EASL,EASD,EASO guidelines for the management of NAFLD:

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Clinical Practice Guidelines

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EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)

Definition

NAFLD is characterised by excessive hepatic fat accumulation, associated with insulin resistance (IR), and defined by the presence

of steatosis in >5% of hepatocytes according to histological analysis or by a proton density fat fraction (providing a rough estimation of the volume fraction of fatty material in the liver) >5.6% assessed by proton magnetic resonance spectroscopy (1HMRS)

or quantitative fat/water selective magnetic resonance imaging (MRI).

NAFLD includes two pathologically distinct conditions with different prognoses: non-alcoholic fatty liver (NAFL)
and non-alcoholic steatohepatitis (NASH); the latter covers a
wide spectrum of disease severity, including fibrosis, cirrhosis
and hepatocellular carcinoma (HCC

Table 2. The spectrum of NAFLD and concurrent diseases.

Disease	Subclassification	Most common concurrent diseases
NAFLD*	NAFL • Pure steatosis • Steatosis and mild lobular inflammation NASH • Early NASH: no or mild (F0–F1) fibrosis • Fibrotic NASH: significant (≥F2) or advanced (≥F3, bridging) fibrosis • NASH-Cirrhosis (F4) Hepatocellular carcinoma^	° AFLD-Alcoholic fatty liver disease ° Drug-induced fatty liver disease ° Hepatitis C virus-associated fatty liver (genotype 3) ° Others • Haemochromatosis • Autoimmune hepatitis • Coeliac disease • Wilson's disease • A/hypo-betalipoproteinaemia lipoatrophy • Hypopituitarism, hypothyroidism • Starvation, parenteral nutrition • Inborn errors of metabolism (Wolman disease [lysosomal acid lipase deficiency])

* Also called Primary NAFLD and associated with metabolic risk factors/components of Metabolic Syndrome:

1. Waist circumference ⩾94/⩾80 cm for Europid men/women.
2. Arterial pressure ⩾130/85 mmHg or treated for hypertension.
3. Fasting glucose ⩾100 mg/dl (5.6 mmol/L) or treated for T2DM.
4. Serum triacylglycerols >150 mg/dl (>1.7 mmol/L).
5. HDL cholesterol <40/50 mg/dl for men/women (<1.0/<1.3 mmol/L).

^Also called secondary NAFLD. Note that primary and secondary NAFLD may coexist in individual patients. Also NAFLD and AFLD may coexist in subjects with metabolic risk factors and drinking habits above safe limits.

^Can occur in the absence of cirrhosis and histological evidence of NASH, but with metabolic risk factors suggestive of "burned-out" NASH.

The diagnosis of NAFLD requires the exclusion of both secondary causes and of a daily alcohol consumption P30 g for men and P20 g for women

Alcohol consumption above these limits indicates alcoholic liver disease. The relationship between alcohol and liver injury depends on several cofactors (type of alcoholic beverage, drinking patterns, duration of exposure, individual/genetic susceptibility), rendering simple quantitative thresholds at least partly arbitrary.

Specifically,
patients consuming moderate amounts of alcohol may be still predisposed to NAFLD if they have metabolic risk factors.

Of note, the overall impact of metabolic risk factors on the occurrence of steatosis appears to be higher than that of alcohol in these patients . The definitive diagnosis of NASH requires aliver biopsy.

Recommendations

Patients with IR and/or metabolic risk factors (i.e. obesity or metabolic syndrome [MetS]) should undergo diagnostic procedures for the diagnosis of NAFLD, which relies onthe demonstration of excessive liver fat (A1)

Individuals with steatosis should be screened for secondary causes of NAFLD, including a careful assessment of alcohol intake.

The interaction between moderate amounts of alcohol and metabolic factors in fatty liver should always be considered

Other chronic liver diseases that may coexist with NAFLD should be identified as this might result in more severe liver injury

Prevalence and incidence

NAFLD is the most common liver disorder in Western countries,
affecting 17–46% of adults, with differences according to the diagnostic method, age, sex and ethnicity .

It parallels the prevalence of MetS and its components, which also increases the risk of more advanced disease, both in adults and in children.

NAFLD is also present in 7% of normal-weight (lean) persons more frequently in females, at a younger age and with normal liver enzymes. Their liver disease may nonetheless be progressive

NAFLD incidence has rarely been measured. It was 20-86/ 1000 person-years based on elevated liver enzymes and/or on ultrasound (US), and 34/1000 per year by 1H-MRS

The need for NAFLD screening in the community has been questioned given the high direct and indirect costs of testing, the low predictive value of non-invasive tests, the risks of liver biopsy and the lack of effective treatments

However, the progressive form of NAFLD (i.e. NASH), particularly when associated with advanced fibrosis, should be identified in patients at risk (age >50 years, type 2 diabetes mellitus [T2DM] or MetS), because of its prognostic implications.

Recommendations

- **All individuals with steatosis should be screened for features of MetS, independent of liver enzymes. All individuals with persistently abnormal liver enzymes should be screened for NAFLD, because NAFLD is the main reason for unexpectedly elevated liver enzymes**

In subjects with obesity or MetS, screening for NAFLD by liver enzymes and/or ultrasound should be part of routine work-up. In high risk individuals (age >50 years, T2DM, MetS) case finding of advanced disease (i.e. NASH with fibrosis) is advisable (A2

Pathogenesis: Lifestyle and genes

**A high-calorie diet, excess (saturated) fats, refined carbohydrates,
sugar-sweetened beverages, a high fructose intake and a Western diet have all been associated with weight gain and obesity, and more recently with NAFLD.**

High fructose consumption may increase the risk of NASH and advanced fibrosis, although the association may be confounded by excess calorie intake or by unhealthy lifestyles and sedentary behaviour , which are more common in NAFLD

Recommendations

• Unhealthy lifestyles play a role in the development and progression of NAFLD. The assessment of dietary and physical activity habits is part of comprehensive NAFLD screening

Several genetic modifiers of NAFLD have been identified , but a minority have been robustly validated .
The best-characterised genetic association is with PNPLA3, initially identified from genome-wide association studies and confirmed in multiple cohorts and ethnicities as a modifier of NAFLD severity across the entire histological spectrum .
Recently, the TM6SF2 gene has been reported as another disease modifier and may have clinical utility assisting risk stratification for liver-related vs. cardiovascular morbidity.

The PNPLA3 rs738409 variant also confers susceptibility and affects the histological pattern of NAFLD and fibrosis in obese children and adolescents .

A NASH risk score based on four polymorphisms has been validated in obese children with increased liver enzymes

Recommendations

• Carriers of the *PNPLA3* I148M and the *TM6SF2* E167K variants have a higher liver fat content and increased risk of NASH.

NAFLD due to these variants is not systematically associated with features of insulin resistance.

Genotyping may be considered in selected patients and clinical studies but is not recommended routinely (B2

Liver biopsy

Liver biopsy is essential for the diagnosis of NASH and is the only procedure that reliably differentiates NAFL from NASH, despite limitations due to sampling variability

NAFL encompasses:

a) **steatosis alone,**

b) **steatosis with lobular or portal inflammation, without ballooning, or**

c) **steatosis with ballooning but without inflammation**

The diagnosis of NASH:

requires the joint presence of steatosis, ballooning and lobular inflammation

Other histological features can be seen in NASH, but are not necessary for the diagnosis:

portal inflammation, polymorphonuclear infiltrates, Mallory-Denk bodies, apoptotic bodies, clear vacuolated nuclei, microvacuolar steatosis and megamitochondria.

The prospectively designed FLIP algorithm increases observer agreement and precisely defines the grading of ballooning

‘Burned-out NASH” describes regression of advanced disease (steatosis, inflammation or ballooning) in patients exposed to metabolic risk factors.

The NAFLD Activity Score (NAS) scoring system should not be used for the diagnosis of NASH but rather for the evaluation of disease severity, once the diagnosis has been established by the overall pathological assessment.

Although NAS is correlated with aminotransferase and homeostasis model assessment of insulin resistance (HOMA-IR)

In children, NASH displays many of the features observed in adults, even though the distribution of lesions may be different.

Portal inflammation is a frequent feature, but can also be seen in adults with more severe disease

Non-invasive assessment

Non-invasive markers should aim to: i) in primary care settings,identify the risk of NAFLD among individuals with increased metabolic risk;

ii) in secondary and tertiary care settings, identify those with worse prognosis, e.g. severe NASH;

iii) monitor disease progression;

iv) predict response to therapeutic interventions. Achieving these objectives could reduce the need for liver biopsy.

Steatosis

Steatosis should be documented when ever NAFLD is suspected as the primary disease or as a coexisting condition. It also predicts future diabetes mellitus, cardiovascular events and arterial hypertension.

In clinical practice, quantification of fat content is not of interest, except as a surrogate of treatment efficacy,and is therefore not generally recommended

In individual patients, especially in tertiary care centres,steatosis should be identified by imaging, preferably US, because it is more widely available and cheaper than the gold standard,MRI

US has limited sensitivity and does not reliably detect steatosis when <20% or in individuals with high body mass index (BMI) (>40 kg/m2)

Despite
observer dependency, US (or computed tomography [CT] orMRI) robustly diagnoses moderate and severe steatosis and provides additional hepatobiliary information, hence it should be
performed as a first-line diagnostic test.

However, for larger scale screening studies, serum biomarkers are preferred, as availability
and cost of imaging substantially impact feasibility

The best-validated steatosis scores are the fatty liver index (FLI), the SteatoTest and the NAFLD liver fat score; they have all been externally validated in the general population or in grade 3 obese persons and variably predict metabolic, hepatic and cardiovascular outcomes/mortality

Recommendations

- **US is the preferred first-line diagnostic procedure for imaging of NAFLD, as it provides**

additional diagnostic information

Whenever imaging tools are not available or feasible (e.g. large epidemiological studies), serum biomarkers and scores are an acceptable alternative for the diagnosis of steatosis

A quantitative estimation of liver fat can only be obtained by 1H-MRS. This technique is of value in clinical trials and experimental studies, but is expensive and not recommended in the clinical setting

Steatohepatitis, NASH

The diagnosis of NASH provides important prognostic information and indicates an increased risk of fibrosis progression,cirrhosis and possibly hepatic comorbidities (HCC).
It may also prompt a closer follow-up and possibly a greater need for more intensive therapy.

Clinical, biochemical or imaging measures cannot distinguish NASH from steatosis .

Cytokeratin-18 fragments (CK-18),whichare generated during cell death(M65fragments) or apoptosis (M30 fragments), have modest accuracy for the diagnosis of NASH(66% sensitivity, 82% specificity) .

CK-18 changes parallel histological improvement but do not perform better than alaninetransaminase (ALT) in identifying histological responders. To date, non-invasive tests are not validated for the diagnosis of NASH

Recommendations

- **NASH has to be diagnosed by a liver biopsy showing steatosis, hepatocyte ballooning and lobular inflammation**

Fibrosis is the most important prognostic factor in NAFLD and is correlated with liver-related outcomes and mortality

The presence of advanced fibrosis identifies patients in need of in-depth hepatological investigation, including, on a case-by-case basis, confirmatory biopsy and intensive therapies.

Monitoring of fibrosis progression is also necessary at variable time intervals.

Many serum markers have shown acceptable diagnostic accuracy as defined by an area under the receiver operating characteristic curve (AUROC) >0.8 .

NAFLD fibrosis score (NFS) and fibrosis 4 calculator (FIB-4) have been externally validated in ethnically different NAFLD populations,with consistent results. NFS, FIB-4, Enhanced Liver Fibrosis (ELF) and FibroTest predict overall mortality, cardiovascular morality an liver related mortality

NFS predicts incident diabetes,
and changes in NFS are associated with mortality. The tests perform best at distinguishing advanced (PF3) vs. non-advanced fibrosis but not significant (PF2) or any (PF1) fibrosis vs. no fibrosis .
Importantly, the negative predictive values (NPVs)
for excluding advanced fibrosis are higher than the corresponding positive predictive values (PPVs

therefore, non-invasive
tests may be confidently used for first-line risk stratification to exclude severe disease.

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Among imaging techniques, transient elastography performs better for cirrhosis (F4) than for advanced fibrosis (F3).
Elastography
has a higher rate of false-positive than false-negative results and higher NPV than PPV , hence the ability to diagnose bridging fibrosis or cirrhosis is insufficient for clinical decision making.

**The main short coming of transient elastography is unreliable
results in the presence of high BMI and/or thoracic fold
thickness. In a large, unselected European series, up to 20% of
examinations had unreliable results , mainly in obese NAFLD The XL probe should be used in these patients to reduce the
failure rate, which remains high (35%)**

There is no consensus on thresholds or strategies for use in clinical practice when trying to avoid liver biopsy . Some data suggest that the combination of elastography and serum markers performs better than either method alone .

Recommendations

• Biomarkers and scores of fibrosis, as well as transient elastography, are acceptable non-invasive procedures for the identification of cases at low risk of advanced fibrosis/cirrhosis (A2). The combination of biomarkers/ scores and transient elastography might confer additional diagnostic accuracy and might save a number of diagnostic liver biopsies

Monitoring of fibrosis progression in clinical practice may rely on a combination of biomarkers/scores and transient elastography, although this strategy requires validation

The identification of advanced fibrosis or cirrhosis by serum biomarkers/scores and/or elastography is less accurate and needs to be confirmed by liver biopsy, according to the clinical context

In selected patients at high risk of liver disease progression, monitoring should include a repeat liver biopsy after at least 5-year follow-up

Recommendations

• In children, predictors of fibrosis, including elastometry, acoustic radiation force impulse (ARFI) imaging and serum biomarkers might help reduce the number of biopsies

Common metabolic disorders related to NAFLD

NAFLD is tightly associated with IR not only in the liver, but also in muscle and adipose tissues , and also with the MetS, defined as the cluster of any three of the following five features associated with IR:
impaired fasting glucose (IFG) or T2DM, hypertriglyceridaemia, low high-density lipoprotein (HDL)-cholesterol (gender-adjusted), increased waist circumference (ethnicity adjusted) and high blood pressure

As all components
of MetS correlate with liver fat content, independently of BMI, the presence of MetS in any given patient should lead to an evaluation of the risk of NAFLD, and vice versa the presence of NAFLD should lead to an assessment of all components of MetS

Hepatic triacylglycerol accumulation is accompanied by abnormal hepatic energy metabolism and impaired insulin mediated suppression of hepatic glucose and very low-density lipoprotein production , leading to hyperglycaemia, hypertriglyceridaemia and hyperinsulinaemia

Recommendations

- **HOMA-IR provides a surrogate estimate of IR in persons without diabetes and can therefore be recommended provided proper reference values have been established**

HOMA-IR is of limited use for NAFLD diagnosis in patients with metabolic risk factors.

During follow-up, HOMA-IR might help identify patients at risk of NASH or fibrosis progression in selected cases. Improvement of HOMA-IR during weight loss may indicate metabolic improvement that could be beneficial for NAFLD

Obesity
BMI and waist circumference, a measure of visceral adiposity,
are positively related to the presence of NAFLD and predict advanced disease, particularly in the elderly

A large proportion of patients with cryptogenic cirrhosis have a high prevalence of metabolic risk factors , suggesting that the majority of cases of cryptogenic cirrhosis are “burned-out” NASH.

Common comorbidities of obesity, such as T2DM, and sleep apnoea , polycystic ovary syndrome and other endocrine disorders (hypogonadism), further drive NAFLD prevalence and severity.

Importantly, patients with BMI <30 kg/m2 (or even <25 kg/m2) but with visceral fat accumulation or dysfunctional adipose tissue can exhibit NAFLD with/without abnormal liver enzymes

The currently used concept of “metabolically healthy” obese individuals should be considered with caution, given that they may exhibit gene expression similar to those of metabolically altered obese patients, and may have altered liver tests and adverse health outcomes when longitudinally examined

Recommendations

- **Follow up is mandatory in obesity, which is the major phenotype and risk condition for NAFLD, driven by IR, and also increases the risk of advanced disease**

Most lean persons with NAFLD display IR and altered body fat distribution even though they have less severe metabolic disturbance than overweight NAFLD. Followup is nonetheless required because of possible disease progression

Recommendations

- **In persons with NAFLD, screening for diabetes is mandatory, by fasting or random blood glucose or HbA1c (A1) and if available by the standardized 75 g OGTT in high-risk groups**

In patients with T2DM, the presence of NAFLD should be looked for irrespective of liver enzyme levels, since T2DM patients are at high risk of disease progression

Table 3. Protocol for a comprehensive evaluation of suspected NAFLD patients.

Level	Variable	
Initial	1.	Alcohol intake: <20 g/day (women), <30 g/day (men)
	2.	Personal and family history of diabetes, hypertension and CVD
	3.	BMI, waist circumference, change in body weight
	4.	Hepatitis B/Hepatitis C virus infection
	5.	History of steatosis-associated drugs
	6.	Liver enzymes (aspartate and alanine transaminases (γ-glutamyl-trans-peptidase))
	7.	Fasting blood glucose, HbA1c, OGTT, (fasting insulin [HOMA-IR])
	8.	Complete blood count
	9.	Serum total and HDL-cholesterol, triacylglycerol, uric acid
	10.	Ultrasonography (if suspected for raised liver enzymes)
Extended *	1.	Ferritin and transferrin saturation
	2.	Tests for coeliac and thyroid diseases, polycystic ovary syndrome
	3.	Tests for rare liver diseases (Wilson, autoimmune disease, α1-antitrypsin deficiency)

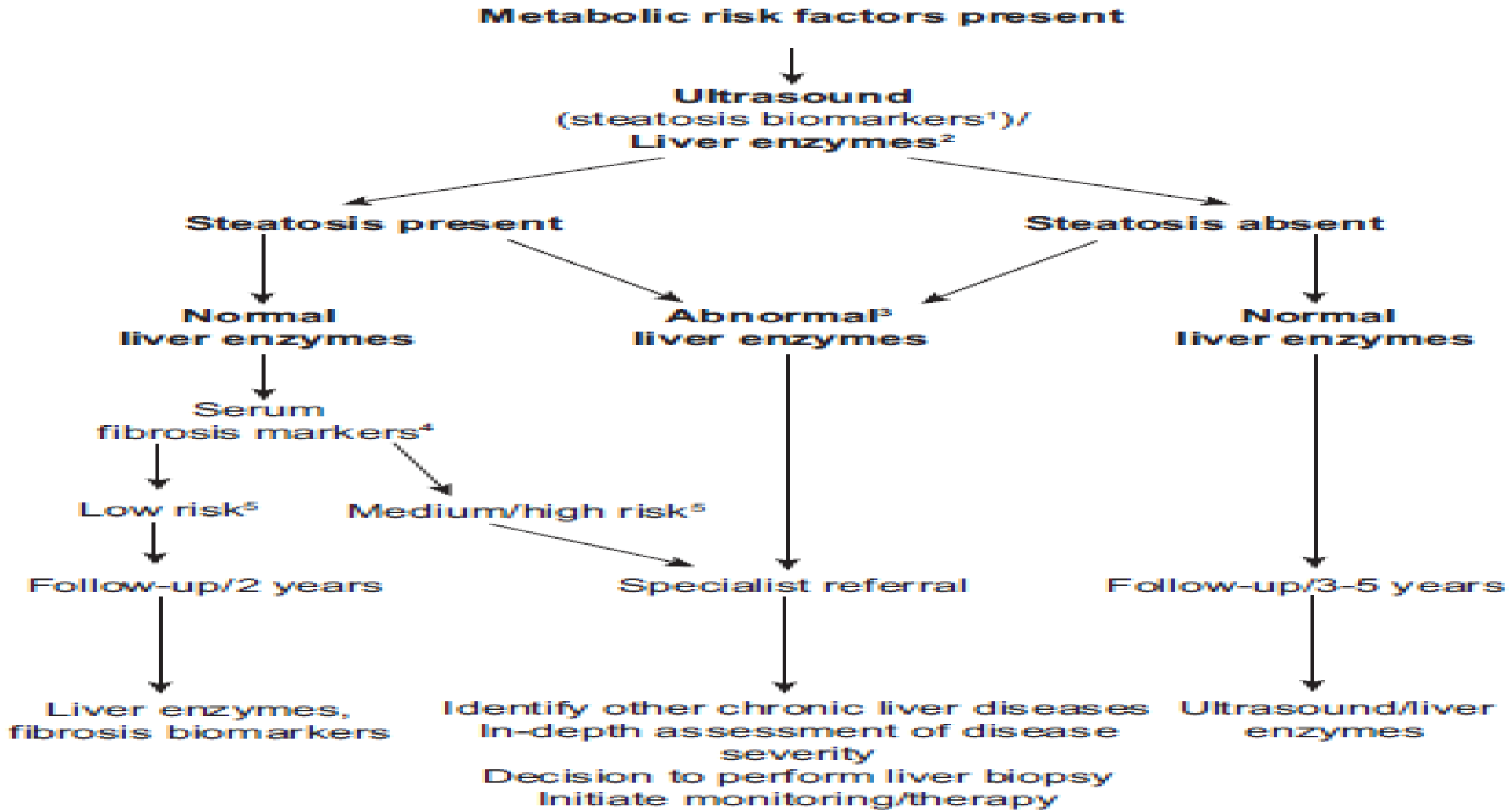

Fig. 1. Diagnostic flow-chart to assess and monitor disease severity in the presence of suspected NAFLD and metabolic risk factors. [1]Steatosis biomark–

The optimal follow-up of patients with NAFLD is as yet undetermined.

Risk of progression of both the hepatic disease and the underlying metabolic conditions as well as the cost and workload for healthcare providers need to be considered. Monitoring should include routine biochemistry, assessment of comorbidities and non-invasive monitoring of fibrosis.

NAFL patients without worsening of metabolic risk factors, should be monitored at 2–3-year intervals. Patients with NASH and/or fibrosis should be monitored annually, those with NASH cirrhosis at 6-month intervals. If indicated on a case-by-case basis, liver biopsy could be repeated after 5 years.

Natural history and complications

Disease progression

In general, NAFLD is a slowly progressive disease, both in adults and in children, but fibrosis rapidly progresses in 20% of cases

The rate of progression corresponds to 1 fibrosis stage every 14 years in NAFL and every 7 years in NASH, and is doubled by arterial hypertension

NASH is associated with an increased standardized mortality ratio compared with the general population and liver disease is the third most common cause of death after CVD and cancer.

US-diagnosed NAFLD is not associated with increased mortality, presumably because progression to NASH and fibrosis is rare for steatosis alone

Recommendations

- **NASH patients with fibrosis associated with hypertension should receive closer monitoring because**
of a higher risk of disease progression

Recommendations

- **Cardiovascular complications frequently dictate the outcome of NAFLD and screening of the cardiovascular system is mandatory in all persons, at least by detailed risk factor assessment**

Recommendations

- **Although NAFLD is a risk factor for HCC, which may also develop in the pre-cirrhotic stage, and the risk is further increased by the presence of the *PNPLA3* rs738409 C>G polymorphism, no recommendation can be currently made on the timing of surveillance and its cost-effectiveness (B1**

Other extrahepatic disorders

Chronic kidney disease (CKD) can be found in 20-50% of NAFLD patients, particularly in biopsy-proven NASH . US-defined NAFLD carries a 1.5- to 2-fold adjusted risk of incident CKD in Type 1 diabetes mellitus .

NAFLD is also associated with colorectal cancer , metabolic bone disease (vitamin D deficiency, osteoporosis)
and rare metabolic diseases (lipodystrophies, glycogen storage diseases).

Treatment

Successful treatment of NASH should improve outcomes, i.e. decrease NASH-related mortality, reduce progression to cirrhosis or HCC. The resolution of the histological lesions defining NASH is now accepted as a surrogate endpoint, particularly in clinical trials.

Only a few properly designed randomized controlled trials (RCTs) are available, with improvement/ regression of hepatic necroinflammation and/or fibrosis as primary outcomes

Table 5. Elements of a comprehensive lifestyle approach to NAFLD treatment.

Area	Suggested intervention	Supportive literature
Energy restriction	• 500-1000 kcal energy defect, to induce a weight loss of 500-1000 g/week	Calorie restriction drives weight loss and the reduction of liver fat, independent of the macronutrient composition of the diet [107]
	• 7-10% total weight loss target	A 12-month intensive lifestyle intervention with an average 8% weight loss leads to significant reduction of hepatic steatosis [108]
	• Long-term maintenance approach, combining physical activity according to the principles of cognitive-behavioural treatment	Hepatic fat increases along with total body fat regain, but most of the beneficial metabolic effects are maintained and progression to T2DM is delayed [109].
Macronutrient composition	• Low-to-moderate fat and moderate-to-high carbohydrate intake • Low-carbohydrate ketogenic diets or high-protein	Adherence to the Mediterranean diet has been reported to reduce liver fat on ^{1}H-MRS, when compared with a low fat/ high carbohydrate diet in a cross-over comparison [110, 111]
Fructose intake	• Avoid fructose-containing beverages and foods	In the general population, an association has been reported between high fructose intake and NAFLD [9]
Alcohol intake	• Strictly keep alcohol below the risk threshold (30 g, men; 20 g, women)	In epidemiological surveys, moderate alcohol intake (namely, wine) below the risk threshold is associated with lower prevalence of NAFLD, NASH and even lower fibrosis at histology [112-114]. Total abstinence is mandatory in NASH-cirrhosis to reduce the HCC risk [115]
Coffee drinking	• No liver-related limitations	Protective in NAFLD, as in liver disease of other aetiologies, reducing histological severity and liver-related outcomes [116]
Exercise/physical activity	• 150-200 min/week of moderate intensity aerobic physical activities in 3-5 sessions are generally preferred (brisk walking, stationery cycling) • Resistance training is also effective and promotes musculoskeletal fitness, with effects on metabolic risk factors • High rates of inactivity-promoting fatigue and daytime sleepiness reduce compliance with exercise	Physical activity follows a dose-effect relationship and vigorous (running) rather than moderate exercise (brisk walking) carries the full benefit, including for NASH and fibrosis [110, 117, 118] Any engagement in physical activity or increase over previous levels is however better than continuing inactivity

Recommendations

- **Structured programmes aimed at lifestyle changes towards healthy diet and habitual physical activity are advisable in NAFLD**

Patients without NASH or fibrosis should only receive counselling for healthy diet and physical activity and no pharmacotherapy for their liver condition

In overweight/obese NAFLD, a 7–10% weight loss is the target of most lifestyle interventions, and results in improvement of liver enzymes and histology

Dietary recommendations should consider energy restriction and exclusion of NAFLD-promoting components (processed food, and food and beverages high in added fructose.

The macronutrient composition should be adjusted according to the Mediterranean diet

Both aerobic exercise and resistance training effectively reduce liver fat. The choice of training should be tailored based on patients' preferences to be maintained in the long-term

Drug treatment

Drug therapy should be indicated for progressive NASH (bridging fibrosis and cirrhosis) but also for early-stage NASH with increased risk of fibrosis progression (age >50 years; diabetes,MetS, increased ALT) or active NASH with high necroinflammatory activity .

No drug has currently been tested in phase III trials and is approved for NASH by regulatory agencies. Therefore, no specific therapy can be firmly recommended and any drug treatment would be off-label

Insulin sensitizers

There is scarce evidence for a histological efficacy of metformin in NASH . The effect of metformin on liver fat is weak, because of its inability to restore serum adiponectin levels in the short-term . Some preclinical data support an anti-tumorigenic activity of metformin on liver cancer , while the demonstration of reduced rates of HCC in humans is limited to retrospective studies and insufficient for evidence-based recommendations

Thiazolidinediones are peroxisome proliferator-activated receptor (PPAR)c agonists with insulin-sensitizing effects.

ThePIVENS trial compared low dose pioglitazone vs. vitamin E vs. placebo for 2 years in patients without overt diabetes.

Pioglitazone improved all histological features (except for fibrosis) and achieved resolution of NASH more often than placebo

The
histological benefit occurred together with ALT improvement and partial correction of IR.

Similar results were reported in two smaller and shorter RCTs .

Prolonged therapy with rosiglitazone, up to 2 years, did not result in further histological improvement , although this was not formally tested with pioglitazone.

Side effects of glitazones are of concern: weight gain, bone fractures in women and, rarely, congestive heart failure.

Despite the safety and tolerability profile, pioglitazone can be used for selected patients with NASH, particularly in T2DM

where the drug has a registered use.

Incretin-mimetics, acting on the glucose-insulin interplay have shown favourable results in pre-marketing studies on liver enzymes . A small pilot trial of daily injections of liraglutide met the histological outcome of NASH remission without worsening of fibrosis

Antioxidants, cytoprotective and lipid lowering agents
In the PIVENS trial, vitamin E (800 IU/day) improved steatosis, inflammation and ballooning and induced resolution of NASH in 36% of patients (21% in the placebo arm) . Reduced ALT correlated with histological improvement and histological nonresponders
did not reduce ALT

In the paediatric TONIC trial

, vitamin E failed to reduce aminotransferases, steatosis and inflammation but improved ballooning and doubled the rate of NASH clearance vs. placebo.

Concerns about long-term safety of vitamin E exist, mainly an

increase in overall mortality , in haemorrhagic stroke

and prostate cancer in males older than 50.

Vitamin E may be used in non-cirrhotic non-diabetic NASH patients but further studies are needed before firm recommendations can be made.

Ursodeoxycholic acid (UDCA) has been investigated in several
RCTs, at different doses and for up to 2 years, but only showed
some biochemical but no histological improvements

A synthetic farnesoid X receptor agonist, obeticholic acid, improved IR in T2DM . In the phase IIb FLINT trial, a 72-week treatment with obeticholic acid in non-cirrhotic NASH patients, improved all NASH lesions while improving fibrosis Main issues with safety and tolerability were increased low-density lipoprotein (LDL)-cholesterol and pruritus

Preliminary data from small or uncontrolled studies suggested that n-3 polyunsaturated fatty acids (PUFA) might reduce liver fat, but two trials testing PUFA on histological outcomes were negative .

Available data on pentoxifylline and orlistat are limited or inconclusive. Also, data on lipid-lowering drugs are poor; recent trials with ezetimibe were negative , whereas

statins have not been adequately tested. Their use in NAFLD is safe, with no increased risk of hepatotoxicity, andmay even significantly reduce aminotransferases

Promising novel agents with anti-inflammatory, antifibrotic or insulin sensitizing properties (dual PPARa/d agonists, dual chemokine receptor [CCR]2/CCR5 antagonists and fatty acid/bile acid conjugates) and antifibrotic agents (anti-lysyl oxidase-like [anti-LOXL2] monoclonal antibodies) are also being tested in late-phase RCTs in NASH

Recommendations

- **Pharmacotherapy should be reserved for patients with NASH, particularly for those with significant fibrosis (stage F2 and higher).**

Patients with less severe disease, but at high risk of disease progression (i.e. with diabetes, MetS, persistently increased ALT, high necroinflammation) could also be candidates to prevent disease progression (B1

While no firm recommendations can be made ,
pioglitazone (most efficacy data, but off-label outside T2DM) or vitamin E (better safety and tolerability in the short-term) or their combination could be used for NASH (B2)

The optimal duration of therapy is unknown;

in patients
with increased ALT at baseline, treatment should be
stopped if there is no reduction in aminotransferases
after 6 months of therapy;

in patients with normal ALT at baseline, no recommendations can be made

Statins may be confidently used to reduce LDLcholesterol and prevent cardiovascular risk, with no benefits or harm on liver disease.

Similarly *n*-3 polyunsaturated fatty acids reduce both plasma and liver lipids, but there are no data to support their use specifically for NASH (B1

Iron depletion

Hepatic iron accumulation is associated with IR, and iron depletion improves IR . In NAFLD, high ferritin levels are common, in the presence of variable transferrin saturation, independent of gene polymorphisms of familial hemochromatosis. In these patients, a phlebotomy programme to reduce iron stores to near iron deficiency improved the NAS score, without worsening fibrosis but more data are needed.

Recommendations

- **Diet and physical activity improve steatosis and hepatic inflammation in paediatric NAFLD, but no beneficial effects on fibrosis have ever been demonstrated. No safe drug treatment has proven effective on fibrosis in paediatric NAFLD (B1)**

By improving obesity and diabetes, bariatric (metabolic) surgery reduces liver fat and is likely to reduce NASH progression;

prospective data have shown an improvement in all histological lesions of NASH, including fibrosis

Recommendations

- **Liver transplantation is an accepted procedure in NASH patients with end-stage liver disease, with comparable overall survival to other indications, despite a higher cardiovascular mortality.**

NASH
patients with liver failure and/or HCC are candidates for liver transplantation