Dyslipidaemia: ↓ Weight: ↓ ↓ ↓
Pioglitazone	Steatosis: ↓ ↓ ↓ Inflammation: ↓ ↓ Fibrosis: ↓ or =	Blood glucose: ↓ ↓ Insulin resistance: ↓ ↓ ↓ Dyslipidaemia: ↓ ↓ Weight: ↑
GLP-1 agonists	Steatosis: ↓ ↓ Inflammation: ↓ Fibrosis: =	Blood glucose: ↓ ↓ Insulin resistance: ↓ ↓ Dyslipidaemia: ↓ Weight: ↓
SGLT-2 inhibitors	Steatosis: ↓ Inflammation: ? Fibrosis: ?	Blood glucose: ↓ ↓ Insulin resistance: ↓ Dyslipidaemia: = Weight: ↓

and, on the other hand, the further development of cost-effective and non-invasive or low-invasive tests. The aim is to reduce the use of liver biopsies for diagnosis and, above all, to assess the course of NAFLD and the effectiveness of therapies. At present, there are still no large studies that have convincingly demonstrated the effectiveness of new monotherapies or combination therapies of existing drugs. However, different innovative therapy concepts are already being tested experimentally and clinically so that specific therapy recommendations for the increasing number of patients with NAFLD and diabetes can be expected in the near future.

Conflict of Interest

NS has participated in Scientific Advisory Boards of Allergan, Intercept Pharma, MSD, Pfizer, Novo Nordisk, Gilead, Genkyotex, Astra-Zeneca, Boehringer Ingelheim, Sanofi, as well as clinical trials of AstraZeneca, Boehringer Ingelheim, Sanofi, DSM Nutritional Products and Roche Diagnostics.
MR has participated in Scientific Advisory Boards of BMS, Boehringer Ingelheim Pharma, Eli Lilly, Fishawack Group, Gilead Sci., Novo Nordisk, Prosciento Inc., Sanofi, Target RWE, Terra Firma as well as clinical trials of Boehringer Ingelheim, Nutricia/Danone and Novartis.

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