Diabetes and Fatty Liver

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published online 01.04.2022

Bibliography
Exp Clin Endocrinol Diabetes 2022; 130: S113–S116
DOI 10.1055/a-1624-3541
ISSN 0947-7349

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

German Diabetes Association: Clinical Practice Guidelines
This is a translation of the DDG clinical practice guideline published in Diabetologie 2021; 16 (Suppl 2): S308–S311
DOI 10.1055/a-1581-6360

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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 (2.3) for the year 2030. At around 70 %, the frequency of NAFLD is particularly high in people with obesity and/or type 2 diabetes [2]. However, NAFLD also occurs in about 7 % of lean people and is then primarily of genetic origin [2]. 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 [3]. 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 [4, 5]. 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 [6].

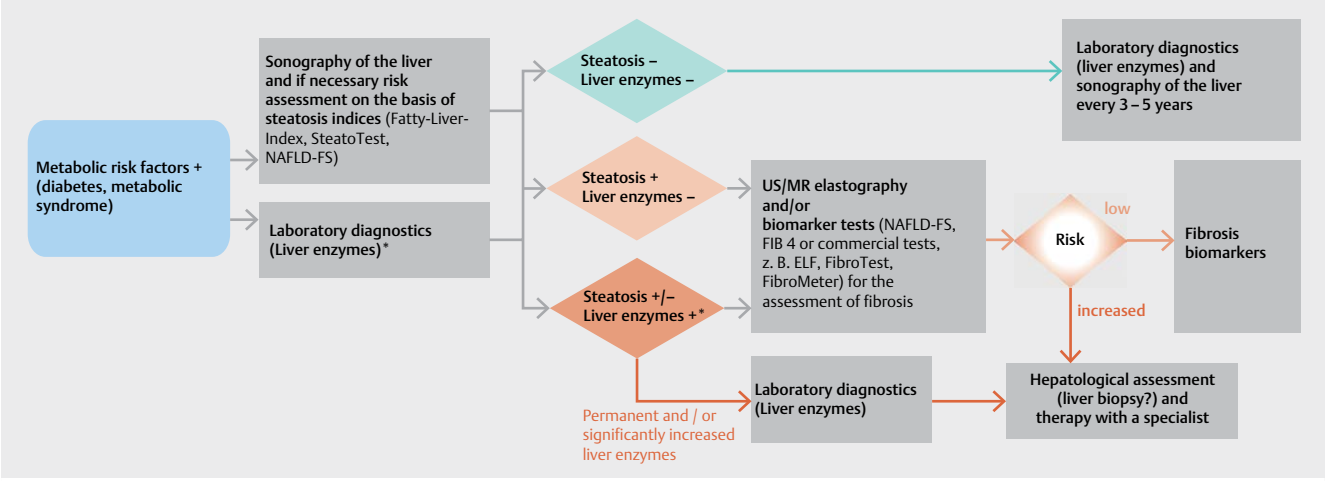
Definition and incidence

A fatty liver can have many causes. First, a systematic evaluation is performed, and if suspected, laboratory tests to confirm specific illnesses or drug therapies are carried out (▶ **Tab. 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

▶ **Tab. 1** Causes of fatty liver.

Causes	Diagnostic
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	Anti-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** Diagnostic flowchart. NAFDL-FS: nonalcoholic fatty liver disease fibrosis score; FIB-4: fibrosis-4 index; US/MR: Ultrasound/ Magnetic resonance. * see European guideline. Data according to [8].

(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 [1, 5].

Diagnostics

NAFLD is currently diagnosed by ultrasound examination, proton magnetic resonance spectroscopy 1H-MRS and MR imaging (MRI) ▶ **Fig. 1** 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 (▶ **Tab. 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 aminotransferase (AST), special tests are available which are primarily used for diagnosing fibrosis stages 3 and 4 [5, 7–9] although their accuracy seems to be lower, especially in diabetes mellitus [10].

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 % [11]. 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 [12]. In NAFLD, hepatocellular carcinoma can also develop directly from NAFL without having had NASH [1].

▶ **Tab. 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)	Body mass index (BMI) Waist circumference Gamma-glutamyltransferase (GGT) Fasting triglycerides	• Widely available • Inexpensive	• Low sensitivity and specificity at lipid content < 25 %.
Indices for fibrosis (non-commercial: NAFLD-FS, FIB-4 Commercial score: ELF, FibroTest, FibroMeter)	Formulas using the following parameters: • Age, • BMI, • Fasting blood glucose, • Diabetes diagnosis, • Glutamyl oxaloacetic transaminase (Aspartate aminotransferase), • Glutamyl pyruvic transaminase (Alanine aminotransferase), • 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

People with NAFLD have a 2–6 times higher risk of type 2 diabetes and/or cardiovascular disease [12]. 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 [1], is of utmost importance to above all diagnose and prevent diabetes-related and 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 (▶ **Tab. 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 [5].

Bariatric surgery for pronounced obesity or moderate obesity and type 2 diabetes causes a pronounced 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 [5]. However, recently in the SPLENDOR study, among patients with NASH and obesity, bariatric surgery was associated with lower risk of adverse liver outcomes and major adverse cardiovascular events, compared to nonsurgical management [13].

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 pioglitazone if there are no associat-

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

Entervention	Effects on the liver	Systemic effects
Lifestyle	Steatosis: ↓ ↓ ↓	Blood glucose: ↓ ↓
	Inflammation: ↓ ↓	Insulin resistance: ↓ ↓
	Fibrosis: ↓ or =	Dyslipidaemia: ↓
		Weight: ↓
Bariatric surgery	Steatosis: ↓ ↓ ↓	Blood glucose: ↓ ↓ ↓
	Inflammation: ↓ ?	Insulin resistance: ↓ ↓ ↓
	Fibrosis: ?	Dyslipidaemia: ↓
		Weight: ↓ ↓ ↓
Pioglitazone	Steatosis: ↓ ↓ ↓	Blood glucose: ↓ ↓
	Inflammation: ↓ ↓	Insulin resistance: ↓ ↓ ↓
	Fibrosis: ↓ or =	Dyslipidaemia: ↓ ↓
		Weight: ↑
Glucagon-like peptide-1 (GLP-1) analogues	Steatosis: ↓ ↓	Blood glucose: ↓ ↓
	Inflammation: ↓	Insulin resistance: ↓ ↓
	Fibrosis: =	Dyslipidaemia: ↓
		Weight: ↓
Sodium-glucose co-transporter-2 (SGLT2) inhibitors	Steatosis: ↓	Blood glucose: ↓ ↓
	Inflammation: ?	Insulin resistance: ↓
	Fibrosis: ?	Dyslipidaemia: =
		Weight: ↓

ed contraindications (heart failure, history of bladder carcinoma, increased risk of bone fractures) [5, 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 (1.8 mg/day) and semaglutide (at daily doses of either 0.1 mg, 0.2 mg or 0.4 mg) and SGLT-2 inhibitors (SGLT-2: sodium-dependent glucose transporter 2) can reduce the liver lipid content and improve NASH in NAFLD and type 2 diabetes. All other pharmacological therapies for type 2 diabetes have so far shown no clinically-relevant effects on the course of NAFLD [5, 14].

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, 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

N. S. has participated in Scientific Advisory Boards of Allergan, Intercept Pharma, MSD, Pfizer, Novo Nordisk, Gilead, Genkyotex, Astra-Zeneca, Boehringer Ingelheim, Sanofi, and clinical trials of AstraZeneca, Boehringer Ingelheim, Sanofi, DSM Nutritional Products and Roche Diagnostics. M. R. has participated on Scientific Advisory Boards of BMS, Boehringer Ingelheim Pharma, Eli Lilly, Fishawack Group, Gilead Sci., Novo Nordisk, Poxel S.A. Sociéte, Prosciento Inc., Sanofi, Servier Lab., Target Pharmasolutions, Terra Firma and in clinical trials of Astra Zeneca, Boehringer Ingelheim, Nutricia/Danone and Novartis.

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