Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2025-B-036 Resmetirom

Stand: April 2025

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Resmetirom
zur Behandlung der metabolischen Dysfunktion-assoziierten Steatohepatitis (MASH)

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Resmetirom	<u>Geplantes Anwendungsgebiet laut Beratungsanforderung:</u> „Zur Behandlung von Erwachsenen mit nicht-zirrhotischer metabolischer Dysfunktion-assoziierter Steatohepatitis (MASH) und moderater bis fortgeschrittener Leberfibrose (entsprechend den Fibrosestadien F2 und F3).“
-	*- keine zugelassenen Arzneimittel*

Quellen: AMIce-Datenbank

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2025-B-036 (Resmetirom)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	25. März 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ECRI	Emergency Care Research Institute
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
KI	Konfidenzintervall
LoE	Level of Evidence
MASH	metabolische Dysfunktion-assoziierte Steatohepatitis
MASLD	metabolic dysfunction-associated steatotic liver disease
NAFLD	non-alcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NICE	National Institute for Health and Care Excellence
OCA	Obeticholic acid
OR	Odds Ratio
RoB	Risk of Bias
ROBINS-I	Risk of Bias in Non-randomized Studies - of Interventions
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
T2DM	Diabetes mellitus Typ 2
TRIP	Turn Research into Practice Database
UDCA	Ursodeoxycholic acid
WHO	World Health Organization

1 Indikation

Behandlung von Erwachsenen mit nicht-zirrhotischer metabolischer Dysfunktion-assoziierter Steatohepatitis (MASH).

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *metabolischer Dysfunktion-assoziierte Steatohepatitis (MASH)* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 26.02.2025 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 1980 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. *Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet.* Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet.

Basierend darauf, wurden insgesamt 3 Referenzen eingeschlossen.

Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es konnten keine Cochrane Reviews im Anwendungsgebiet identifiziert werden.

3.2 Systematische Reviews

Es konnten keine systematischen Reviews im Anwendungsgebiet identifiziert werden.

3.3 Leitlinien

European Association for the Study of the Liver et al., 2024 [3].

European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO), EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD)

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium. Patientenbeteiligung unklar.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt, aber nicht beschrieben, wie im Entscheidungsprozess damit umgegangen wurde.
- Systematische Suche, Auswahl und Bewertung der Evidenz.
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt.
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- a systematic review of the literature was conducted on the most important scientific databases (PubMed, Scopus, Embase, Google Scholar) by performing a free-text search.

LoE

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic Reviews (SR) (with homogeneity) of randomised controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	Randomised controlled trials (RCT) or observational studies with dramatic effects; Systematic Reviews (SR) of lower quality studies (i.e. non-randomised, retrospective)	
3	Non-randomised controlled cohort/follow-up study/control arm of randomised trial (systematic review is generally better than an individual study)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain

*Level may be graded down based on study quality, imprecision, indirectness (study does not match questions), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

GoR

Table 1. Grades of recommendation

Grade	Wording	Criteria
Strong	Must, shall, should, is recommended Shall not, should not, is not recommended	Evidence, consistency of studies, risk-benefit ratio, individual preferences, ethical obligations, feasibility
Weak or open	Can, may, is suggested May not, is not suggested	

Treatment of MASLD: Non-Pharmacological Therapy

In adults with MASLD, what is the efficacy of dietary and behavioural therapy-induced weight loss on histologically/non-invasively assessed liver damage/ fibrosis and liver-related outcomes compared with no intervention?

- In adults with MASLD, dietary and behavioural therapy induced weight loss should be recommended to improve liver injury, as assessed histologically or non-invasively (LoE 1, strong recommendation, strong consensus).
- In adults with MASLD and overweight, dietary and behavioural therapy-induced weight loss should aim at a sustained reduction of ≥5% to reduce liver fat, 7-10% to improve liver inflammation, and ≥10% to improve fibrosis (LoE 2, strong recommendation, strong consensus).

Hintergrund

It has repeatedly been demonstrated in clinical trials that weight reduction achieved by caloric restriction, either with or without increased physical activity, leads to improvements in MASLD biomarkers, including liver enzymes, steatosis, MASH, and fibrosis [293–295] (Fig. 3). There is a dose-dependent association between the amount of weight loss and the extent of improvement in biomarkers of liver damage [294]. However, evidence for an effect of weight reduction by lifestyle modification on advanced fibrosis or cirrhosis is insufficient, owing to the minority of individuals with advanced fibrosis in most clinical trials and the lack of subgroup analyses [296]. A stringent interventional trial with histological endpoints suggested a bodyweight reduction of ≥5% is required to reduce liver lipid content, 7-10% to improve inflammation, and ≥10% to improve fibrosis [296]. However, a limited proportion of individuals achieve a weight reduction of ≥5% [296, 297]. In addition, long-term adherence to behavioural changes is often insufficient, as seen in obesity trials [298]. There is limited data on long term dietary interventions in MASLD since study durations range from 2-24 months [299–301]. Only a few studies have performed 12-24-month follow-ups, showing a maximal weight loss at 6 months, followed by a gradual weight regain to a net weight loss of about 5% at 12-24 months and partial regain of liver lipid content and stiffness [302–304]. These data emphasise the importance of accessible and affordable long-term structured lifestyle modification programmes, including diet, physical activity, and behavioural therapy, for individuals with MASLD, and highlight the need for longer-term (≥2 years) RCTs on lifestyle interventions.

There are multiple beneficial dietary approaches to lose weight and improve MASLD. Hypocaloric low-carbohydrate diets and low-fat diets appear to be similarly effective in reducing liver lipid content and related biomarkers [305, 306]. However, the Mediterranean diet seems to have added value for liver lipid reduction and cardiometabolic health and may be easier to maintain in the long-term [301, 303]. There is currently insufficient evidence on the efficacy or safety of very low carbohydrate ketogenic diets – characterised by extreme carbohydrate restriction to <20-50 g/day (10-25% of total calories) and high fat and protein contents – in individuals with MASLD [307], taking into consideration potential cardiovascular, kidney and other side effects [308]. Time-restricted eating, also called intermittent fasting, is a new dietary strategy in which calories are consumed in a defined time window [309]. There is currently very little evidence for a beneficial effect of time-restricted eating over regular caloric restriction on hepatic lipid content in individuals with MASLD [299, 304, 310]. The long-term adherence can be improved by taking into account the individual's preferences, clinical, cultural, and economic characteristics. In a Cochrane systematic review of

RCTs in people with MASLD, with follow-up periods of 2–24 months, data were sparse regarding the effects of lifestyle interventions on any clinical outcome (death, liver-related complications, and liver cancer) [311]. Long-term, large RCTs are needed to test the effect of lifestyle interventions on clinical outcomes.

Treatment of MASLD: Pharmacological Therapy

In adults with MASH, is there sufficient evidence to recommend prescription of existing non-glucose lowering drugs to reduce histologically/non-invasively assessed liver damage/fibrosis and liver-related outcomes compared to no pharmacological intervention?

- If approved locally and dependent on the label, adults with non-cirrhotic MASH with significant liver fibrosis (stage ≥2) should be considered for treatment with resmetirom as a MASH-targeted therapy, as this treatment demonstrated histological efficacy on steatohepatitis and fibrosis in a large phase III registrational trial with an acceptable safety and tolerability profile (LoE 2, strong recommendation, consensus).
- Treatment with resmetirom, if approved locally, may be considered for individuals with MASLD who are non-cirrhotic and with documentation of either: (A) advanced fibrosis; (B) at-risk steatohepatitis with significant fibrosis (by liver biopsy, when available, or by non-invasive panels validated for that purpose); or (C) risk of adverse liver-related outcomes (e.g., by elastography- or biomarker-defined thresholds) (LoE 3, open recommendation, consensus).
- No MASH-targeted pharmacotherapy can currently be recommended for adults with MASH at the cirrhotic stage (LoE 5, weak recommendation, strong consensus).
- Given the lack of robust demonstration of histological efficacy on steatohepatitis and liver fibrosis derived from large phase III trials and potential long-term risks, vitamin E cannot be recommended as a MASH-targeted therapy (LoE 2, weak recommendation, strong consensus).
- Statement: For individuals with MASLD undergoing therapy with resmetirom, data on sustainability of histological benefits, individual prediction of response, liver-related outcomes and long-term safety are not currently available (LoE 5, strong consensus).

Hintergrund

Liver-Directed Thyroid Hormone Receptor Agonists The incidence of clinical and subclinical hypothyroidism appears to be higher in individuals with MASLD or MASH relative to age-matched controls, and low thyroid function is associated with more severe outcomes [361, 362]. Thyroid hormones reduce hepatic steatosis by stimulating hepatic lipophagy and mitochondrial biogenesis, and by inhibiting hepatic lipogenesis. They can also interfere with fibrogenesis by inhibiting TGF-β signalling [363, 364]. Thyromimetics that are selective for the β subtype (liver expressed) of the thyroid hormone receptor have been evaluated as a treatment for MASH. Resmetirom is an orally active, liver-directed, thyroid hormone receptor agonist with high selectivity for the β1 receptor [365]. Results of a registrational, phase III trial of resmetirom in individuals with non-cirrhotic MASH (mostly fibrosis stages 2 and 3) of 1 year duration have been reported [366]. In the US, this led to the accelerated approval of resmetirom in March 2024. Resmetirom performed better than placebo as it improved both disease activity (resolution of steatohepatitis) and fibrosis. Progression of fibrosis in individuals with stage 2 fibrosis was lower than in the placebo arm. Liver enzymes and serum lipids were also significantly reduced while the effects on glycaemic control and body weight were neutral. Side effects were mostly gastrointestinal with good overall safety and tolerability. Predictive criteria of response and optimal duration of therapy are currently unknown. The phase III trial is continuing to determine if longer treatment results in improved clinical outcomes [367], including preventing the progression to cirrhosis. A trial exploring clinical outcomes in a cirrhotic population is also ongoing.

The MAESTRO-NASH phase III registrational trial of resmetirom included individuals with at-risk MASH defined histologically by active steatohepatitis (NAS ≥4) and significant fibrosis (stage 2 or 3). While individuals selected for pharmacotherapy would ideally fit the same histological profile as

those included in the registrational trial(s), it is anticipated that liver biopsy will be used sparingly in clinical practice, and a liver biopsy is not required by the drug label in the US. Therefore alternative non-invasive panels with high predictive value validated for the detection of at-risk MASH (e.g. NIS2+ [179, 368, 369], FAST [169, 370], or MRI-based panels [168, 170, 173, 371, 372]) or those with well-validated thresholds to define risk of advanced fibrosis or liver-related outcomes (e.g. VCTE-LSM ≥10 kPa [174, 191], MRE ≥5 kPa [178, 373], or ELF ≥9.8 [177, 374, 375]) could play an important role in selecting individuals for pharmacotherapy (Table 6], as long as thresholds for a high likelihood of cirrhosis are not met. Notably, resmetirom significantly improved MRI-PDFF and liver stiffness measurements in the MAESTRO-NAFLD phase III trial that did not require a liver biopsy for study inclusion [376].

In the US, resmetirom is given at a daily dose of 80 mg in individuals with a body weight <100 kg and at 100 mg in those with a body weight ≥100 kg (dose reduction is advised with concomitant use of moderate CYP2C8 inhibitors such as clopidogrel). At these doses, the most common side effects were diarrhoea (up to 33%), nausea (up to 22%), pruritus (up to 11%) and vomiting (up to 11%) [366]. Individuals receiving resmetirom should be monitored for gastrointestinal side effects and thyroid hormone function. Circulating sex hormone-binding globulin (SHGB) levels have been suggested as a surrogate for target engagement.

Importantly, evidence is currently limited to 52-week histological outcome data. This raises uncertainty as to whether responses will be sustained in the long-term. Similarly, there is currently no evidence to provide confident guidance on when to stop treatment, particularly considering that about 70-80 % of participants did not respond to treatment according to histological criteria. In the MAESTRO-NASH trial, a ≥30 % reduction in hepatic lipid content by MRI-PDFF and a 120% increase in SHGB were associated with a positive treatment response [366]. Linked to the lack of long-term data, there is uncertainty regarding long-term safety and effectiveness of resmetirom. Particularly the effects on the pituitary-thyroid hormone axis and increases in SHGB levels warrant close monitoring for thyroid, gonadal or bone disease [377].

Many individuals who may be eligible for treatment with resmetirom will already be receiving other pharmacological treatments, e.g. GLP1RA, which raises the question of how to integrate resmetirom into combination treatments. About 14% of participants in the MAESTRO-NASH trial were on GLP1RA treatment, with stable dosage in the 6 months and stable body weight in the 3 months preceding screening liver biopsy [366]. Therefore, it appears reasonable to use resmetirom according to the same criteria in individuals already receiving GLP1RA treatment. Given the burden of the disease at current epidemiological estimates and corresponding financial strains on healthcare systems, future cost-effectiveness studies are warranted.

Currently, resmetirom is the only MASH-targeting drug with positive results from a registrational phase III clinical trial. However, considering the expected evolution of MASH-targeted treatment options in coming years [378], recommendations will need to be continuously updated to reflect the latest evidence.

Vitamin E

Vitamin E is a lipid-soluble vitamin acting as a peroxyl radical scavenger with antioxidant, anti-inflammatory, and anti-apoptotic properties. It reduces de novo lipogenesis and therefore contributes to a reduction in liver lipid content. Higher dietary intake of vitamin E, as measured by serum alpha tocopherol levels, was associated with reduced mortality from several chronic conditions (cardiovascular diseases, stroke, cancer) [379, 380], suggesting that current levels of dietary intake are insufficient [380]. Phenome-wide analyses in the general population suggested that increased dietary vitamin E intake protects against MASLD, both clinically and radiologically defined, particularly in individuals with T2D [381]. Nonetheless, the impact of vitamin E supplementation on cardiovascular mortality or prostate cancer is still not settled and clinical intervention studies have shown no benefit [382–384]. For individuals with MASH and bridging fibrosis or cirrhosis, case-control studies have shown that long-term exposure to vitamin E is associated with decreased risk of death, transplant and hepatic decompensation [385]. In the largest RCT to date, vitamin E supplementation (800 IU daily over 2 years) in individuals with non-diabeticMASH resulted in improvement in both steatosis and disease activity, which was corroborated by a reduction in liver enzymes [386]. Smaller studies have suggested reduction in

liver enzymes but there is currently no clear data on fibrosis improvement and no large phase III trial has been performed.

Ursodeoxycholic Acid

Ursodeoxycholic acid (UDCA) is a natural hydrophobic bile acid with wide hepatoprotective effects including antioxidant, immunomodulatory and anti-apoptotic properties. There are three larger, placebo-controlled trials of UDCA in MASH differing in the dose of UDCA used [387–389] and only two of them report histological endpoints [387, 388]. Despite several limitations and methodological differences, there is a strong indication of biochemical efficacy (ALT reduction) and a good safety profile, but no proof of histological efficacy. A synthetic UDCA derivative, 24-norursodeoxycholic acid (norucholic acid), has shown anti-cholestatic, anti-inflammatory and antifibrotic properties in preclinical models [390] and is being tested for MASH with initial results showing improvement in ALT and liver steatosis [391].

Obeticholic Acid

Obeticholic acid (OCA) is an oral, synthetic analogue of chenodeoxycholic acid designed to have a much stronger, nanomolar, potency as a FXR (farnesoid X receptor) agonist than the native bile acid [392]. The drug is approved at a 5 or 10 mg daily dose for secondline therapy in primary biliary cholangitis [393] and was developed for MASH at a higher dose (25 mg daily), based on a phase II placebo-controlled trial showing improvement in fibrosis and liver enzymes after 18 months of treatment [394]. These results were confirmed in a large phase III registrational trial of individuals with MASH and significant fibrosis (cirrhosis excluded) both at the interim analysis of 931 individuals [395] and at a subsequent analysis on 1,607 individuals by a different, consensus, pathologists' panel [396]. At 25 mg daily, OCA achieved both a higher proportion of fibrosis improvement and a lower proportion of worsening than placebo. Despite improved disease activity (hepatocellular ballooning and lobular inflammation) there was no significant difference in resolution of steatohepatitis. Dose-related pruritus and increases in LDL cholesterol are expected class effects of FXR agonists [397, 398] but additional concerns over the risk-benefit ratio (including hepatotoxicity and hepatic events) resulted in a denial of accelerated approval, leading to discontinuation of the clinical outcome phase of the registrational trial and of the development programme in MASH.

Omega-3 Polyunsaturated Fatty Acids

Omega-3 polyunsaturated fatty acids have hepatic anti-inflammatory and insulin-sensitising effects but are decreased in the livers of individuals with MASH [399]. However, supplementation with eicosapentaenoic acid (in ethyl ester formulation) did not show any histological efficacy vs. placebo in RCTs [400, 401]. Studies with icosabutate, a structurally engineered omega 3 fatty acid with distinct intracellular distribution and metabolism [402] are ongoing.

Statins

MASLD induces atherogenic dyslipidaemia and statin therapy is therefore often indicated to prevent cardiovascular events [403]. The safety of statins has been well established in individuals with MASLD [403, 404] with no increased risk of hepatotoxicity [405], yet many individuals with MASLD are undertreated [406]. Casecontrol studies have shown that statin intake is associated with a reduced risk of MASLD, MASH and liver fibrosis [407], as well as a reduction in the risk of hepatic decompensation, mortality and HCC in individuals with cirrhosis [408]. Nonetheless the efficacy of statins, specifically for treating MASH, cannot be established, since there are no large RCTs of statins with histological endpoints. The same holds true for fibrates and ezetimibe. Silymarin (an extract of milk thistle) may improve liver enzymes but the few, small, RCTs available [409, 410] did not document histological improvement.

In adults with MASH, is there sufficient evidence to recommend prescription of existing glucose-lowering drugs to reduce histologically/non-invasively assessed liver damage/fibrosis and liver-related outcomes compared to no pharmacological intervention?

- In the absence of a formal demonstration of histological improvement in large, well conducted, phase III trials, glucagon-like peptide 1 receptor agonists (GLP1RA) cannot currently be recommended as MASH-targeted therapies (LoE 5, strong recommendation, strong consensus).

- GLP1RAs are safe to use in MASH (including compensated cirrhosis) and should be used for their respective indications, namely type 2 diabetes and obesity, as their use improves cardiometabolic outcomes (LoE 2, strong recommendation, strong consensus).
- Where available, pioglitazone is safe to use in adults with non-cirrhotic MASH but given the lack of robust demonstration of histological efficacy on steatohepatitis and liver fibrosis in large phase III trials, pioglitazone cannot be recommended as a MASH-targeted therapy (LoE 2, weak recommendation, consensus).
- There is insufficient evidence to recommend the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors or metformin as MASH-targeted therapies; however, they are safe to use in MASLD and should be used for their respective indications, namely type 2 diabetes, heart failure and chronic kidney disease (LoE 3, strong recommendation, strong consensus).

Statements:

- In case of substantial weight loss induced by GLP1RAs, a hepatic histological benefit could be expected, although this has not been extensively documented so far (LoE 2, strong consensus).
- There is insufficient evidence to support using any other glucose-lowering drug class as MASH-targeted therapies (LoE 5, strong consensus).

Hintergrund

Incretin Mimetics

Glucagon-like peptide-1 receptor agonists (GLP1RAs), single or dual (i.e., glucose-dependent insulinotropic polypeptide [GIP]-GLP1RAs), are approved for the treatment of T2D, with some also approved for obesity (liraglutide, semaglutide, and tirzepatide); these incretin mimetics have shown beneficial effects on cardiovascular and renal outcomes [411]. Their different actions include potentiation of prandial insulin secretion, as well as an inhibition of appetite and increased satiety, mediated both centrally and through reduced gastric motility, which mainly accounts for the weight-loss effects [412]. Other hormones or their analogues potentiate the anorexigenic effects of GLP1 (GIP, glucagon, cagrilintide) or have additional peripheral effects such as increasing lipolysis, lipid oxidation and energy expenditure and are now being developed as dual or triple co-agonists that can induce a similar magnitude of weight loss as bariatric surgery [413]. Some of the studies performed in T2D or obesity documented a reduction in liver enzymes and hepatic lipid content, reinforcing the rationale to test coagonists in MASH [411].

While an initial study with liraglutide indicated a histological benefit in MASH [414], drugs that are being developed for MASH now include semaglutide, and dual GLP1-GIP (e.g. tirzepatide), dual GLP1-glucagon (e.g. cotadutide, survodutide, efinopegdutide) or triple GLP1- GIP-glucagon (e.g. retatrutide) agonists. The largest available trial on semaglutide in MASH (vs. placebo over an 18-month treatment period) demonstrated resolution of steatohepatitis but no fibrosis improvement [415]. A large registrational, phase III study with semaglutide is ongoing. Combining semaglutide with lipogenesis inhibitors may provide additional benefit [416, 417] and such approaches are being tested in larger trials. Histology data are not yet available for the newer dual and triple agonists. Tirzepatide (GLP1-GIP RA) has been shown to significantly reduce both liver and visceral fat in those with T2D, in association with major weight loss (comparable to bariatric surgery) [418], and promising results on steatohepatitis resolution from a phase II study inMASH have been communicated. Dual GLP1-glucagon RAs (cotadutide and efinopegdutide) have also been shown to improve liver steatosis, liver enzymes and indexes of fibrosis in individuals with MASLD [419, 420]. Weight-loss effects of survodutide are promising [421] as are the preliminary histology data from a phase IIb trial [422].

Case-control studies have suggested that exposure to GLP1RAs or SGLT2 inhibitors in people with T2D is associated with a reduction in liver-related outcomes [423, 424] although the only available pilot trial of semaglutide in individuals with cirrhosis did not demonstrate a histological improvement [425].

Sodium-Glucose Co-Transporter-2 Inhibitors

SGLT2 inhibitors are approved for T2D, with some (empagliflozin, dapagliflozin) also approved for chronic kidney disease and heart failure because of their beneficial effect on cardiovascular and renal outcomes [426]. They induce renal glucosuria, weight loss, blood pressure reduction, and protection from major cardiovascular outcomes, including heart failure. The weight loss is due to renal energy loss and reduction in fat mass, with reductions in both visceral and abdominal subcutaneous adipose tissue [427]. Controlled clinical trials with liver histological endpoints are currently not available. Trials in people with T2D (not all with MASLD and some excluding high ALT values) have shown a moderate reduction in liver lipid content

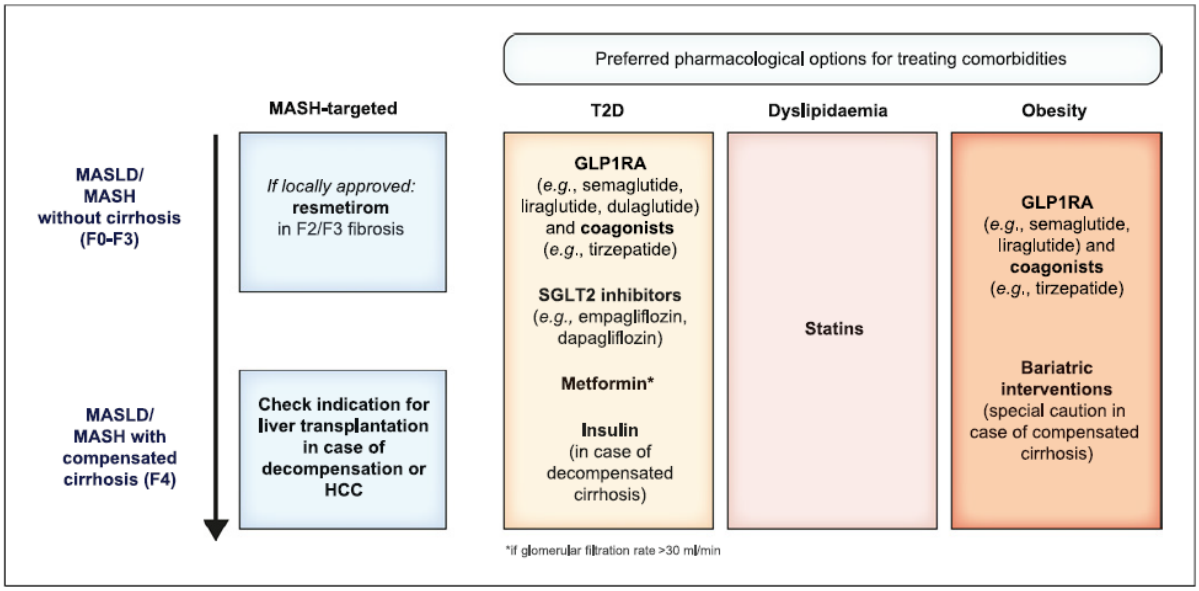
with empagliflozin [428, 429], dapagliflozin [430] and licogliflozin [431]. Reductions in ALT were shown with empagliflozin [428] and licogliflozin
[431].

Peroxisome Proliferator-Activated Receptor Agonists

In several RCTs, pioglitazone, a thiazolidinedione which mainly activates peroxisome proliferator-activated receptor (PPAR)γ, has been shown to improve histological features of steatohepatitis [386, 432–434], without a clear effect on fibrosis regression even after prolonged (3-year) therapy [433]. However, no large, international, phase III trial has been conducted and pioglitazone has been withdrawn from the market in several European countries. The drug has beneficial effects on insulin sensitivity, glycaemic control, serum lipids and prevention of cardiovascular events in individuals with T2D [435, 436] but the side effect profile (weight gain, pedal oedema, haemodilution, bone loss in post-menopausal women and a debate around the risk of bladder cancer) has limited its development for MASH [437]. Pioglitazone R-enantiomers lacking PPARγ activity but retaining non-genomic effects through inhibition of the mitochondrial pyruvate carrier have shown preliminary biochemical and antifibrotic responses with improved side effect profiles [438]. A phase IIb trial showed a dose-dependent histological improvement of steatohepatitis and fibrosis with the pan-PPAR agonist lanifibranor [439], though side effects were reminiscent of PPARγ agonists, namely a 2.5% increase in weight, pedal oedema and mild anaemia. A large egistrational, phase III trial is ongoing. Saroglitazar, a dual PPARα/γ agonist has been shown to improve insulin resistance, liver steatosis and liver enzymes [440] and is approved in India for the treatment of T2D and MASH [441]. Trials with liver histological endpoints are ongoing.

Metformin

Small and uncontrolled initial trials of metformin have shown an ALT reduction and an insulinsensitising effect [442, 443], but were not followed by sufficiently large and well-conducted RCTs. Currently, there is no evidence that metformin alone can improve histology in MASH. As far as clinical outcomes, there is some indication from observational and case-control studies that, in people with T2D and MASLD-related advanced fibrosis or cirrhosis, metformin may improve transplant-free survival (but not the risk of hepatic decompensation), and reduce the risk of primary liver and extrahepatic cancer [444, 445]. Thus, metformin should not be discontinued in those individuals with cirrhosis (unless discontinuation is required due to hepatic decompensation or renal failure), as this could increase mortality [446]. Fig. 4 summarises our recommended choice of pharmacological treatment options in individuals with MASH, depending on comorbidities and stage of disease.



In adults with MASH, is there sufficient evidence to recommend prescription of existing weight-loss agents to reduce histologically/non-invasively assessed liver damage/fibrosis and liver-related outcomes compared to no pharmacological intervention?

- Non-incretin-based weight-loss agents are not recommended as MASH-targeted therapies (LoE 5, strong recommendation, strong consensus).

Hintergund

Controlled trials (with histological endpoints or liverrelated outcomes) of weight-loss agents other than incretin hormone analogues [447] (e.g., orlistat, phenterminetopiramate, naltrexone-bupropion) have either not been performed or have been inconclusive [448].

Treatment of MASLD: Surgical and Endoscopic Therapy

In adults with MASLD and obesity, are bariatric/metabolic surgery procedures or endoscopic weightloss interventions effective to reduce histologically/ non-invasively assessed liver damage and liver-related outcomes compared with no intervention?

- In adults with non-cirrhotic MASLD who have an approved indication, bariatric surgery should be considered, because it can induce long-term beneficial effects on the liver and is associated with remission of type 2 diabetes and improvement of cardiometabolic risk factors (LoE 3, strong recommendation, strong consensus).
- In adults with MASLD-related compensated advanced chronic liver disease/compensated cirrhosis who have an approved indication, bariatric surgery can be considered but careful evaluation (indication, type of surgery, presence of clinically significant portal hypertension) by a multidisciplinary team with experience in bariatric surgery in this particular population is required (LoE 4, weak recommendation, strong consensus).
- Metabolic/bariatric endoscopic procedures require further validation as MASH-targeted therapy and cannot currently be recommended (LoE 4, weak recommendation, strong consensus).

Hintergund

The most common bariatric surgery procedures include purely gastric components like gastric banding (either adjustable or nonadjustable), sleeve gastrectomy and vertical banded gastroplasty, or techniques that divert gastric content distally into the small intestine (gastric with diversion) like Roux-en-Y gastric bypass, biliopancreatic diversion or one anastomosis gastric bypass. Indications for bariatric surgery are BMI ≥40 kg/m2, or BMI ≥35–40 kg/m2 in the presence of associated comorbidities, or BMI ≥30–35 kg/m2 if people have T2D and/or hypertension with poor control despite optimal medical therapy [449]. In the Asian population, the threshold is lower since clinical obesity is recognised in individuals with BMI >25 kg/m2 [41].

Many prospective studies have shown that bariatric surgery induces stable weight loss, remission of T2D [450], improvement in cardiovascular risk [451], and a reduction in cancer (including liver cancer) risk [452]. In line with data from prospective studies, the large retrospective SPLENDOR study found significantly lower rates of adverse liver-related outcomes and major adverse cardiovascular events in individuals who underwent metabolic surgery compared to non-surgical controls [453]. Two meta-analyses that included more than 30 studies and enrolled more than 3,700 individuals with MASLD/MASH undergoing bariatric surgery showed that Roux-en-Y gastric bypass was associated with the most individuals achieving improvement in steatohepatitis, and had a greater impact on MASLD histology compared with other procedures [454, 455]. Roux-en-Y gastric bypass improved or resolved liver fibrosis in 30% of individuals [454]. Interestingly, the percentage of individuals with improved steatosis and hepatic fibrosis was higher in Asian countries [455]. However, in a study with control biopsies after surgery, advanced fibrosis (bridging fibrosis or cirrhosis) persisted in 47% of individuals sometimes even 5 years or more post-surgery and despite significant weight loss [456]. A better understanding of weight loss-dependent and -independent effects on hepatic fibrosis is warranted.

In an observational study, MASH was resolved in 84% of 180 individuals with class 2 obesity and MASH 5 years after Roux-en-Y gastric bypass (66%), sleeve gastrectomy (12%) or gastric banding (22%) [457]. The BRAVES multicentre, open-label, randomised study demonstrated histological resolution of MASH without worsening of fibrosis in 55% of those assigned to Roux-en-Y gastric bypass or sleeve gastrectomy at 1-year follow-up vs. 15% in the lifestyle modification group in the intention-totreat analysis [458]. In this open-label RCT, fibrosis improvement by ≥1 stage without worsening of MASH after 1 year was achieved in 37% and 39% of patients after Roux-en-Y gastric bypass and sleeve gastrectomy, respectively, vs. 23% after lifestyle modification. However, the majority of study participants had mild fibrosis [458]. In this RCT, about 6% of participants had severe adverse events related to surgery [458]. Endoscopic bariatric/ metabolic therapies for weight loss are more affordable and associated with a lower risk of complications. These endoscopic procedures include intragastric balloon, endoscopic sleeve gastroplasty, aspiration device, transpyloric shuttle, Botox injection, duodenal jejunal bypass liner, duodenal mucosa resurfacing,

incisionless magnetic anastomosis system, and primary obesity surgery endoluminal. A meta-analysis that included 33 studies with 1,710 individuals reporting liver-related endpoints (e.g., NITs, liver fibrosis, steatosis) showed a significant improvement in parameters related to liver steatosis and fibrosis with various endoscopic bariatric therapies [459]. However, most included studies were retrospective, with few histology data.

End-Stage Liver Disease and Liver Transplantation

In adults with MASH-related cirrhosis, should dietary and lifestyle recommendations be adapted to the severity of liver disease, nutritional status, and sarcopenia?

- In adults with MASH cirrhosis, it is recommended that dietary and lifestyle recommendations be adapted to the severity of liver disease, nutritional status and the presence of sarcopenia/sarcopenic obesity (LoE 2, strong recommendation, strong consensus).
- In adults with sarcopenia, sarcopenic obesity or decompensated cirrhosis, it is recommended that a highprotein diet is provided, as well as a late-evening snack. (LoE 2, strong recommendation, consensus).
- Moderate weight reduction can be suggested in adults with compensated cirrhosis and obesity, with an emphasis on high protein intake and physical activity to maintain muscle mass and reduce the risk of sarcopenia (LoE 3, weak recommendation, strong consensus).

Hintergrund

Among individuals with cirrhosis awaiting liver transplantation, malnutrition and sarcopenia (a progressive decline in skeletal muscle mass and function [460]) are prevalent. Sarcopenia affects 50-60% of individuals [461] and is associated with higher rates of wait-list complications, morbidity, and mortality [462, 463]. Sarcopenic obesity, the state of decreased muscle mass in the setting of increased fat mass, occurs mainly in MASH-related cirrhosis and is found in 20–35% of individuals with cirrhosis pre-and-post liver transplant [460, 464].Obesity and sarcopenic obesity are risk factors for clinical decompensation and worsen prognosis [45, 464]. Evaluation for sarcopenia includes the skeletal muscle index or psoas muscle area at the third lumbar vertebra, if a CT scan has been performed, and the measurement of frailty using tools like hand grip or liver frailty index and other diagnostic procedures summarised in the joint European Society for Clinical Nutrition and Metabolism (ESPEN)-EASO consensus statement [465].

Nutritional intervention improves nutritional status, hepatic encephalopathy, survival, and quality of life in people with cirrhosis [466, 467]. In an RCT among individuals with decompensated cirrhosis, a 6- month dietitian-supported home-based intensive high-calorie, protein-rich nutrition therapy was associated with improvement in frailty, sarcopenia and, among treatment-adherent individuals, liver disease scores and survival [468]. The EASL CPGs on nutrition in chronic liver disease provide a comprehensive review of the recommended nutritional intake in individuals with cirrhosis [463]. The approach of the majority of nutritional interventions in cirrhosis is to supply at least 35 kcal/kg of body weight/day, with a daily recommended protein intake of 1.2–1.5 g/kg of body weight/day (sufficiently rich in branched-chain amino acids) to prevent or reverse muscle mass loss [460, 461, 463] (Table 10). In individuals with compensated cirrhosis and obesity, a reduction in body weight through lifestyle interventions, including moderate caloric restriction and supervised moderateintensity physical exercise, has been shown to reduce portal pressure and may prevent clinical decompensation [45, 469]. For individuals with cirrhosis and obesity, weight-loss interventions require special attention to avoid sarcopenia [470].

To prevent accelerated starvation and the related proteolysis, there is a need to shorten fasting intervals between meals by eating every 4-6 hours and having a late-evening snack [463]. A late-evening snack containing complex carbohydrates and protein reduces lipid oxidation, improves nitrogen balance, reduces skeletal muscle proteolysis, increases muscle mass, reduces hepatic encephalopathy and improves quality of life [471, 472].

Physical activity and exercise are anabolic stimuli that can improve muscle mass and function. Consistent benefits of exercise demonstrated in RCTs include reversal of sarcopenia and improvements in aerobic capacity, muscle mass and strength, performance measures, health-related quality of life and hepatic venous pressure gradient [473, 474].

In adults with MASH-related cirrhosis, how should pharmacologic interventions for diabetes and lipid control or cardiovascular prevention be adapted to the severity of the liver condition?

- Metformin can be used in adults with compensated cirrhosis and preserved renal function but should not be used in adults with decompensated cirrhosis, especially when there is concomitant renal impairment, because of the risk of lactic acidosis (LoE 3, strong recommendation, strong consensus).
- Sulfonylureas should be avoided in adults with hepatic decompensation because of the risk of hypoglycaemia (LoE 4, weak recommendation, strong consensus).
- GLP1 receptor agonists can be used in adults with Child-Pugh class A cirrhosis, according to its indication (LoE 2, weak recommendation, strong consensus).
- SGLT2 inhibitors can be used in adults with Child- Pugh class A and B cirrhosis (LoE 4, weak recommendation, consensus).
- Statins can be used in adults with chronic liver disease, including those with compensated cirrhosis; they should be used in adults according to cardiovascular risk guidelines to reduce cardiovascular events (LoE 1, strong recommendation, strong consensus).

Hintergund

Metformin improves ALT but not histological steatosis, inflammation and fibrosis in individuals with MASLD [475]. However, observational data suggest a potential protective effect against HCC [476, 477]. Metformin may cause lactic acidosis through impairment of oxidative phosphorylation [478]. The risk of metformin-associated lactic acidosis is increased in individuals with renal impairment and hepatic decompensation, especially when both are present [479].

The risk of sulfonylurea-induced hypoglycaemia is increased in individuals with advanced liver disease. Gliclazide has significant hepatic metabolism. Hepatotoxicity has also been reported for glibenclamide and is rarely seen with gliclazide [480, 481].

SGLT2 inhibitors increase glycosuria. Apart from an improvement in blood glucose, they reduce bodyweight and blood pressure, and have been shown to have beneficial cardiovascular effects, prevent progression of renal disease, and potentially even improve ALT and MRI-measured intrahepatic triglyceride content [482]. Drug exposure to empagliflozin and dapagliflozin increased by 67-75% in individuals with Child-Pugh class C cirrhosis. Drug exposure to canagliflozin increased by 96-111% in individuals with Child-Pugh class B cirrhosis, and the drug has not been studied in individuals with Child- Pugh class C cirrhosis. SGLT2 inhibitors should be used with caution or avoided in people with severe renal impairment.

Data on the use of GLP1RAs in advanced liver disease are limited. In a small RCT of 71 participants with compensated MASH-related cirrhosis, semaglutide at a dose of 2.4 mg weekly was well tolerated and improved steatosis, liver enzymes, bodyweight and HbA1c [425]. Future studies should also scrutinise the impact of GLP1RAs on adipose tissue and skeletal muscle mass, especially as sarcopenia is a risk factor for mortality in individuals with cirrhosis.

Statins are important treatments to prevent cardiovascular events. Multiple observational studies suggest a benefit of statins on the prevention of HCC and/or cirrhotic complications [483]. ALT elevation may be observed in up to 3% of individuals during statin treatment, but severe liver injury is rare, and liver fibrosis progression has not been observed [484]. There are few studies on the use of statins in individuals with decompensated cirrhosis. One RCT testing simvastatin in individuals with variceal haemorrhage failed to show an impact on rebleeding and suggested an improvement in overall survival, and the drug was safe in this high-risk population [485]. However, using high-dose statins in decompensated cirrhosis confers an increased risk of severe adverse events. In a multicentre European clinical trial in individuals with Child-Pugh class B or C cirrhosis, 19% of those receiving simvastatin 40 mg daily developed liver toxicity and rhabdomyolysis [486].

AISF, SID, SIO, 2022 [1].

Associazione Italiana per lo Studio del Fegato (AISF), Società Italiana di Diabetologia (SID) and Società Italiana dell'Obesità(SIO)

Non-alcoholic fatty liver disease in adults 2021: a clinical practice guideline of the Italian Association for the Study of the Liver (AISF), the Italian Society of Diabetology (SID) and the Italian Society of Obesity (SIO)

Zielsetzung/Fragestellung

The present report is a summary of Clinical Practice Guidelines resulting from a cooperative work of the Associazione Italiana per lo Studio del Fegato (AISF), the Società Italiana di Diabetologia (SID) and the Società Italiana dell'Obesità(SIO). Current knowledge on the diagnosis and treatment of non-alcoholic fatty liver disease (NAFLD) is translated into relevant practical recommendations for management following the rules and the methodology suggested in Italy by the Centro Nazionale per l'Eccellenza delle cure (CNEC) and Istituto Superiore di Sanità (ISS).

Methodik

Grundlage der Leitlinie

The present document was made according to the rules dictated by the Italian Center for the Cure Excellence (Centro Nazionale per l'Eccellenza delle Cure - CNEC), an institution recently set up by the Italian National Institute of Health (Istituto Superiore di Sanità- ISS) to outline the methodologies needed to provide evidence-based clinical, diagnostic and therapeutic guidelines in Italy.

- Repräsentatives Gremium; trifft zu
- Interessenkonflikte und finanzielle Unabhängigkeit trifft teilweise zu
- Systematische Suche, Auswahl und Bewertung der Evidenz trifft zu
- Formale Konsensusprozesse und externes Begutachtungsverfahren sind dargelegt
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; trifft teilweise zu (das RoB assessment für einzelne Studien ist nicht dargestellt und eine Verknüpfung zum Evidenzgrad geht aus den Hintergrundinformationen nicht eindeutig hervor)
- Regelmäßige Überprüfung der Aktualität ist unklar

Recherche/Suchzeitraum:

- Recherchedatum unklar, PubMed, Embase, Scopus

LoE

- Revised tool for Risk of Bias in randomized trials (Cochrane RoB 2)
- "Risk of Bias in Non-randomized Studies - of Interventions" tool (ROBINS-I)

GoR

- GRADE und GRADE-Evidence to Decision (EtD) framework

Empfehlungen

Weight loss and behavioral intervention for NAFLD

PICO 5 - In adult patients with NAFLD, what is the efficacy of weight loss on histologically-assessed liver damage and liver-related outcomes in comparison with no intervention?

Recommendations:

- All subjects with NAFLD, including lean (non-obese) NAFLD, should be involved in lifestyle programs aimed at healthy diet and habitual physical activity to a ≥7–10% weight loss target, repeatedly associated with improved histology, including fibrosis (*B*, 1).
- The dietary approach to NAFLD should favor adherence to the principles of the Mediterranean diet, including a reduced intake of refined and industrial sugars, associated with reduced hepatic fat content and decreased cardiovascular risk (*B*, 1).
- Low-modest alcohol intake in noncirrhotic NAFLD patients should not be encouraged (C, 2) and total abstinence in NAFLD-cirrhosis is recommended (B, 1).
- In patients with NAFLD, any types of physical activity, as well as reduced sedentariness, should be counseled, in order to reduce liver fat, independently of changes in body weight (*B*, 1).
- Clinicians should recommend weight loss by intensive, structured lifestyle programs delivered under specialist control and/or pharmacotherapy and/or bariatric surgery in NAFLD subjects with obesity to reduce liver disease severity (*A*, 1).

Hintergrundinformation zu PICO 5

Weight loss by appropriate behavioral intervention (dietary restriction and physical activity) improves fatty liver [133-138]. At histology, the severity of necroinflammation (NAS score) is reduced and 10% weight loss is also associated with reduced fibrosis (139, 140). Similarly, GLP-1 receptor agonists currently used for pharmacotherapy of obesity have demonstrated favorable effects on NAFLD histology [141]

Behavioral changes aimed at weight loss, including healthy diet and habitual physical activity, are thus the backbone of NAFLD treatment. This evidence relies on very few controlled studies [134, 142], but several real-world data and systematic reviews of cohort studies testing different outcomes [138,143-146]. Considering the pathogenic role of overweight/obesity, any attempt to reduce body weight by calorie restriction provides potential beneficial effects on steatosis, also extending to necroinflammation and fibrosis [138]. Sequential biopsy studies pointed out that a 7-10% weight loss in 12 months produced NASH resolution in two thirds of cases; a weight loss >10% resolved NASH in 90% of cases and reduced fibrosis in 45% of cases [140]. Notably, these effects were also observed in lean NAFLD, i.e., in the absence of obesity [142, 147].

The macronutrient composition of the diet was associated with NAFLD prevalence in epidemiological studies [148]. Conversely, the adherence to a diet based on Mediterranean style, rich in olive oil, nuts, legumes, fruit and vegetables, and fish reduced hepatic fat content [149] and the effect was independent of reduced body weight/reduced visceral adiposity [150]. This beneficial dietary pattern was relatively abundant in monounsaturated fats, and poor in refined carbohydrates and industrial sugars, implicated in NAFLD prevalence and progression [151].

Reduced physical activity [152] and sedentariness [153] were both independently associated with NAFLD prevalence, and any change in energy expenditure by moderate-intensity physical activity reduced liver fat [154]. Any type of physical exercise (aerobic vs. resistance training [155] was effective [156] also in the absence of significant weight loss.

Contrasting results are available about the impact of nonheavy drinking and NAFLD. A meta-analysis suggested that low alcohol intake was protective against steatosis (157) and cross-sectional studies reported a lower prevalence of NASH and fibrosis in modest alcohol users (158). On the contrary, recent prospective studies in NAFLD individuals showed an increased risk of fibrosis progression, tested by noninvasive scores (159, 160), a lower probability of NASH resolution at histology (161), the lack of protective effects on cardiovascular damage, and an increased risk of developing diabetes, advanced liver disease, cancer and mortality [162-165]. All these data, even if biased by the use of different thresholds of alcohol intake, do not support the use of low alcohol dose in NAFLD patients, while recommend total abstinence in NASH-cirrhosis to reduce the HCC risk [166]

An integrated approach coupling healthy diet and physical activity, supported by cognitive restructuring, represents the most challenging treatment for NAFLD, as well as other non-communicable diseases. Following the strategy of the Diabetes Prevention Program [167]), a proof-of-concept trial showed NASH resolution by cognitive-behavioral treatment [134]. The results were extensively confirmed in a large single-arm study of nearly 300 patients undergoing a second biopsy after 12 months [140]. Such approaches require dedicated teams in order to prevent weight regain; long-term studies in the area of diabetes confirmed the difficulties in maintaining weight loss despite intensive treatment [168]. Technology-supported interventions may be used to reinforce patients' motivation and adherence in the long-term [137], but RCT are needed to confirm the effectiveness.
Bariatric surgery constitutes a possible treatment to reduce NASH burden. In the Swedish Obese Subjects (SOS) study, both the incidence of and the remission from high transaminase levels – more favorable in the surgery group – were proportional to the degree of weight loss [169]. Bariatric surgery was associated with a lower risk of complications [170], and repeated liver biopsies revealed a remarkable improvement in histological severity [171], with long-term fibrosis regression [172]. The positive effects of bariatric surgery on the liver adds to the decreased risk of cardiovascular events [173] and T2DM remission [174,175]. A cost/benefit analysis concluded that bariatric (metabolic) surgery was both effective and cost-effective for all F0-F3 NASH patients with grade II/III or complicated obesity [176].

Pharmacologic treatment for NAFLD

PICO 6 - In adult patients with NAFLD, what is the efficacy of pharmacological treatment on histologically-assessed liver damage and liver-related outcomes in comparison with no pharmacological intervention?

Recommendations:

- In patients with NASH pioglitazone may be used to improve NASH and fibrosis, although the drug is off-label and the risk/benefit balance *related to pioglitazone side-effects* should be discussed with each patient (*B*, 2).
- In patients with NASH vitamin E may be used to improve NASH and fibrosis, even if risks and benefits should be discussed with each patient (*B*, 2).
- *In patients with NASH standard or high-dose ursodeoxycholic acid (UDCA) should not be used to treat NASH and fibrosis, because ineffective (B, 2).*
- In patients with NASH obeticholic acid may improve fibrosis without worsening of NASH, but its use is waiting for approval by regulatory agencies, based on additional safety and efficacy data (*B*, 2).

Hintergrundinformation zu PICO 6
[…]. Eight placebo-controlled or active-controlled RCTs used either pioglitazone (n =6) or rosiglitazone (n =2) to treat NAFLD or NASH [179-186] including nearly 850 individuals, most of whom did not have diabetes, who were treated for a median of 12 months. Only one study was undertaken in patients with imaging-defined NAFLD [185] all other RCTs included patients with biopsy-confirmed NAFLD. When compared to placebo or reference therapy, both pioglitazone and rosiglitazone significantly improved liver fat content and even NASH, at the same time reducing liver enzymes. With regard to liver fibrosis, glitazones were superior to placebo or other active molecules in only one RCT on patients with pre-diabetes or diabetes using pioglitazone 45 mg/day for a long period of time (18 months) [186]. A meta-analysis in 516 adults with biopsy-confirmed NASH also showed that pioglitazone improved advanced fibrosis too, both in patients with and without T2DM [187]. A very recent "real world" analysis on 5095 propensity-score paired thiazolidinedione users (also including rosiglitazone) and nonusers found that the adjusted hazard ratios of cirrhosis, hepatic decompensation, hepatic failure and all-cause mortality were 0.39 (95% confidence interval: 0.21-0.72), 0.86 (0.52-1.44), 0.46 (0.18-1.17) and 1.18 (95% CI: 0.87-1.61), respectively, in thiazolidinedione users, which is consistent with a possible protective role on the risk of cirrhosis [188]. In addition, pioglitazone also exerts some CV benefits to decrease risk of incident acute myocardial infarction and ischemic stroke in patients with T2DM or prediabetes [189, 190]. Weight gain is the most common side effect associated with pioglitazone treatment, likely from improved insulin action in adipose tissue and adipocyte tissue remodeling; it ranges from 2.5 to 4.7 kg in RCTs of 12- to 36-month duration [180, 182, 186].

While contrasting results were previously reported about bladder cancer risk and pioglitazone, a recent analysis on more than 190,000 persons with diabetes for up to 16 years did not find any statistically significant association between its use and/or duration of therapy with bladder cancer [191]. Bone loss may occur in women treated with thiazolidinediones [192] and a risk of fracture exists, as well as of congestive heart failure [193]. Finally, a cost-effective analysis demonstrated that in patients with advanced fibrosis due to NASH, pioglitazone treatment in addition to standard lifestyle modification is likely to be cost-effective [194]. It should be noted that pioglitazone is not approved by most national Medicines agencies outside the treatment for T2DM, and its 'off-label' use for NAFLD/NASH treatment requires patients' consent.

Vitamin E at the dose of 800 IU/day for 96 weeks has been tested versus pioglitazone and placebo in the PIVENS trial in nondiabetic patients with noncirrhotic biopsy-proven NASH. Vitamin E improved steatosis, inflammation and ballooning and induced NASH resolution in 36% of patients compared to 21% in the placebo arm (p=0.05), without a significant effect on fibrosis [182]. Vitamin E also lead to a significant improvement in ALT levels compared to placebo [182] and this reduction was correlated with histological improvement [195]. Two meta-analysis pooling data on 183 and 214 adult patients observed a significant effect of vitamin E respect to placebo in improving not only AST and ALT serum levels, but also histological findings including fibrosis [196, 197]. A recent trial on diabetic patients with NAFLD confirmed that 18 months of vitamin E 800 IU per day increase the rate of NASH resolution compared to placebo (33% vs 12%, p=0.04), without any effect of fibrosis [198]. The same trial showed an additional advantage of the combination of vitamin E with pioglitazone. Finally, a propensity score-matched analysis on patients with NASH and bridging fibrosis or cirrhosis showed that 800 IU per day of vitamin E for ≥2 years, during a median follow-up of 5.6 years, lead to a significantly decreased risk of death or transplant (aHR 0.30) and hepatic decompensation (aHR 0.52), and these results were confirmed after stratifying for diabetes [199]. An analysis demonstrated that Vitamin E is likely to be cost-effective in patients with advanced fibrosis related to NAFLD [194]. Concerns about long-term safety of vitamin E exist in terms of reported increase in overall mortality [200] hemorrhagic stroke [201] and prostate cancer in males older than 50 [202].

Ursodeoxycholic acid (UDCA) at standard (13-15 mg/kg) or high (23-35 mg/kg) dose was tested as pharmacological treatment of NASH in several RCTs. Data showed a mild effect on ALT levels but no histological benefit respect to placebo [203-206].

Obeticholic acid (OCA) is an agonist of farnesoid X receptor, a liver nuclear receptor that plays a central role in the regulation of bile acids and metabolism, but also on hepatic fibrosis and inflammation. The 18-month interim analysis of the REGENERATE study, the phase 3 trial investigating OCA treatment (10 and 25 mg/day) versus placebo in patients with biopsy-proven noncirrhotic NASH, showed that OCA 25 mg significantly increased the rate of patients obtaining fibrosis improvement without worsening of NASH compared to placebo (23% vs 12%, p=0.0002)[207]. OCA 25 mg also led to improvement of both lobular inflammation and ballooning, but not met the endpoint of NASH resolution without fibrosis impairment. This phase 3 trial also confirmed the safety concerns raised in the phase 2 trial [208] regarding treatment-associated pruritus and the increase of LDL-cholesterol serum levels, sensitive to statin therapy. To date no data are available about long-term impact of OCA on hepatic and extrahepatic (most cardiovascular) events. Noteworthy, to date the drug is not available for use in NASH, but conditional approval by FDA and EMA will depend on additional post-interim efficacy and safety data [209].

PICO 7 - In adult patients with NAFLD and type 2 diabetes mellitus, what is the efficacy of glucose-lowering treatment on histologically-assessed liver damage and liver-related outcomes?

Recommendations:

- In T2DM patients with NAFLD/NASH, pioglitazone is specifically recommended to treat liver disease (*B*, 2).
- In T2DM patients with NAFLD/NASH, metformin use is safe for the liver, but it is not specifically recommended to treat liver disease (*B*, 2).
- In T2DM patients with NAFLD/NASH, DPP-4 inhibitors are safe for the liver, but their use is not specifically recommended to treat liver disease (*C*, 2).
- In T2DM patients with NAFLD/NASH, GLP-1 receptor agonists are safe for the liver, but, despite preliminary evidence that may decrease liver damage, their use is not specifically approved to treat liver disease (*B*, 2).
- In T2DM patients with NAFLD/NASH, SGLT-2 inhibitors are safe for the liver, but their use is not specifically recommended to treat liver disease (*C*, 2).

Hintergrundinformation zu PICO 7

Pioglitazone

The description of effectiveness and safety of pioglitazone in patients with NASH with/without diabetes is reported in the previous section. It is noteworthy that pioglitazone can be prescribed in patients with diabetes and it can be an option to consider in presence of NASH in selected patients.

Metformin

Metformin represents the first-line choice for T2DM treatment. Six placebo-controlled or active-controlled RCTs with clinically relevant end-points used metformin to treat NAFLD or NASH [185,210-214], with clinically endpoints. Overall, these RCTs enrolled nearly 600 individuals, most of whom did not have diabetes, who were treated for a median of 9 months (inter-quartile range [IQR] 6-12 months). Metformin had a small beneficial effect on liver steatosis and inflammation, but no beneficial effect on liver fibrosis or resolution of NASH [210-213]. In two RCTs involving patients with ultrasound-detected NAFLD, metformin had a neutral effect on liver steatosis, when compared to placebo or reference therapy [185,214]. In most RCTs, metformin significantly improved serum levels of aminotransferases (especially serum ALT levels), with neutral effects on body weight. There is some evidence from observational studies for a possible hepato-protective effect of metformin against the risk of incident HCC in patients with T2DM, although it is unclear whether this outcome is independent of metformin-induced metabolic effects [215]. Future mechanistic studies and appropriately designed RCTs are warranted for confirmation.

Dipeptidyl peptidase-4 inhibitors

DPP-4 inhibitors are broadly prescribed as additional oral treatment for T2DM. Four small placebo-controlled or active-controlled RCTs used either sitagliptin (n=3) or vildagliptin (n=1) to treat NAFLD [216-219]. Overall, these RCTs included nearly 250 individuals with T2DM or prediabetes, treated for a median of 6 months. When compared to placebo or reference therapy, vildagliptin had a marginal significant effect on liver fat [217] whereas sitagliptin did not [216, 218, 219]. When compared to placebo or reference therapy, DPP-4 inhibitors showed a substantial neutral effect on body weight and serum aminotransferase levels, except for vildagliptin that showed a small, although statistically significant, reduction (around 7 IU/L) in ALT levels [217]. DPP-4 inhibitors also have a neutral effect on CV outcomes in patients with T2DM [220], thus making this class of antihyperglycemic agents safe but less attractive for the treatment of NAFLD in patients with T2DM.

Glucagon-like peptide-1 receptor agonists

GLP-1RAs are broadly prescribed as additional therapy in patients with T2DM. Seven placebo-controlled or active-controlled RCTs used either liraglutide (n=5) or exenatide (n=2) to treat NAFLD [141, 219, 221-225]. These RCTs included nearly 2,300 individuals, most of whom had T2DM, treated for a median of 6 months. Only a small phase 2b RCT (LEAN trial) included 52 patients (only 33% with T2DM) with biopsy-confirmed NASH, who were treated with liraglutide 1.8 mg/day for 48 weeks [141] whereas in the others NAFLD was diagnosed either by liver enzymes or by imaging techniques. When compared to placebo or reference therapy, GLP-1RAs (especially liraglutide) significantly improved liver fat and reduced serum

aminotransferase levels in a dose-dependent manner, as well as body weight (3-5 kg) and HbA1c levels (1-1.2%). In a meta-analysis of T2DM patients using patient-level data combined from six 26-week, phase-III RCTs of the LEAD program, liraglutide improved serum ALT levels in a dose dependent manner; however, this beneficial effect was lost after adjusting for liraglutide-associated reduction in body weight and HbA1c levels [221]. In a cardiovascular outcome trial, participants with elevated ALT at baseline treated by 1mg/week semaglutide had a higher probability of ALT normalization, but changes were not significant after adjustment for weight changes [226]. Data on histology have so far been published only in the LEAN trial, where liraglutide failed to produce any significant improvement of liver fibrosis vs. placebo [141], but a phase 2 dose-escalating study of semaglutide, a longer-acting, weekly GLP-1 analogue, has also been completed in 320 NASH patients. After 72 weeks of therapy, 59% of patients with fibrosis F2-F3 met the primary end-point of NASH resolution without worsening of fibrosis with the highest dosage tested (0.4 mg) vs. 40% and 36% at the two lower doses and only 17% in the control arm, but no effects were demonstrated on fibrosis [227]. GLP-1RAs have also been demonstrated to reduce the risk of incident CV and renal outcomes in patients with T2DM [228]. For such reasons, they qualify as preferable treatment option in T2DM patients with NAFLD, but final conclusions on liver disease progression are still pending.

Sodium-glucose cotransporter-2 inhibitors (SGLT-2Is)

SGLT-2Is reduce glucose reabsorption by the kidneys. Nine placebo-controlled or active-controlled RCTs used empagliflozin (n=2), dapagliflozin (n=3), canagliflozin (n=3) or ipragliflozin (n=1) to treat NAFLD [229-237]. Overall, these RCTs included nearly 16,000 individuals with T2DM treated for a median of 6 months. In all RCTs, SGLT-2Is reduced aminotransferase levels and imaging-assessed liver fat, along with a reduction of body weight (~2-3 kg), with the notable exception of a RCT, where treatment with 10-mg dapagliflozin for 24 weeks did not show any significant reduction of liver fat content, assessed by magnetic resonance imaging [238].Overall, most RCTs are small and have a short period of treatment and there are no head-to-head or placebo-controlled RCTs examining the long-term effect of SGLT-2Is on histologic outcomes. SGLT-2Is have shown significant cardio-renal benefits in large trials [239] and may represent attractive drugs in patients with T2DM and NAFLD in the future.

Cusi K et al., 2022 [2].

American Association of Clinical Endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings

Zielsetzung/Fragestellung

To provide evidence-based recommendations regarding the diagnosis and management of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) to endocrinologists, primary care clinicians, health care professionals, and other stakeholders.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium; trifft nicht zu (keine Patientenvertretung)
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; trifft zu
- Systematische Suche, Auswahl und Bewertung der Evidenz; trifft zu
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt; trifft zu
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; trifft zu
- Regelmäßige Überprüfung der Aktualität aller 3-5 Jahre

Recherche/Suchzeitraum:

- PubMed
- published in English between January 1, 2010, and November 15, 2021

LoE / GoR

- The American Association of Clinical Endocrinology (AACE) Protocol for Standardized Production of Clinical Practice Guidelines
- Recommendation Grade A = "Very Strong"; B = "Strong"; C = "Not Strong"; D = "Primarily Based on Expert Opinion."
- Semantic descriptors of "must," "should," and "may" are generally but not strictly correlated with grade A (strong), B (intermediate), and C (weak) recommendations, respectively; each semantic descriptor can be used with grade D (no conclusive evidence and/or expert opinion) recommendations. Deviations from this mapping take into consideration further decision making based on clinical expertise

Empfehlungen

Q3.2 What lifestyle modifications (dietary intervention and exercise) should be recommended in adults with NAFLD?

- R3.2.1 Clinicians should recommend lifestyle changes in persons with excess adiposity and NAFLD with a goal of at least 5%, preferably ≥ 10%, weight loss, as more weight loss is often associated with greater liver histologic and cardiometabolic benefit, depending on individualized risk assessments. Clinicians must recommend participation in a structured weight loss program, when possible, tailored to the individual's lifestyle and personal preferences. *Grade B; Intermediate/High Strength of Evidence; BEL 1; downgraded due to small sample sizes, large heterogeneity of interventions, short duration, and few studies with liver biopsy*
- R3.2.2 Clinicians must recommend dietary modification in persons with NAFLD, including a reduction of macronutrient content to induce an energy deficit (with restriction of saturated fat, starch, and added sugar) and adoption of healthier eating patterns, such as the Mediterranean diet. *Grade A; Intermediate Strength of Evidence; BEL 1*
- R3.2.3 In persons with NAFLD, clinicians must recommend physical activity that improves body composition and cardiometabolic health. Participation in a structured exercise program should be recommended, when possible, tailored to the individual's lifestyle and personal preferences. *Grade A; Intermediate Strength of Evidence; BEL 1*

Q3.3 What medications have proven to be effective for the treatment of liver disease and cardiometabolic conditions associated with NAFLD or NASH?

- R3.3.1a Pioglitazone and GLP-1 RAs are recommended for persons with T2D and biopsy-proven NASH. *Grade A; High Strength of Evidence; BEL 1*
- R3.3.1b Clinicians must consider treating diabetes with pioglitazone and/or GLP-1 RAs when there is an elevated probability of having NASH based on elevated plasma aminotransferase levels and noninvasive tests. *Grade A; High Strength of Evidence; BEL 1*
- R3.3.2 To offer cardiometabolic benefit in persons with T2D and NAFLD, clinicians must consider treatment with GLP-1 RAs, pioglitazone, or SGLT2 inhibitors; however, there is no evidence of benefit for treatment of steatohepatitis with SGLT2 inhibitors. *Grade A; High Strength of Evidence; BEL 1*
- R3.3.3 Due to the lack of evidence of efficacy, metformin, acarbose, dipeptidyl peptidase IV inhibitors, and insulin are not recommended for the treatment of steatohepatitis (no benefit on hepatocyte necrosis or inflammation) but may be continued as needed for the treatment of hyperglycemia in persons with T2D and NAFLD or NASH. *Grade B; High*

Strength of Evidence; BEL 1; downgraded due to the use of surrogate outcome measures in many of the studies

- R3.3.4 Vitamin E can be considered for the treatment of NASH in persons without T2D, but there is not enough evidence at this time to recommend for persons with T2D or advanced fibrosis. *Grade B; High Strength of Evidence; BEL 1; downgraded due to risk/benefit*
- R3.3.5 Other pharmacotherapies for persons with NASH cannot be recommended at the present time due to the lack of robust evidence of clinical benefit. *Grade A; High Strength of Evidence; BEL 1*

Q3.4 What obesity pharmacotherapies have proven benefit for the treatment of liver disease and cardiometabolic conditions associated with NAFLD or NASH in adults?

- R3.4.1 Clinicians should recommend the use of obesity pharmacotherapy as adjunctive therapy to lifestyle modification for individuals with obesity and NAFLD or NASH with a goal of at least 5%, preferably ≥ 10 %, weight loss, as more weight loss is often associated with greater liver histologic and cardiometabolic benefit, when this is not effectively achieved by lifestyle modification alone. *Grade B; Intermediate Strength of Evidence; BEL 1; downgraded due to small sample sizes used in studies and short duration of trials*
- R3.4.2 For chronic weight management in individuals with a BMI of ≥27 kg/m2 and NAFLD or NASH, clinicians should give preference to semaglutide 2.4 mg/week (best evidence) or liraglutide 3 mg/day. *Grade B; High/Intermediate Strength of Evidence; BEL 1; downgraded due to different formulations and doses used in the semaglutide and liraglutide NASH trials*
- R3.4.3 Clinicians must consider obesity pharmacotherapy (with preference to semaglutide 2.4 mg/week [best evidence] or liraglutide 3 mg/day) as adjunctive therapy to lifestyle modification for individuals with obesity and NAFLD or NASH to promote cardiometabolic health and treat or prevent T2D, CVD, and other end-stage manifestations of obesity. *Grade A; High/Intermediate Strength of Evidence; BEL 1*

Q3.5 What is the effect of bariatric surgery on liver disease and cardiometabolic conditions associated with NAFLD or NASH in adults?

- R3.5.1 Clinicians should consider bariatric surgery as an option to treat NAFLD (Grade B; Intermediate/Weak Strength of Evidence; BEL 2) and improve cardiometabolic health (Grade A; High/Intermediate Strength of Evidence; BEL 2; upgraded based on the cardiometabolic and all-cause mortality benefits in all persons with or without NAFLD) in persons with NAFLD and a BMI of ≥35 kg/m2 (≥32.5 kg/m2 in Asian populations), particularly if T2D is present. It should also be considered an option in those with a BMI of ≥30 to 34.9 kg/m2 (≥27.5 to 32.4 kg/m2 in Asian populations) *(Grade B; Intermediate/Weak Strength of Evidence; BEL 2).*
- R3.5.2 For persons with NASH and compensated cirrhosis, clinicians should exercise caution in recommending bariatric surgery, which should be highly individualized if prescribed and performed at experienced centers *(Grade B; Intermediate/Weak Strength of Evidence; BEL 2).*
- In persons with decompensated cirrhosis, bariatric surgery should not be recommended due to limited evidence and potential for harm *(Grade B; Intermediate/Weak Strength of Evidence; BEL 2).*
- R3.5.3 Endoscopic bariatric and metabolic therapies and orally ingested devices should not be recommended in persons with NAFLD due to insufficient evidence. *Grade C; Intermediate/Weak Strength of Evidence; BEL 2; downgraded due to the quality of studies and small sample sizes*

Hintergrundinformationen (pharmacologic treatment):

Evidence Base. The rationale for pharmacologic treatment of NASH in persons with T2D (in addition to lifestyle changes) is based on the following aspects, as discussed earlier: (1) NASH has reached epidemic proportions with clinically significant fibrosis (stage F2) being present in approximately 12% to 21% of individuals in T2D[9,10,102,110,114,188-190]; (2) NASH with clinically significant fibrosis is associated with an increased risk of mortality from liver-related complications[279]; (3) early diagnosis and treatment offer a window of opportunity to prevent disease progression; (4) T2D appears to accelerate progression to cirrhosis in NASH, making a dual intervention versus diabetes and NASH more cost-effective[28,147]; (5)while weight loss alone may reverse NASH, usually in proportion to the magnitude of weight loss, halting fibrosis progression is less predictable and highly variable among individuals[106]; and (6) some medications effective to treat T2D and NASH (pioglitazone and GLP-1 RAs) also reduce CVD, the leading cause of death in this population.[29,59] Taken together, it follows that adding pharmacologic therapy with agents proven to reverse NASH is warranted to prevent progression to cirrhosis more effectively. At present, there are no FDA-approved drugs for the treatment of NASH. Therefore, treatment recommendations for persons with T2D and NASH are centered on the dual purpose of treating hyperglycemia and/or obesity and NASH, especially if clinically significant fibrosis (stage, F2) is present, to prevent development of cirrhosis. As discussed, a liver biopsy is the optimal approach to confirm the diagnosis and stage of the severity of liver fibrosis. However, it is recognized that this may not be feasible or acceptable to several individuals. Therefore, in high-risk populations (ie, those with obesity and T2D), pharmacologic therapy to treat obesity or diabetes may also be considered in the presence of elevated plasma aminotransferase levels and/or FIB-4 scores of >1.3 and confirmatory imaging (TE and MRE) or proprietary fibrosis biomarkers, such as the ELF test,[143] when suggestive of clinically significant liver fibrosis, if imaging not available.[134,147,148] Additional biomarkers are undergoing further evaluation in NAFLD (ie, NIS4,[141] propeptide of type III collagen,[142,144-146] and others[134]). Two antidiabetic agents have proven to be safe and effective to reverse NASH in persons with obesity, prediabetes, or T2D: pioglitazone and GLP-1 RA. Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-g that improves IR, primarily targeting adipose tissue and improving lipid storage/redistribution and glucose utilization.[29] It was the first diabetes agent to show efficacy in an early RCT in 55 individuals with prediabetes or diabetes and biopsy-proven NASH.[280] This was followed by positive 12- to 24-month RCTs showing histologic improvement in persons without diabetes.[97,98,281,282] A 2016 single-center study in 101 persons with obesity, and either prediabetes or T2D, confirmed its sustained benefit on glucose and lipid metabolism and NASH over 36months of follow-up.98With pioglitazone treatment (45mg), 58% of individuals achieved the primary outcome of a reduction of at least 2 points in NAS, while 51% had resolution of NASH (treatment difference of 41% and 32% vs placebo, respectively; both P< .001 vs placebo). There was also improvement in the mean fibrosis score (P= .039).[98] A 2017 meta-analysis of available pioglitazone RCTs in persons with biopsy proven NASH noted a significant improvement versus placebo for NASH resolution (OR, 3.22; 95% CI, 2.17-4.79; P < .001) and for any stage of fibrosis (OR,1.66; 95% CI,1.12-2.47; P=.01),with even greater ORs for the effect on advanced fibrosis (OR, 3.15; 95% CI,1.25-7.93; P=.01), with similar results for those with and without T2D.[283] A 2020 incremental cost-effectiveness ratio analysis that added a more recent 2019 study combining pioglitazone with vitamin E confirmed the aforementioned findings.[284] The side effects of pioglitazone include dose-dependent weight gain (1% with pioglitazone 15 mg/ day up to 3%-5% with 45mg/day), increased fracture risk, heart failure if used in persons with preexisting heart disease, and bladder cancer. A meta-analysis of 17 cohort or case-control studies revealed a minimal prevalence of bladder cancer compared with robust CV benefits and improvements for those with NASH (the numbers needed to treat for 1 additional case of bladder cancer ranged from 899 to 6380, while the numbers needed to benefit CVD and NASH were 4-256 and 2-12, respectively).[285] GLP-1 RAs have become pillars of pharmacotherapy for obesity and T2D because of robust clinical benefits, including weight loss, glycemic control, and cardiometabolic improvements. The challenge of systematic reviews of GLP-1 RAs in NAFLD is the heterogeneity of populations included and study designs, with broad differences in treatment duration, primary end points, and assessment of treatment efficacy with random liver imaging modalities and rare use of liver biopsy as the “gold standard” for grading NASH. However, taken together, studies agree that GLP-1 RAs normalize plasma aminotransferase levels and reduce liver fat content on imaging in individuals with NAFLD [222,286,287].A small (n=52) 2016 proof of-concept RCT suggested that liraglutide improved some features of liver histology in persons with NASH, including delaying fibrosis progression versus placebo.[288] In 2021, a phase 2 RCT compared the doses of 0.1, 0.2, and 0.4mg of semaglutide daily with placebo in 320 persons with NASH (of whom 230 had stage F2 or F3 fibrosis). Resolution of steatohepatitis was found in 40% of those in the 0.1-mg group, 36% of those in the 0.2-mg group, 59% of those in the 0.4-mg group, and 17% of those in the placebo group (P < .001 for semaglutide 0.4mg vs placebo) in the context of significant weight loss (13% in the 0.4-mg group vs 1% in the placebo group).[99] There were no significant between-group differences in the percentage of individuals with an improvement in fibrosis stage, but progression of liver fibrosis was significantly less with the highest dose of the GLP-1 RA (4.9%) versus placebo (18.8%).Of note, the semaglutide dose of 0.4mg/ day employed is equivalent to the dose of semaglutide 2.4 mg/week shown in phase 3 trials to be highly effective for weight loss in persons with

obesity.[289-292] SGLT2 inhibitors, approved for the treatment of T2D and heart failure and associated with robust cardiorenal benefits, have been considered potentially beneficial for NAFLD because of the reduced lipid burden on the liver from glycosuria creating energy deficit and weight loss.[293] Several small, open-label studies have suggested benefit in persons with T2D and NAFLD.[29,222,294] More recent RCTs have been performed showing the potential benefit of these medications in NAFLD and NASH in persons with obesity and T2D via imaging of hepatic steatosis using "gold standard" MRI-based techniques, but none yet has been performed with histologic evaluation.[295-297] SGLT2 inhibitors may be considered as adjunctive pharmacotherapy for individuals with T2D and NAFLD as they reduce hepatic steatosis and offer significant cardiometabolic and renal protection. Metformin is a biguanide that improves hepatic and muscular insulin sensitivity; however, in several paired-biopsy studies in persons with NASH, there was no clinical evidence of benefit on disease activity or liver fibrosis. Early studies suggested a modest effect, largely on hepatic steatosis and associated with weight loss,[298,299] but a meta-analysis of metformin trials has shown that weighted liver histologic scores for steatosis, ballooning, and fibrosis did not significantly improve and lobular inflammation significantly worsened (weighted mean increase, 0.21; 95% CI, 0.11-0.31; P < .0001),[300] consistent with other systematic reviews and meta-analyses.[301,302] Early studies suggested benefit from dipeptidyl peptidase IV inhibitors, but this was not confirmed in recent RCTs.[286,303-305] Insulin may reduce hepatic steatosis, but the effect is modest, and no liver biopsy study to assess its effects on liver histology is available.[177,178,306] Among other agents, only vitamin E showed efficacy to ameliorate steatohepatitis (but not fibrosis) in individuals without T2D and biopsy-proven NASH in a 2-year RCT.[97] Improvement in steatohepatitis has also been reported in a single-center, uncontrolled retrospective observational study in persons with advanced liver fibrosis.[307] However, the results in persons with T2D have been mixed, and vitamin E cannot be recommended with the current evidence, as benefit has been modest overall, and fibrosis has not been improved in any of the studies.[282] Controversy remains about vitamin E being associated with a modest increased risk of cardiovascular disease and of prostate cancer,[101] although not confirmed in more recent studies. Finally, a number of agents have been tested in individuals with NAFLD or NASH; however, studies have been generally uncontrolled, small, used only imaging as the primary end point, and/or been overall negative.[300,301,308,309]

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 02 of 12, February 2025) am 18.02.2025

#	Suchschritt
1	[mh "Non-alcoholic Fatty Liver Disease"]
2	(("non" NEXT alcohol*):ti,ab,kw OR nonalcohol*:ti,ab,kw)
3	("fatty liver" OR Steatohepatitis OR "Steato hepatitis" OR Steatos*):ti,ab,kw
4	#2 AND #3
5	(NAFLD OR NAFL OR NASH):ti,ab,kw
6	(Metabolic:ti,ab,kw AND ("fatty liver":ti,ab,kw OR steatohepatitis:ti,ab,kw OR "steato hepatitis":ti,ab,kw OR (steatotic:ti,ab,kw AND liver:ti,ab,kw)))
7	(MASH OR MASLD OR MASL OR MAFLD OR MAFL):ti,ab,kw
8	#1 OR #4 OR #5 OR #6 OR #7
9	[mh ^"Liver Cirrhosis"]
10	(liver:ti,ab,kw OR hepatic:ti,ab,kw) AND (cirrhos*:ti,ab,kw OR fibros*:ti,ab,kw)
11	#9 OR #10
12	#11 AND #2
13	#8 OR #12
14	#13 with Cochrane Library publication date from Feb 2020 to present

Leitlinien und systematische Reviews in PubMed am 17.02.2025

verwendeter Suchfilter für Leitlinien ohne Änderung:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

verwendeter Suchfilter für systematische Reviews ohne Änderung:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 15.01.2025.

#	Suchschritt
	Leitlinien
1	Non-alcoholic Fatty Liver Disease[mh]
2	(non alcohol*[tiab] OR nonalcohol*[tiab])
3	("fatty liver"[tiab] OR Steatohepatitis[tiab] OR "Steato hepatitis"[tiab] OR Steatos*[tiab])
4	#2 AND #3
5	NAFLD[tiab] OR NAFL[tiab] OR NASH[tiab]
6	metabolic[tiab] AND ("fatty liver"[tiab] OR steatohepatitis[tiab] OR "steato hepatitis"[tiab] OR (steatotic[tiab] AND liver[tiab]))
7	MASH[tiab] OR MASLD[tiab] OR MASL[tiab] OR MAFLD[tiab] OR MAFL[tiab]

#	Suchschritt
8	#1 OR #4 OR #5 OR #6 OR #7
9	"Liver Cirrhosis"[Mesh:NoExp]
10	(liver[tiab] OR hepatic[tiab]) AND (cirrhos*[tiab] OR fibros*[tiab])
11	#9 OR #10
12	#11 AND #2
13	#8 OR #12
14	(#13) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
15	(#14) AND ("2020/02/01"[PDAT] : "3000"[PDAT])
16	(#15) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews
17	(#13) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[mh] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
18	(#17) AND ("2020/02/01"[PDAT] : "3000"[PDAT])
19	(#18) NOT "The Cochrane database of systematic reviews"[Journal]
20	(#19) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])

#	Suchschritt
	systematische Reviews ohne Leitlinien
21	#20 NOT #16
22	(#21) AND ("2023/02/01"[PDAT] : "3000"[PDAT])
23	(#21) NOT (#22)

Iterative Handsuche nach grauer Literatur, abgeschlossen am 26.02.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **Associazione Italiana per lo Studio del Fegato (AISF), Societa Italiana di Diabetologia (SID), Societa Italiana dell'Obesita (SIO).** Non-alcoholic fatty liver disease in adults 2021: a clinical practice guideline of the Italian Association for the Study of the Liver (AISF), the Italian Society of Diabetology (SID) and the Italian Society of Obesity (SIO). Dig Liver Dis 2022;54(2):170-182.
2. **Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, et al.** American Association of Clinical Endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD). Endocr Pract 2022;28(5):528-562.
3. **European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO).** EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). Obes Facts 2024:1-70.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2025-B-046 & 2025-B-036

Verfasser	
Name der Institution (federführend)	DGVS
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Datum der Erstellung	3. März 2025

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
„[…] ist indiziert zur Behandlung erwachsener Patienten mit metabolischer Dysfunktion-assoziierter Steatohepatitis (MASH) und Nachweis einer signifikanten Leberfibrose (Fibrosestadium 2 (F2) oder höher).“ „[...] ist angezeigt als Ergänzung zu Diät und Bewegung zur Verringerung des Risikos für schwerwiegende unerwünschte Leberereignisse bei Erwachsenen mit metabolischer Dysfunktion-assoziierter steatotischer Lebererkrankung (MASLD).“ „[...] ist angezeigt zur Behandlung von Erwachsenen mit nicht-zirrhotischer metabolischer Dysfunktion-assoziierter Steatohepatitis (MASH) und moderater bis fortgeschrittener Leberfibrose (entsprechend den Fibrosestadien F2 und F3).“
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Antwort 1: Der Behandlungsstandard in Deutschland bei MASLD sowie MASH und signifikanter Leberfibrose ist eine Lebensstilmodifikation. Übergewichtige bzw. adipöse MASLD Patienten (MASLD: Metabolische Dysfunktion-assoziierte steatotische Lebererkrankung; der Begriff MASLD ersetzt seit Juni 2023 den Begriff NAFLD [1, 2]), zu denen auch die Patienten mit MASH und/oder nicht-zirrhotischer Leberfibrose gehören, sollen ihr Gewicht um mindestens 5% reduzieren, um eine Verbesserung von Steatose, Inflammation bzw. Transaminasen zu erreichen. Zur Verbesserung der Fibrose sollte bei übergewichtigen/adipösen Patienten eine Gewichtsreduktion von mindestens 10% angestrebt werden. MASLD Patienten sollten wöchentlich 3 Stunden aerobes Training von moderater bis mittlerer Intensität praktizieren. Es gibt zurzeit im Geltungsbereich der EMA noch keine für die Indikation MASLD (einschl. MASH, MASH-Fibrose, MASH-Zirrhose) zugelassene Medikation. Daten aus der 52-wöchigen MAESTRO-NASH-Studie zusammen mit Daten aus MAESTRO-NAFLD-1, MAESTRO-NAFLD-OLE, einschließlich der Sicherheitsparameter, bildeten die Grundlage, bei der FDA eine beschleunigte Zulassung von Resmetirom zur Behandlung von NASH mit Leberfibrose zu beantragen [3-5]. Resmetirom wurde im März 2024 von der FDA zur Behandlung der nicht-zirrhotischen MASH zugelassen und ist bislang in Deutschland nur in klinischen Studien verfügbar.

Neben der Lebensstilmodifikation gehört die optimale Behandlung von kardiometabolischen Begleiterkrankungen ebenfalls zur Standardtherapie, auch wenn die u.g. Medikamente nicht zur Behandlung der MASLD/MASH selbst eingesetzt werden sollen. Aufgrund der erwarteten günstigen begleitenden Effekte auf die MASH sollten bei nicht-zirrhotischen MASLD-Patienten mit Typ-2-Diabetes (Metformin plus) Glucagon-like Peptide 1 (GLP-1) Agonisten (z.B. Liraglutid oder Semaglutid) oder (Metformin plus) SGLT2 Inhibitoren (z.B. Empagliflozin oder Dapagliflozin) eingesetzt werden. Der Einsatz des Thiazolidindions Pioglitazone kann bei diesen Patienten erwogen werden. Bei Vorliegen einer Fettstoffwechselstörung soll diese bei MASLD/MASH Patienten effektiv therapiert werden. Statine können in Anbetracht der insgesamt günstigen Effekte auch bei MASLD Patienten mit kompensierter MASH-Zirrhose verwendet werden.

Ausführungen zur bariatrischen Chirurgie und endoskopischen Verfahren siehe Antwort 2.

Begründung: Die **Verminderung des Körpergewichts** ist bei übergewichtigen bzw. adipösen MASLD/MASH Patienten von einer Regression der Steatose begleitet [6-10]. Die Abnahme von Steatose und ALT ist dem Gewichtsverlust proportional; es besteht eine klare Beziehung von Dosis und Wirkung [11-13]. Dabei ist es unerheblich, auf welche Art der Gewichtsverlust erreicht wird [6-8, 14]. Die Auswertung gepaarter Leberbiopsien von MASH-Patienten vor und nach Gewichtsreduktion zeigen, dass eine Gewichtsreduktion von mindestens 10% erzielt werden muss, um eine Regression von Fibrose und eine vollständige Rückbildung der Steatohepatitis zu erreichen [15-26]. Zu diesem Ergebnis kommen auch systematische Reviews [27] bzw. Leitlinien [7, 8, 14, 28-30]. Sie zeigen zudem, dass eine geringere Gewichtsabnahme vornehmlich zu einer Verbesserung von Steatose und Transaminasen führt [21, 24, 27, 28, 31-34]. Bei normalgewichtigen MASLD Patienten zeigte eine kontrollierte Studie in 50% eine Remission der Steatose, wenn eine Gewichtsreduktion um 3-5% erzielt wurde [35].

In summa ist eine **dauerhafte Gewichtsreduktion** um mindestens 10% äußerst wirksam in der Behandlung einer MASH (90% Heilungsrate) bei übergewichtigen/adipösen Patienten, aber in der klinischen Praxis ein Ziel, das nur von 10% der Patienten auch erreicht wurde [27]. Konzepte wie Web-basiertes Training [36, 37], Text-Messaging [38] oder Motivationsverstärkung durch Spende für caritative Zwecke [39] sind neue Ansätze zur Lösung dieses Dilemmas. Bestimmungen des Leberfetts mittels 1H-MRS zeigten, dass aerobes Training ohne Änderung des Körpergewichts zu einer Abnahme des hepatischen Fettgehalts führte [40-43]. Metaanalysen zeigen, dass aerobes Training und/oder isometrisches Training bei MASLD Patienten die Transaminasen und den hepatischen Fettgehalt auch unabhängig von einem Gewichtsverlust verbesserten [12, 44-47]. Beide Trainingskonzepte sind offenbar gleichermaßen wirksam [12, 45, 47].

Auch wenn die Gewichtsreduktion ein wesentliches Element der Behandlung einer MASLD/MASH darstellt, scheint ein mediterranes Ernährungsmuster [48] und zumindest bei Typ-2-Diabetikern eine **isokalorische Zufuhr eines hohen Proteinanteils** (sowohl pflanzlich als auch tierischem Protein) [49] zu einer Verringerung des Leberfettgehaltes (MRS-basierte Daten) zu führen.

GLP-1-Rezeptoragonisten sind zur Therapie eines Typ-2-Diabetes und teilweise auch zur Gewichtsreduktion zugelassen. Die nationale Versorgungsleitlinie Typ-2-Diabetes sieht bei Typ-2-Diabetes mit Risikofaktoren eine Kombinationstherapie von Metformin + SGLT2-Hemmer oder GLP-1-RA vor. Die Nationale Versorgungsleitlinie Typ-2-Diabetes (Version 3, publiziert 15. Mai 2023) ist abrufbar unter: https://www.leitlinien.de/themen/diabetes .

Es liegen keine belastbaren Studien vor, welche eine Therapie einer MASLD/MASH bei Fettstoffwechsel-Störungen untersucht haben. Da Fettstoffwechselstörungen, wie z.B. Erhöhung des LDL-Cholesterins, ggf. als Folge einer Familiären Hypercholesterinämie, Lipoprotein(a)-Erhöhung oder isolierte HDL-Cholesterin-Erniedrigung, ein stark erhöhtes Risiko für kardiovaskuläre Erkrankungen darstellen und die MASLD unabhängig von einer Fettstoffwechselstörung das Risiko für kardiovaskuläre Erkrankungen erhöht [50, 51], soll bei Vorliegen einer MASLD die Fettstoffwechselstörung

effektiv therapiert werden. Es liegen aber keine kontrollierten Studien vor, die die Wirksamkeit von Lipidsenkern, einschließlich Statinen, auf die Leberhistologie bei MASLD/MASH zeigen. In großen Kohorten wurde der Einsatz von Statinen bei MASLD mit einem niedrigeren Risiko der Progression der Lebererkrankung assoziiert [52-54]. Hepatotoxische Nebenwirkungen scheinen sehr selten aufzutreten, selbst wenn Statine bei Patienten mit dekompensierter Zirrhose eingesetzt werden [55]. Aus klinischen Beobachtungen ist ein reduziertes HCC-Risiko bekannt [56], zudem wurde eine Verminderung des portalen Hypertonus, eine Verbesserung der endothelialen Dysfunktion und eine geringere Fibrogenese beschrieben [57].

Die Anwendung zukünftig neu zugelassener MASH spezifischer Medikamente im Fibrosestadium F2 oder höher kann derzeit nicht abschließend beurteilt werden. Neue Therapieansätze wie das von der FDA schon zugelassene Resmetirom oder andere Substanzen, die derzeit in klinischen Studien untersucht werden, sind für die Zukunft sehr viel versprechend. Bislang fehlt aber der wissenschaftliche Nachweis, dass diese Substanzen das langfristige Outcome (Überleben, kardiovaskuläre Ereignisse, Krebserkrankungen, Leber-assoziierte Komplikationen) verbessern.

Als „Surrogat" für solche langfristigen Outcome-Daten wird von den europäischen und amerikanischen Zulassungsbehörden eine erhebliche Verbesserung der Leberhistologie durch die Intervention gegenüber einer Vergleichsbehandlung (derzeit Placebo) für eine „konditionale Zulassung" akzeptiert. Hierbei wird gefordert, dass in der Folgebiopsie entweder die histologischen Merkmale der Steatohepatitis (früher NASH) wie Ballooning und Inflammation ohne Verschlechterung der Fibrose verschwunden sind („NASH-Resolution") und/oder die Leberfibrose um mindestens einen Schweregrad gebessert ist, ohne Verschlechterung der NASH-Charakteristika („Fibrosis Improvement") [58, 59]. Der wichtigste Aspekt ist dabei die signifikante Reduktion der prognostisch relevanten hepatischen Fibrose durch MASH-spezifische Medikamente. Da diese Endpunkte klinisch plausibel und wissenschaftlich akzeptiert sind, sollten Patienten mit einer entsprechenden Risikokonstellation, d.h. insbesondere mit fortgeschrittener brückenbildender Fibrose (F3) und/oder hoher Krankheitsaktivität und/oder schweren kardiometabolischen Risikofaktoren, bevorzugt in klinische Studien eingeschlossen werden, die diese Endpunkte untersuchen. Selbst wenn die Patienten im Rahmen der Studie nur Placebo erhalten, profitieren sie generell von der engen Überwachung und Lebensstil-Beratung, wie sich aus „Placebo-Ansprechraten" für die histologischen Endpunkte ableiten lässt, die etwa zwischen 15-35% liegen [60].

Derzeit werden eine Reihe von Substanzen in klinischen Phase 3 und Phase 2 Studien untersucht [10, 29, 61-63], deren Wirkmechanismus im Bereich der pathophysiologischen Prozesse des Glukose-Metabolismus, der Hemmung der *de novo* Lipogenese, der Inflammation oder Fibrogenese liegen. Die Substanzklassen umfassen Agonisten der nukleären Rezeptoren FXR (bzw. dessen Wirkungsvermittler Fibroblast-Growth-Factor/FGF19) und PPAR, Chemokinrezeptor (CCR) Inhibitoren, Thyroidhormonrezeptor-ß (THR-ß) Agonisten (z.B. Resmetirom), Inhibitoren lipogener Schlüsselenzyme sowie enterohepatischer Hormone und deren Agonisten wie Glucagon-like-Peptide-1 (GLP-1), FGF19 oder FGF21. Auch Medikamente mit primär antidiabetischem Wirkansatz wie die Gruppe der SGLT2 Inhibitoren sind hier zu nennen. Aktuelle Daten weisen hier auf eine dosisabhängige Reduktion der Steatose (nicht aber der Fibrose) unter GLP-1-Agonisten-Therapie hin [64]. Für PPARγ-Agonisten (Rosiglitazon und Pioglitazon), aber nicht für PPARα-Agonisten (Fibrate), konnte ebenfalls histologisch eine Reduktion von Steatose und Inflammation, aber nicht der Fibrose gezeigt werden [65].

Versorgungspraxis: Eine MASLD/MASH verläuft in der Regel asymptomatisch und wird häufig inzidentell diagnostiziert [66]. Insbesondere Diabetes und Adipositas sind mit MASLD/MASH assoziiert. Ein systematischer Review schätzte die globale Prävalenz von MASLD bei Diabetikern auf etwa 58% [67]. Die Prävalenz von MASH liegt bei Diabetikern nahe 65% [67, 68]. Darüber hinaus ist MASLD und MASH bei Übergewicht und Adipositas weit verbreitet. Die Prävalenz von MASLD bei Patienten, die sich einer bariatrischen Operation unterziehen, wird mit bis zu 95% angegeben [69].

Ein allgemeines Bevölkerungsscreening ist aufgrund der niedrigen Rate an progredienten Verläufen (nur ca. 4% Prävalenz der Steatohepatitis in Deutschland) und der eingeschränkten Therapieoptionen derzeit nicht indiziert [70, 71]. Die Testung von Krankheitsdispositionen multifaktoriell bedingter „Volkskrankheiten“ wie der MASLD ist zurzeit nicht sinnvoll und stellt einen relevanten Kostenfaktor dar. Derartige Testungen könnten dann sinnvoll sein, wenn gesicherte Interventionsstrategien für die untersuchten Personen in Abhängigkeit vom Testergebnis zur Verfügung stünden. Umso wichtiger erscheint das Screening in der Gruppe von Patienten mit erhöhtem Risiko. Allein erhöhte Leberwerte reichen als Entscheidungskriterium nicht aus, da auch bei normalen Transaminasen eine MASLD vorliegen kann. T2DM und Übergewicht sind eindeutige unabhängige Risikofaktoren für die Entwicklung einer MASH bedingten Fibrose [72, 73]. Mehrere Studien zeigen die deutliche Assoziation mit Faktoren des metabolischen Syndroms [74-76]. Bei Vorliegen der genannten Risikofaktoren steigt die Prävalenz auf 60-75% an und rechtfertigt damit ein Screening [70]. In deutschen Kohorten wiesen Patienten mit MASLD zusätzlich zu den oben genannten Risikofaktoren außerdem ein höheres Lebensalter >50 Jahre auf [77, 78]. Bei verschiedenen Begleiterkrankungen sollte zusätzlich eine MASLD abgeklärt werden. So besteht eine wechselseitige Korrelation zur koronaren Herzerkrankung. Auch bei dem polyzystischen Ovarsyndrom, der Schlafapnoe, einer Hypothyreose, Depressionen oder einer Niereninsuffizienz sollte an eine MASLD gedacht werden [14, 79]. Ein generelles Verwandten-Screening erscheint nicht gerechtfertigt. Ein Screening unter Berücksichtigung der oben genannten Faktoren ist durch die Vermeidung leberspezifischer Erkrankungen und Endpunkte zumindest in den USA kosteneffektiv [80]. In Deutschland werden fast alle Patienten primär durch Hausärzte versorgt. Ein gewisser Anteil der in der Risikopopulation definierten Patienten wird Spezialisten zugewiesen (Diabetologen, Endokrinologen, Kardiologen). Zahlreiche Patienten mit T2DM, Adipositas und arteriellem Hypertonus werden jedoch ausschließlich durch Hausärzte behandelt (z.B. im Rahmen sogenannter Disease-Management-Programme).

Ein umfassendes Risikopopulationsscreening in Deutschland kann aufgrund des Zugangs zu den Patienten nur in den Händen der primärärztlich tätigen Mediziner liegen [10]. Diese Ärztegruppe ist besonders geeignet, in der Breite die wesentlichen Risikoerkrankungen für MASLD zu identifizieren und somit das individuelle MASLD-Risiko bei diesen Patienten zu bestimmen [81]. Diese Einschätzung entspricht auch aktuellen Empfehlungen der EASL [82, 83] und einem erst kürzlich entwickelten Algorithmus für Allgemeinmediziner und Diabetologen [84]. Ein Zwei-Schritt-Design mit Überprüfung von Steatose und Fibroserisikos verbessert die Spezifität (und teilweise sogar die Sensitivität) des Screenings [85, 86]. Positiv gescreente Patienten müssen einem Gastroenterologen/Hepatologen vorgestellt werden, um eine weitere Abklärung zu ermöglichen. Grundsätzlich sollten Patienten mit langdauernden oder wiederholten Erhöhungen der GPT/ALT zur weiteren Abklärung überwiesen werden, da sie generell ein erhöhtes Risiko für eine Lebererkrankung aufweisen [87-89].

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)

Antwort 2: Behandlungsentscheidungen bei der MASLD/MASH haben zum Ziel, Patienten-relevante Endpunkte zu verbessern. Dies gilt vor allem für die hepatischen Komplikationen (Leberzirrhose, Dekompensation einer Zirrhose, hepatozelluläres Karzinom, Lebertransplantation, Leberbedingter Tod), aber natürlich auch für kardiometabolische Komplikationen (Schlaganfall, Herzinfarkt). Wesentliches Surrogat für das individuelle Risiko dieser Endpunkte ist das Leberfibrose-Stadium. Neben dem Stadium der Leberfibrose (bzw. Zirrhose) werden Begleiterkrankungen für die Behandlungsentscheidungen berücksichtigt.
Die **Behandlungsentscheidungen** bei der Behandlung erwachsener Patientinnen und Patienten mit MASH **orientieren sich an den Komorbiditäten Typ-2-Diabetes, Fettstoffwechselstörungen und Adipositas**. Dies wurde oben bereits für Typ-2-Diabetes und Hyperlipoproteinämie ausgeführt. Das

Erkrankungsstadium (also der Schweregrad der Erkrankung) wird daneben durch das Ausmaß der Leberfibrose bestimmt. Das Fibrosestadium (Staging) ist entscheidend für die Prognose der MASLD. Die Behandlung ist stark von den jeweiligen Komorbiditäten abhängig (s.o.).
Bei Adipositas Grad III (BMI ≥40 kg/m²) und MASLD soll eine metabolisch chirurgische Operation empfohlen werden, sofern keine Kontraindikationen vorliegen und konservative Maßnahmen ausgeschöpft sind. Bei Adipositas Grad II (BMI ≥35 kg/m² und <40kg/m^2) und MASLD sollte eine metabolisch chirurgische Operation empfohlen werden, sofern keine Kontraindikationen vorliegen und konservative Maßnahmen ausgeschöpft sind. Bei BMI <35 kg/m² und NAFLD sollte eine metabolisch chirurgische Operation nur im Rahmen wissenschaftlicher Studien erfolgen.
Bei Adipositas und MASLD können als metabolisch chirurgische Operationsverfahren die Sleeve-Gastrektomie, der Roux-Y-Magenbypass und ein Ein-Anastomosen-Magenbypass empfohlen/durchgeführt werden.
Endoskopische Verfahren können bei MASLD und Adipositas bei Versagen einer konservativen Therapie und bei Ablehnung bzw. bei Kontraindikation für ein operatives bariatrisches Verfahren eingesetzt werden. Bei Entscheidung für ein endoskopisches Verfahren sollte aufgrund der vorliegenden Evidenz eine endoskopisch intragastrale Ballonanlage (IGB) oder ein endoskopischer Schlauchmagen (ESG) erfolgen.
Die Indikation zur Lebertransplantation/LTX (z.B. beim MASH-HCC) soll nach den gleichen Kriterien wie bei Patienten mit Leberzirrhose oder HCC anderer Genese gestellt werden

Begründung: Der entscheidende Faktor für die Prognose der MASLD/MASH ist das zugrundeliegende Fibrosestadium. Eine Meta-Analyse aus 5 Studien mit 1495 bioptisch gesicherten MASLD-Patienten und einem Follow-Up von 17.452 Patienten-Jahren zeigte, dass im Vergleich zu MASLD-Patienten ohne Fibrose (F0) diejenigen mit Fibrose ein erhöhtes Risiko sowohl für die Gesamt- als auch leberspezifische Mortalität hatten, welches mit jedem weiteren Fibrosestadium anstieg. Hinsichtlich der leberspezifischen Mortalität war dabei ein exponentieller Anstieg des Risikos zu verzeichnen [90]. Das größte Risiko für eine leberspezifische aber auch die Gesamt-Morbidität und -Mortalität der MASLD zeigt sich für die fortgeschrittene Fibrose (F3) und die Leberzirrhose (F4). So bestanden in einem durchschnittlichen Beobachtungszeitraum von 5,5 Jahren folgende Ereignisraten: 8% Gesamtmortalität, 8% Lebertransplantationen, 19% erstmalige hepatische Dekompensationen, 9% HCC, 3% vaskuläre Ereignisse und 7% nicht-hepatische Malignome. Das transplantationsfreie 10-Jahres-Überleben lag für F3 bei 94% und für F4 bei 45,5%. Bei F3 fanden sich höhere kumulative Inzidenzen für vaskuläre Ereignisse (7% vs. 2%) und nicht-hepatische Malignome (14% vs. 6%). Bei Patienten mit Leberzirrhose war hingegen der Anteil an hepatischen Dekompensationen und HCC erhöht: 44% vs. 6% und 17% vs. 2,3% [91].

Diese Daten deuten darauf hin, **dass die kardiovaskuläre** und nicht-hepatische **Morbidität und Mortalität bei nicht-zirrhotischen MASLD Patienten und MASH-Patienten im Vordergrund steht,** während bei manifester Leberzirrhose die Komplikationen der fortgeschrittenen Lebererkrankung die weitere Prognose bestimmen.

Die Adipositaschirurgie hat sich als effektive Therapie der morbiden Adipositas erwiesen. Weiterhin führen adipositaschirurgische Operationen regelhaft zu einer Verbesserung und oft auch der vollen Remission von Adipositas-assoziierten Begleiterkrankungen [92]. Gemäß der aktuellen deutschen S3 Leitlinie der DGAV von 2018 ist bei Vorliegen einer schweren Adipositas mit BMI ≥40 kg/m² (auch ohne Begleiterkrankungen) eine adipositaschirurgische Operation indiziert, sofern alleinige konservative Maßnahmen zur Gewichtsreduktion (Ernährungsumstellung, Bewegungsmaßnahmen und ggf. Verhaltenstherapie) versagt haben. Darüber hinaus sollte eine solche schon bei einem BMI ≥35 kg/m² und mindestens einer wesentlichen adipositasspezifischen Begleiterkrankung wie z.B. einer MASLD und MASH angeboten werden, sofern alleinige konservative Maßnahmen zur Gewichtsreduktion versagt haben [92]. Endoskopische Verfahren sind hinsichtlich der Gewichtsreduktion weniger effektiv und langanhaltend als die operativen Verfahren, können aber bei Versagen der konservativen Therapie und bei Kontraindikationen für ein operatives bariatrisches

Verfahren Anwendung finden. Die AWMF Leitlinie Adipositas Chirurgie aus 2018 spricht eine „kann Empfehlung“ für die endoskopischen Verfahren – hier insbesondere für den Magenballon basierend auf der zum Entstehungszeitpunkt der LL gegebenen Datenlage aus [93] (Adipositaschirurgie 2018 AWMF 088-001).
Das am besten untersuchte endoskopische Verfahren ist der intragastrale Ballon (IGB). Er ist indiziert ab einem BMI von ≥30-40 kg/m^2 mit einer zugelassenen Liegedauer von 6 Monaten. Eine aktuelle Metaanalyse untersuchte 13 RCTs (endoskopisch intragastraler Ballon vs. Sham oder Lifestyle Änderung) mit 1.523 Patienten und zeigte einen signifikanten Vorteil für den IGB hinsichtlich EWL (prozentualer Übergewichtsverlust) und TWL (prozentualer Gesamtgewichtsverlust) (-17.98% bzw. -4.40%) [94]. Eine ältere Metaanalyse aus dem Jahr 2008 [95] mit 3.698 eingeschlossenen Patienten belegte ein gutes Sicherheitsprofil der Methode mit ernsten Komplikation unter 1% (Dünndarmobstruktion 0,8%, Magenperforation 0,1%) und der Notwendigkeit einer früheren Entfernung bei Schmerzen/Druckgefühl in 4,2% der Patienten. Der IGB zum Bridging bei einem BMI >50 kg/m2 vor bariatrischer Chirurgie erwies sich in einer neueren Meta-Analyse hinsichtlich der Gewichtsreduktion als nicht signifikant effektiv [96], so dass bei derart stark Übergewichtigen zumindest im Hinblick auf den Gewichtsverlust kein Vorteil für ein Bridging durch IGB besteht. Der IGB ist bezüglich metabolischer und hepatologischer Parameter das am besten untersuchte endoskopische Verfahren.
Offen bleibt auch die Frage nach der Zielgruppe einer zukünftigen spezifischen medikamentösen MASH-Therapie. Einige der jüngst durchgeführten Phase 3 Studien haben Patienten im Fibrosestadium F1 im Falle begleitender Risikofaktoren eingeschlossen, während andere mindestens F2 oder gar ausschließlich F3 als Zielpopulation definiert haben. Primär kommen vor allem Patienten mit weiter fortgeschrittener Fibrose (>F2) mit hoher Dringlichkeit in Betracht, denn hier ist sowohl die leberassoziierte als auch die extrahepatische Mortalität signifikant erhöht [97]. Es bleibt zu klären, inwiefern Patienten mit früheren Fibrosestadien oder nur diese mit dem unmittelbar höchsten Progressionsrisiko bei F3 eine spezifische medikamentöse Therapie erhalten sollten.

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