Review

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From NAFLD in clinical practice to answers from guidelines

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Summary

This review of the literature consists of three sections.

First, papers concerning non-alcoholic fatty liver disease (NAFLD) awareness among the general population, general practitioners, and liver and non-liver specialists were retrieved and analyzed to highlight the perception of disease, verify knowledge of current recommendations, and identify the main difficulties experienced in clinical practice.

Next, position papers and clinical practice guidelines issued by International and National Hepatological Scientific Societies were identified and critically assessed in order to pinpoint the areas of convergence/difference.

Finally, practical suggestions on NAFLD diagnosis and management in daily practice are provided and the open questions highlighted.

Introduction

Non-alcoholic fatty liver disease (NAFLD), the hepatic counterpart of the metabolic syndrome (MS) [1,2], encompasses a disease spectrum spanning steatosis through non-alcoholic steatohepatitis (NASH) with/without cirrhosis, and hepatocellular carcinoma (HCC) [3]. The obesity and type 2 diabetes (T2D) pandemic and the improved management of chronic viral hepatitis have resulted in NAFLD becoming a leading cause of chronic liver disease (CLD) [4] and a major health concern owing to hepatic and extrahepatic morbidity/mortality [5–7].

Such a shift in the epidemiology of CLD has left practicing clinicians somewhat puzzled in identifying and treating this NAFLD "epidemic" [8–12]. Moreover, an ever increasing number of practice guidelines on NAFLD diagnosis and management issued by eminent Scientific Societies may probably add to the uncertainties concerning the best conduct to follow in clinical practice.

Our paper aims at (1) highlighting the perception of NAFLD among practicing physicians, (2) providing a critical, comparative analysis of the statements on NAFLD diagnosis and management, issued by clinical practice guidelines and technical reviews of Scientific Societies, (3) offering practical suggestions on the controversial topics and defining the unsettled questions.

Methods

We conducted a PubMed database search (keywords: general practice and/or primary care and/or specialists and/or physicians and/or awareness and/or perception and/or liver steatosis and/or fatty liver and/or NAFLD and/or NASH and/or guidelines and/or recommendations. Limits: December 2012 and English language) aimed at ascertaining: (a) the awareness/perception of the importance of NAFLD-NASH among potential patients and practicing physicians [both general practitioners (GPs) and specialists] and (b) guidelines/consensus/recommendations for NAFLD diagnosis and management issued by Medical Societies.

Six studies meeting the inclusion and exclusion criteria investigated current beliefs and practices of NAFLD among the general population, GPs and liver and non-liver specialists [8–13]. Moreover, three further studies [14–16] addressing the clinical approach of practicing physicians towards pediatric NAFLD were identified (Table 1).

Five position papers and clinical practice guidelines, issued by the European Association for the Study of the Liver (EASL) [17], Asian-Pacific Working Party for NAFLD (APWP-NAFLD) [18], Chinese Liver Disease Association (CLDA) [19], Italian Association for the Study of the Liver (IASL) [20] and American Gastroenterological Association (AGA)-American Association for the Study of Liver Disease (AASLD)-American College of Gastroenterology (ACG) [21], were identified. Three out of five such reports are evidence-based [19–21]. A single position paper on diagnosis of

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Abbreviations: NAFLD, non-alcoholic fatty liver disease; MS, metabolic syndrome; NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma; T2D, type 2 diabetes; CLD, chronic liver disease; GPs, general practitioners; EASL, European Association for the Study of the Liver; APWP, Asian-Pacific Working Party; CLDA, Chinese Liver Disease Association; IASL, Italian Association for the Study of the Liver; AGA, American Gastroenterological Association; AASLD, American Association for the Study of Liver Disease; ACG, American College of Gastroenterology; ESPGHAN, European Society for Pediatric Gastroenterology, Hepatology and Nutrition; LB, liver biopsy; US, ultrasonography; IR, insulin resistance; MRFs, metabolic risk factors; AFLD, alcoholic fatty liver disease; LTs, liver tests; CVD, cardiovascular disease.

Table 1. Analysis of reports from real-life clinical practice.

Author, yr [Ref.]	Methods	Main findings
Leung CM, *et al.*, 2009 [13]	Telephone survey on NAFLD knowledge among 521 subjects randomly selected from the general population in Hong Kong.	Among those interviewed, 83% had never come across the term "NAFLD." Among those who had heard of NAFLD, 42% had no idea about prevalence, 47% knew nothing about clinical presentation, 78% thought that blood tests could provide definite diagnosis, about 50% mistook associated risk factors and 81% perceived their knowledge of NAFLD as inadequate.
Grattagliano I, *et al.*, 2008 [8]	Online questionnaire and clinical survey about NAFLD knowledge and management before and after attending a teaching workshop among 56 GPs in Italy.	Before/after teaching workshop - Questionnaire (%): 4.7/42.7 indicated NAFLD as the first cause of undefined persistent hypertransaminasemia, 70/<10 underestimated NAFLD prevalence in general population, 36.6/76.2 would screen diabetic subjects, 39.5/100 should make diagnosis after exclusion of all other causes of liver steatosis, 23.2/61.9 should manage NAFLD patients with diet and a new check after 6 months, 2.3/80.9 should ask for LB in over 50 diabetic patients with persistent hypertransaminaseima, 78/91 indicated diet as the first approach. 34.1% should avoid statins. Practice check: improvement in screening of risk patients, searching for NASH and managing NAFLD.
Loguercio C, *et al.*, 2011 [10]	5-yr retrospective analysis from 104 GPs and 6550 patients with CLD in Italy.	Drinking habits registered in only 20.4% of CLD patients. 81.9% of patients with undefined CLD were overweight/obese. In patients with liver steatosis (NAFLD + AFLD): alcohol consumption recorded in 30.2%, BMI recorded in 59.5%, US performed in 37.9% of patients. No record of additional tests including insulin, HOMA index, ferritin, GGT, lipids and HBV- HCV markers.
Kallman JB, *et al.*, 2009 [9]	Survey questionnaire about screening for HBV, HCV and NAFLD among 103 GPs, 59 gastroenterologists and 52 hepatologists in USA.	Compared to specialists, GPs significantly less likely to be aware of official guidelines, to rate NAFLD as a common cause of liver disease, to screen for NAFLD in asymptomatic patients with diabetes but believed more strongly that available treatments for NAFLD are effective. Hepatologists endorsed appropriate screening scenarios more frequently than gastroenterologists and GPs.
Bergqvist CJ, *et al.*, 2012 [11]	Face-to-face questionnaire assessing beliefs and practices regarding NAFLD among 100 non-liver specialists in Australia.	75% underestimated the prevalence of NAFLD in the general population and 89% in high-risk patients. 57% considered alcohol consumption to be strongly associated with NAFLD. 60% deemed simple steatosis to confer excess liver-related mortality. 66% thought that NASH can be diagnosed with liver imaging. 71% made no referrals to hepatology services for suspected NAFLD.
Ratziu V, *et al.*, 2012 [12]	Survey assessing the clinical burden, perceived severity, and management patterns of NAFLD among 352, board-certified, hepato-gastroenterologists in France.	Most NAFLD patients were referred by GPs and only 20% by specialists. Conversely, 87% of hepatologists referred NAFLD patients for specialistic evaluation of potential co-morbidities. 65% would diagnose NASH irrespective of the concurrent CLD due to other etiology if MRFs were present. No agreement on the threshold of daily alcohol consumption that rules out NASH. Most physicians would overrate the importance of raised transaminases for the diagnosis of NASH. 62% delay LB after diet and lifestyle changes. 90% used non-invasive fibrosis markers. Roughy half did not measure fasting insulin/HOMA, 22% did not measure waist circumference. 73% monitored NAFLD patients themselves; most with yearly US and only 16% with fasting insulin/HOMA. 72% of patients were treated with non-pharmacological measures, often following referral to the endocrinologist/nutritionist. 42% recommended total abstinence from alcohol. Drugs treatment (metformin, UDCA, venesection, glitazones and vitamin E) was prescribed in only 28% of NAFLD patients.
Fishbein M, *et al.*, 2005 [15]	Analysis of physical examination findings and requests for diagnostic testing of 18 physicians involved in pediatric primary care on 11 obese children (4 with NAFLD) in USA.	Hepatomegaly was identified in 0.5% of obese children. Most commonly performed laboratory tests: fasting blood glucose (23%), lipid profile (20%), thyroid function tests (10%), and LTs (8.6%). Most common consultations: dietary (46%) and endocrinology (16%). Exercise program recommended in 4%. Abdominal imaging was requested in none of the encounters. In obese children with NAFLD, clinicians detected hepatomegaly in only 1.4% and requested LTs in 12.5% of encounters.
Sivertsen LM, *et al.*, 2008 [14]	Questionnaire assessing attitudes on diagnosis and management of overweight/obese children and awareness of clinical practice guidelines among 137 GPs in Australia.	The guidelines on the management of childhood obesity in general practice were reported to be used by 30% of respondents. 9% of GPs used BMI charts to correctly diagnose childhood obesity. 30% assessed for fatty liver in overweight/obese children. Over 80% of prescribed interventions were consistent with guidelines.
Riley MR, *et al.*, 2005 [16]	Retrospective chart review of 2256 pediatric outpatient visits at 2 academic hospitals (general pediatricians, pediatric endocrinologists and gastroenterologists) in USA.	Children with BMI 85 to 89%, 90 to 94% and ≥95% were given a diagnosis of overweight during 4, 8 and 48% of visits, respectively. General pediatrics, pediatric endocrinology and gastroenterology visits of overweight children included NAFLD screening in 2, 10 and 23% and metabolic screening in 8, 34 and 3% of cases, respectively.

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NAFLD in pediatrics was found (European Society for Pediatric Gastroenterology, Hepatology, and Nutrition [ESPGHAN]) [22].

The "real world" reports were analyzed to highlight the actual perception of NAFLD, verify the awareness of current recommendations, and identify the main difficulties experienced in clinical practice [8–16].

The recommendations issued by Scientific Societies were critically assessed in order to pinpoint the areas of convergence/difference.

The single position paper for pediatric medicine [22] was also examined in order to provide information useful to those involved in pediatric care.

Finally, prompted by the analysis of the reports of practicing physicians [8–16] and the systematic analysis/comparison of guidelines [17–22], we provide practical suggestions on NAFLD diagnosis and management in daily practice and highlight the open questions and future research.

Results and comments

Analysis of reports concerning issues from "real-life" practice and selected guidelines disclosed the following major topics regarding NAFLD diagnosis and management that remain a matter of dispute (Tables 1 and 2):

(1) Definition and initial assessment of suspected NAFLD patients;
(2) Screening strategies for NAFLD;
(3) Diagnostic strategies: non-invasive assessment and liver biopsy (LB);
(4) Management of NAFLD patients;
(5) Follow-up strategies of NAFLD patients;
(6) Pediatric NAFLD.

What is the definition of NAFLD and which is the initial assessment of suspected NAFLD patients?

Analysis of reports from real-life clinical practice

The single study evaluating the awareness of NAFLD in the general population demonstrated that the vast majority of people (83%) had never come across the term NAFLD; knowledge about NAFLD diagnosis and risk factors was also inadequate among those who had ever heard of it [13].

Similarly, several studies showed that knowledge about NAFLD diagnosis and assessment is relatively poor among GPs. An American study showed that GPs were less likely to consider NAFLD as a common cause of liver disease than Hepato-Gastroenterologists [9]. These findings are consistent with an Italian survey: only 4.7% of GPs indicated a metabolic cause as the first determinant of an "undefined" persistent hypertransaminasemia. Moreover, a great variability in diagnostic approach to NAFLD was described [8]. In Loguercio's retrospective analysis involving 104 GPs, alcohol consumption, BMI, transaminases, and ultrasonography (US) were assessed only in a minority of patients with liver steatosis; no additional tests [markers of insulin resistance (IR), lipid profile, viral hepatitis serologies] were recorded [10].

In a recent survey of 100 hospital non-liver specialists, >90% appreciated that traditional cardiovascular risk factors predicted NAFLD and acknowledged these to be common in non-liver patients. Moreover, 57% considered alcohol consumption to be strongly associated with NAFLD [11].

A French survey among 352 Hepato-Gastroenterologists showed that two-thirds would diagnose NAFLD irrespective of the co-existence of other CLD, as long as metabolic risk factors (MRFs) were present. There was no agreement on the threshold of daily alcohol consumption that ruled out the diagnosis of NAFLD. In the initial assessment of NAFLD patients, a large majority of surveyed specialists collected information on BMI, blood pressure, and glucose or lipid parameters; nonetheless, a sizeable proportion never assessed surrogate markers of IR or measurements of regional adiposity [12].

Analysis of guidelines

All guidelines agree that diagnosis of NAFLD relies on both imaging or histological evidence of hepatic steatosis and exclusion of causes of secondary hepatic fat accumulation; there is full agreement that NAFLD is strictly associated with MRFs. All Scientific Societies state that, because of the high prevalence of MRFs, NAFLD can co-exist with other CLDs. There is universal consensus that the metabolic profile should be assessed, competing etiologies of steatosis and co-existing CLD should be ruled out, and alcohol consumption should be estimated [17–21].

Regarding metabolic assessment, the majority of guidelines [17–20] highlight the importance of testing insulin sensitivity. However, there seems to be no consensus on how this should be done. All societies agree that presence of overweight/obesity should be evaluated through anthropometric measures (BMI, waist circumference) and that blood pressure and serum lipids measurement should be performed as a minimal initial assessment [17–21]. Regarding the criteria to adopt for the diagnosis of MS, the American guideline [21] recommends the Adult Treatment Panel III definition [23,24], whereas Asian-Pacific Societies [18,19] recommend the International Diabetes Federation criteria [25].

All guidelines concur that all NAFLD patients should undergo a careful familial and medical history, viral hepatitis and autoimmune serology, alpha1-antitrypsin, iron and copper status measurement. The common association between chronic HCV infection and hepatic steatosis and its implications for fibrosis progression and/or treatment response rate are mentioned by all guidelines [17–21].

The threshold for hepatotoxic alcohol consumption to rule out alcoholic liver disease varies as a function of local drinking culture/habits. European Associations [17,20] maintain a threshold of 30 and 20 g of alcohol daily for men and women, respectively. Similarly, the American guideline [21] suggests 210/140 g (=21/14 drinks) of alcohol weekly, whereas Asian-Pacific countries [18,19] restrict to 140/70 g of alcohol weekly for men and women, respectively. Moreover, the American guideline specifically recommends a 2-year alcohol withdrawal for NASH clinical trials candidate eligibility purposes [21]. This point is not discussed in other guidelines.

Comments

In recent years, the diagnostic strategy for NAFLD has evolved from a diagnosis of exclusion towards a *chiefly positive* approach based on the recognition of the underlying dysmetabolic milieu [1,2]. In patients with suspected NAFLD, exclusion of competing etiologies for steatosis is essential. To this end, endocrine disorders [26], familial hypobetalipoproteinemia [27], alcohol abuse,

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Table 2. Analysis of guidelines.

	AGA, AASLD, ACG [21]	CLDA [19]	IASL [20]	EASL [17]	APWP [18]	ESPGHAN [22]
Screening	-	+ (US and LTs in patients with MS)	/	+ (US and LTs in patients with MS and IR)	+ (US and LTs in patients with MS)	+ (US and LTs in overweight/obese children older than 3)
Initial evaluation						
Metabolic assessment	+	+	+	+	+	+
Competing causes of steatosis	+	+	+	+	+	+
Alcohol consumption	+ (M/F 21/14 drinks per wk)	+ (M/F 140/70 g weekly)	+ (M/F 30/20 g daily)	+ (M/F 30/20 g daily)	+ (M/F 140/70 g weekly)	/
Coexisting liver disease	+	+	+	+	+	+
Non-invasive assessment	+ (NAFLD Fibrosis Score)	- (only for research study)	+ (NAFLD Fibrosis Score and FibroScan®)	+ (serum markers and FibroScan®)	- (only for research study)	- (only for research study)
Liver biopsy	+ (restricted to selected patients)	+ (restricted to selected patients)	+ (restricted to selected patients)	+ (restricted to selected patients)	+ (restricted to selected patients)	+ (restricted to selected patients)
Management						/
Lifestyle intervention	+	+	+	+	+	
Pharmacological treatment	+ (pioglitazone and vitamin E in non-diabetic biopsy-proven NASH)	+	- (reserved to controlled studies)	+ (glitazones, vitamin E and high-dose UDCA in NASH)	- (reserved to controlled studies)	
Bariatric surgery	- (but is not contraindicated in eligible obese NAFLD)	+ (in obese patients refractory to medical measures)	- (reserved to controlled studies)	+ (in morbidly obese advanced fibrotic NASH)	+ (in obese patients refractory to medical measures)	
Metabolic control	+	+	+	+	+	
Follow-up						/
Hepatologic	+	+	+	+	+	
Cardiovascular	+	+	+	+	+	
Oncologic	-	+	+ (on individual basis)	-	+	
Children	Pediatric NAFLD section	/	/	/	/	Diagnostic aspects of pediatric NAFLD

+, recommended; -, not recommended; /, not mentioned.

and, particularly, HCV infection, given that HCV infection, diabetes and steatosis are closely linked to one another [28–30], need to be ruled out. Moreover, it is also necessary to carefully assess for MRFs and the cardiovascular risk profile. Furthermore, NAFLD can occur together with other CLD, which may accelerate the progression of liver injury [31–35]. Accordingly, in liver patients with MRFs, the presence of concurrent NAFLD should be evaluated. Conversely, when steatosis is detected in patients with CLD due to non-NAFLD etiology, a metabolic assessment is needed. It is critical to define the appropriate standard anthropometric, biochemical and imaging protocol to be followed to detect NAFLD in clinical practice.

NAFLD definitely needs to be differentiated from alcoholic fatty liver disease (AFLD). However, due to the low reliability of the diagnostic methods (patient interview and biomarkers), a clear distinction between the two conditions is difficult [36–39]. Moreover, the recommended thresholds of "significant alcohol consumption" and the duration of alcohol withdrawal in those with suspected NAFLD are arbitrary. In addition, an overlap between alcohol consumption and metabolic disorders exists,

making a clear attribution of steatosis to AFLD as opposed to NAFLD virtually impossible in the individual patient. For these reasons, some authors consider this distinction of fatty liver disease artificial and poorly useful [40].

Key Points 1

- Awareness of NAFLD, its diagnosis, and risk factors in the general population is poor. Knowledge about NAFLD diagnosis and assessment is relatively inadequate among general practitioners, particularly so in NAFLD pediatric patients. Specialists other than hepatologists under-appreciate the overlap between NAFLD and metabolic risk factors, thus missing a significant proportion of high-risk NAFLD patients. Hepatologists themselves risk under-diagnosing NAFLD due to over-reliance on transaminases

Who and how to screen for NAFLD?

Analysis of reports from real-life clinical practice

Grattagliano's survey showed that 70% of Italian GPs underestimated the prevalence of NAFLD among the general adult population, only 36.6% would screen for NAFLD diabetic subjects and a substantial subset of hypertransaminasemic patients were not considered for NAFLD even in the presence of MRFs. Specific training significantly improved GPs' ability in screening at-risk patients [8]. The underestimation of the NAFLD problem by GPs was confirmed by another Italian study, in which an extremely low prevalence of fatty liver was reported, and a high proportion of patients were considered as affected by "undefined" CLD despite a high rate of overweight/obesity and an incomplete diagnostic work-up [10]. GPs are reported to be less familiar with current recommendations and to use appropriate screening strategies less frequently than hepato-gastroenterologists unless they are fully aware of guidelines [9].

An Australian survey showed that also non-liver Specialists underestimated the prevalence of NAFLD both in the general population and in high-risk patients, thus reflecting a low grade of referrals to Hepatology services [11]. Accordingly, a French study reported that only 20% of NAFLD patients seen in gastroenterology practice were referred by specialists in the metabolic field. This survey stressed that among liver specialists there was an over-reliance on transaminases instead of MRFs or US steatosis, when considering the diagnosis of NAFLD [12].

Analysis of guidelines

The majority of guidelines [17–19] explicitly suggest the opportunity to implement a screening policy in individuals at high risk of NAFLD identified by the presence of MRFs and/or IR. Two guidelines either fail to mention [20] or discourage any screening policies [21]. Indeed, the most recent American guideline [21] states that systematic screening for NAFLD is not recommended not only in the general population but also in high-risk patients, in family members and in obese children, due to paucity of evidence.

All Scientific Societies who support screening suggest that it should be done through both US and Liver Tests (LTs).

Comments

The prevalence of NAFLD in the general population ranges from 6.3% to 51% depending on the method used to assess liver steatosis and the population/ethnicity studied [41–45]. This prevalence can be significantly higher in individuals with MRFs [46–48]. Moreover, familial aggregation and heritability of NAFLD have been consistently reported [49–52].

There are important differences concerning the definitions of overweight/obesity and MS between Western and Asia-Pacific patients. In the Asian population, morbidity and mortality occur at lower BMIs and smaller waist circumferences than in Caucasians, justifying specific criteria for overweight/obesity and MS representative of people living in the Asia-Pacific region [25,53–55].

Although the majority of NAFLD cases are strongly associated with overweight/obesity and T2D, different studies reported a prevalence of NAFLD in the normal-weight population between 7% and 16% [42,56–59]. These studies invariably demonstrated that NAFLD is closely associated with metabolic disorders, particularly IR, even in lean patients. NAFLD should be considered an early predictor of metabolic derangements, thus suggesting that IR, rather than frank diabetes or obesity, is the alteration to be detected when screening for NAFLD. Therefore, methods and thresholds to define subtle IR are strongly needed in order to detect those patients at increased risk of hepatic complications.

Compared to the general population, NAFLD is independently associated with a significantly higher all-cause mortality [5–7,60–65], and cancer incidence [66,67], principally HCC [68,69], increased incident T2D risk [6,70,71], greater prevalence/incidence of cardiovascular disease (CVD) [72–75], and a higher rate of major complications and death after surgery [76–78].

Based on the above reasons, detection of NAFLD should be considered as a major task in the management of patients with features of IR. Nevertheless, due to uncertainties surrounding the best diagnostic and management strategy, unequivocal indications in NAFLD screening policies are lacking.

US, being safe, inexpensive, widely available, and having a good performance when steatosis is present in at least 20–30% of hepatocytes is an acceptable first-line screening procedure for NAFLD in clinical practice. However, the relatively low acuity for mild steatosis, the low accuracy in morbid obesity, and its operator-dependency are the main limitations [79,80]. Interestingly, although not so sensitive as magnetic resonance spectroscopy [81,82], US can nevertheless have a lower threshold for fat detection than previously appreciated [80]. Criteria used to define US steatosis need to be standardized and semi-quantitated. Once such semi-quantitation is performed through simple scores, US is able to predict metabolic derangements and liver histology changes [83,84].

Despite the almost universal reliance on transaminases in real-life practice, LTs are not considered a useful tool in NAFLD screening. Indeed, the majority of NAFLD patients have normal transaminases [42], which do not rule out histologically advanced disease [85,86]. The definition of the "normal" transaminases range is controversial. Transaminases reference ranges currently used underestimate the prevalence of patients with liver diseases and the upper limit of "normal" alanine aminotransferase has been downgraded to 30 U/L for men and 19 U/L for women [87–92].

Key Points 2

- All guidelines agree that the diagnosis of NAFLD relies on both imaging and histological evidence of hepatic steatosis after exclusion of competing etiologies of liver fat deposition (typically HCV infection, alcohol consumption and other) in individuals with metabolic risk factors. NAFLD patients should undergo a careful familial and medical history, viral hepatitis and autoimmune serology, alpha 1-antitrypsin, iron and copper status measurement. The threshold for hepatotoxic alcohol consumption and the extent of alcohol withdrawal to rule out alcoholic liver disease remain to be defined. NAFLD may well co-exist with other chronic liver diseases, typically HCV infection. The majority of guidelines suggest the opportunity to implement a screening policy (through both US and LTs) in individuals at high risk of NAFLD identified by the presence of metabolic risk factors and/or IR. LB should not be performed in all NAFLD patients but should be restricted to those NAFLD patients presenting an increased risk for NASH or advanced fibrosis

How to non-invasively assess inflammation and fibrosis and when to obtain an LB?

Analysis of reports from real-life clinical practice

Grattagliano reported that the majority of GPs indicated hypertransaminasemia or none as the best reason to ask for LB in NAFLD subjects. Only 2.3% of GPs chose over 50 year-old diabetic patients as potential candidates for LB. However, after attending a tailored workshop, 80.9% indicated the latter as good candidates for LB and a substantial proportion reconsidered a fraction of their previously diagnosed NAFLD patients at potential risk of NASH [8].

The Australian survey among non-liver Specialists reported that 98% correctly identified that NASH can be diagnosed on LB, about three-quarters agreed that LTs are not sufficiently sensitive to detect NASH, but 66% deemed that a diagnosis of NASH can be based on imaging [11].

Ratziu showed that about two-thirds of Hepato-Gastroenterologists considered important the identification of steatohepatitis or the staging of fibrosis. However, the main indication for LB was to gauge the fibrosis stage. In fact, given the invasive nature of LB, 38% would not perform this procedure to estimate hepatic inflammation. Confirming that transaminases levels impact on the decision to perform an LB, 43% of hypertransaminasemic *vs.* 6% of normotransaminasemic NAFLD patients would be asked to undergo an LB. Non-invasive fibrosis markers were used by 90% of the surveyed physicians in clinical practice: the majority used both serum markers and elastometry [12].

Analysis of guidelines

Initial non-invasive assessment of inflammation and fibrosis is suggested in clinical practice by some [17,20,21] but not all guidelines. CLDA and APWP restrict non-invasive assessment of NASH and fibrosis to research purposes alone [18,19]. European and Italian guidelines suggest the combined use of clinical and laboratory parameters, serum markers, composite scores (particularly the NAFLD fibrosis score) and imaging methods (transient elastography – FibroScan) in order to reduce the number of NAFLD patients requiring LB [17,20]. The American guideline confirms the clinical utility of NAFLD fibrosis score in identifying NAFLD patients with higher likelihood of having advanced fibrosis and highlights the importance of MS as strong predictor of NASH [21].

There is universal agreement that LB should not be performed in all patients. All guidelines recommend LB in NAFLD patients presenting an increased risk for NASH or advanced fibrosis [17–21]. LB is considered in suspected NAFLD patients in whom there is diagnostic uncertainty due to difficulties in excluding competing etiologies for hepatic steatosis and co-existing CLD by the majority of guidelines [18,19,21]. The European guideline recommends performing LB to assess concurrent NAFLD in patients with other CLD, MRFs, and US steatosis [17]. Asian-Pacific and European guidelines suggest the opportunity to perform LB in NAFLD patients subjected to surgical procedures for other purposes [17,18]. All guidelines (implicitly or explicitly) recommend LB in NALFD patients enrolled in clinical trials [17–21].

Comments

Simple steatosis is associated with a normal life expectancy and its progression is limited to anecdotal case reports [93–95]. Conversely, NASH worsens in up to 30% of cases, evolving in cirrhosis in a substantial fraction of cases [3,61,96]. Moreover, 30–75% of cases of cryptogenic cirrhosis can be attributed to previously unrecognized NASH [68,97–101]. Given that the presence of inflammation at the initial LB is the strongest predictor of NAFLD progression and that the degree of fibrosis is the most important prognostic factor, efforts of practicing physicians should be oriented towards identification of those patients with steatohepatitis and/or advanced fibrosis.

LB is the gold-standard for direct diagnosis of NASH and evaluation of inflammation/fibrosis, however, its use is limited by invasiveness, cost and sampling error [102]. Several non-invasive methods for identifying patients with NASH or fibrosis have been proposed [5,103–106], but validated decisional algorithms adequate for clinical practice are still lacking.

Key Points 3

- All NAFLD patients should undergo interventions aimed at promoting healthier lifestyles and strict control of metabolic risk factors associated with NAFLD. Pharmacotherapy (glitazones, vitamin E, possibly associated with high-dose UDCA) should be reserved for NASH patients possibly in randomized controlled trials. Concurrent metabolic risk factors associated with NAFLD should be managed as clinically required and drugs given as needed. Bariatric surgery, if otherwise indicated, is considered a valid option for obese patients with NAFLD/NASH. Heavy alcohol consumption should be discouraged. Light-moderate alcohol consumption may exert favorable metabolic effects and, perhaps, on liver outcomes. However, in the absence of randomized controlled trials, all guidelines advise against prescribing low-moderate alcohol consumption as a preventive/therapeutic strategy fort NAFLD. Hepatological and cardiovascular follow-up is indicated in NAFLD patients. Oncologic screening/surveillance should be considered on individual risk

How to treat NAFLD patients?

Analysis of reports from real-life clinical practice

In the Italian survey, 78% and 91% of GPs, before and after the workshop, respectively, indicated diet as the first and best approach to NAFLD. 34.1% stated that statins should be avoided in NAFLD patients [8].

In Bergqvist's study, 95% of non-hepatologists agreed that management of NAFLD involves weight loss, physical exercise, and treatment of concurrent MRFs. Further to lifestyle changes, drugs to lose weight and bariatric surgery were included in NAFLD management, whereas 75% of respondents excluded specific liver-directed drug therapy [11].

The French survey among hepatologists showed that 72% of patients were treated with lifestyle changes only, while 28% were treated with drugs further to non-pharmacological interventions. The most frequently prescribed regimens were: metformin, ursodesoxycholic acid, phlebotomy, glitazones, and vitamin E. 42% recommended total abstinence from alcohol; about 50% allowed daily alcohol consumption of 10–30 g in male and 10–20 g in female patients [12].

Analysis of guidelines (Table 3)

There is universal consensus that all patients should undergo interventions aimed at promoting healthier lifestyles and strict control of MRFs associated with NAFLD. All guidelines agree that lifestyle changes including weight loss, dietary changes, and physical exercise should always be implemented as first-line option in all NAFLD patients [17–21].

With regard to the entity of weight loss, the Italian guideline simply states that 0.5 kg/week weight loss should be considered in overweight individuals [20], whereas the Chinese guideline recommends more than 5% weight reduction in 6–12 months [19]. The European guideline suggests that a weight loss of 7% should be reasonable in overweight and mildly obese patients [17]. Finally, American societies provide more specific indications: loss of at least 3–5% of body weight to improve steatosis, and up to 10% to improve necroinflammation [21].

All societies concur in recommending a hypocaloric diet to promote weight-loss [17–21]. However, while the Chinese guideline provides quantitative details (intake of 500–1000 kcal daily for obese adults) [19], almost all guidelines identify qualitative directions (low carbohydrate and saturated fat intake, avoidance of fructose-enriched soft drinks and increased consumption of fibers and antioxidants-rich fruits and vegetables) [17,19,20].

All guidelines agree that heavy alcohol consumption should be avoided in NAFLD patients. However, no guidelines encourage mild-moderate intake [17–21].

All guidelines strongly recommend avoidance of sedentariness and implementation of physical activity. The European guideline is more accurate in suggesting at least 150 min per week of moderate-intensity physical activity and at least 75 min per week of vigorous-intensity physical activity, further to muscle strengthening twice a week [17]. Similarly, the Chinese guideline recommends moderate aerobic exercise at least 4 times weekly, with a minimum cumulated exercise time of 150 min [19]. Moreover, European societies [17,20] and the Chinese guideline [19] highlight behavior therapy as important in accomplishing weight loss.

Pharmacologic therapy should be reserved only to NASH. The more conservative suggestion is to limit the use of drugs to randomized controlled trials [18,20]. However, EASL suggests a 1–2 year course of therapy with glitazones or vitamin E, preferably associated with high-dose UDCA [17]; the AGA-AASLD-ACG guideline advocates pioglitazone and vitamin E in non-diabetic biopsy-proven NASH [21]; and the Chinese guideline proposes liver protective and anti-inflammatory drugs, including Chinese traditional and western medicines, in biopsy-proven NASH [19].

All guidelines agree that the underlying MRFs should be managed as clinically required in NAFLD patients and drugs (particularly statins for dyslipidemia) given as needed [17–21]. Bariatric surgery, if otherwise indicated, is considered a valid option for obese patients with NAFLD/NASH by all but one guideline [20].

Comments

The management of NAFLD patients is based on treatment of liver disease alongside the associated MRFs [107,108]. Data on this topic are many and perhaps confusing. Guidelines are influenced by the year of publication. There are no medications specifically approved for NASH, therefore drug treatments specifically aimed at liver disease should be reserved to randomized trials with histological end points. Interestingly, there is increasing evidence for a beneficial effect of pioglitazone and vitamin E on liver outcomes in non-diabetic patients with biopsy-proven NASH [109], and a recent cost-utility analysis indicated that, in subjects with NASH and advanced fibrosis, treatment with either pioglitazone or vitamin E further to standard lifestyle changes is likely cost-effective [110]. However, pioglitazone, vitamin E, and UDCA are not free of side and toxic effects. Pioglitazone is associated with weight gain and an increased risk of congestive heart failure, bone fractures, and bladder cancer [111,112]. High-dose vitamin E has been linked to increased all-cause mortality and an excess hemorrhagic stroke and prostate cancer [113,114]. High-dose UDCA determines diarrhea and abdominal discomfort [115].

From a practical perspective, ameliorating cardiometabolic risk profile and histological disease activity, lifestyle-induced weight loss should be recommended in all NAFLD patients, but clear targets and suggestions on how to reach them are needed. It should be highlighted that the common pharmacological treatment of MRFs (particularly statins) is not contraindicated in NAFLD [116].

As far as alcohol intake concerns, on the one hand, heavy consumption is harmful to the liver [117] and should be discouraged. On the other hand, light-moderate alcohol consumption might well exert favorable effects on MRFs and, perhaps, on liver outcomes [118–121]. However, in the absence of randomized controlled trials, all guidelines discourage from prescribing low-moderate alcohol consumption as preventive/therapeutic strategy against NAFLD.

How to follow-up NAFLD patients?

Analysis of reports from real-life clinical practice

Two-thirds and 22% of the surveyed Australian non-liver Specialists considered semi-annual LTs and 5 yearly LB as the most effective method for monitoring NAFLD patients [11]. The majority of French Hepatologists stated to monitor their NAFLD

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Table 3. How to manage NAFLD patients?

	AGA, AASLD, ACG [21]	CLDA [19]	IASL [20]	EASL [17]	APWP [18]
Weight loss	+ (3-5% to improve steatosis, 10% to improve NASH)	+ (more than 5%)	+ (0.5 Kg/wk)	+ (7%)	+
Hypocaloric diet	+	+ (500-1000 Kcal)	+	+	+
Alcohol	-,?	-	- (particularly in obese NAFLD)	?	/
Physical exercise	+	+ (4 times per week, 150 min of aerobic exercise)	+	+ (150 min/wk moderate and 75 min/wk vigorous exercise)	+
Educational therapy	/	+	+	+	/
Metformin	-	- (not contraindicated in diabetic NAFLD)	- (not contraindicated in diabetic NAFLD)	- (not contraindicated in diabetic NAFLD)	- (not contraindicated in diabetic NAFLD)
Glitazones	+ (pioglitazone in non-diabetic biopsy-proven NASH)	- (not contraindicated in diabetic NAFLD)	- (not contraindicated in diabetic NAFLD)	+ (NASH)	- (not contraindicated in diabetic NAFLD)
Vitamin E	+ (in non-diabetic biopsy-proven NASH)	+	-	+ (NASH)	-
UDCA	-	+	-	+ (NASH)	-
Omega-3 FA	- (not contraindicated in hypertriglyceridemic NAFLD)	+	- (not contraindicated in hypertriglyceridemic NAFLD)	- (not contraindicated in hypertriglyceridemic NAFLD)	- (not contraindicated in hypertriglyceridemic NAFLD)
Statins	- (not contraindicated in dyslipidemic NAFLD)	- (not contraindicated in dyslipidemic NAFLD)	- (not contraindicated in dyslipidemic NAFLD)	- (not contraindicated in dyslipidemic NAFLD)	- (not contraindicated in dyslipidemic NAFLD)
Bariatric surgery	- (not contraindicated in eligible obese NAFLD)	+ (in obese patients refractory to medical measures)	- (reserved to controlled studies)	+ (in morbidly obese advanced fibrotic NASH)	+ (in obese patients refractory to medical measures)

+, recommended; –, not recommended; /, not mentioned.

patients with a mean number of two annual visits. LTs and US were the most frequently performed procedures. 57% did not perform follow-up LB. With regards to MRFs, the majority of surveyed specialists monitored glycemic and lipid profile, and half of those who assessed these parameters did so twice a year. However, surrogate markers of IR were never monitored by at least 50% [12].

Analysis of guidelines

There is universal consensus on the opportunity to perform hepatological and cardiovascular follow-up in NAFLD patients [17–21]. In NAFLD patients, semi-annual to annual hepatic monitoring (non-invasive follow-up of fibrosis, liver US, transaminases and LTs, markers of IR) is warranted [17,19]. Routine repetition of LB is not indicated [21]. LB may be repeated not earlier than 5 years after baseline LB in those patients in whom fibrosis progression is suspected [17]. Surveillance for esophago-gastric varices [17,19,21] and HCC [17,19–21] in patients with NASH-cirrhosis is advocated by the majority of societies.

All societies agree that a thorough assessment of MRFs and a risk stratification for CVD should be done in all NAFLD patients [17–21]. These evaluations should be repeated every 6 months–1 or 2 years [17,19,20]; the interval between check-ups should be modulated on an individual basis, mirroring the severity of liver disease and clustering of MRFs [17,20]. Generalized cancer screening programs cannot be proposed to all NAFLD patients [20]. Three out of five guidelines support the practice of oncologic

follow-up on individual basis [18–20]. Four scientific societies specifically mention HCC among the cancer types to which NAFLD patients may be prone [17,19–21]. The guideline of the Asia-Pacific region suggests to extend screening to those "*cancers whose incidence is increased by MS*" [18].

Comments

Considering the natural history of NAFLD, in terms of liver-related, metabolic, cardiovascular and neoplastic complications, patients affected warrant screening for MRFs and progressive liver disease [5]. However, most of our understanding of the natural course of hepatic and extrahepatic co-morbidities of NAFLD is based on data from hepatological referral centers evaluating selected groups of individuals [78]. Despite such limitations, the increasing burden of NAFLD-related primary liver cancers, principally HCCs [68,69] that may occur in non-cirrhotic NAFLD [122], suggests the opportunity of more liberal surveillance programs in these patients. However, specific recommendations about screening for HCC in NAFLD patients are lacking and there are no data on the cost-effectiveness of surveillance programs in these patients. Moreover, an increased risk of colorectal and other types of cancers has been described in NAFLD patients [66,67]. Efforts should be made to identify the cardiometabolic, hepatologic, and oncologic risks in the individual patient and to develop personally tailored follow-up schedules.

Key Points 4

More attention should be paid to medical education and emphasis be placed in integrated NAFLD management. Questions to be answered are:

- The definition of NAFLD natural history in the general population rather than in cohorts selected in tertiary referral centers,
- The definition of unequivocal NAFLD screening policies,
- The assessment of methods and thresholds to define subtle IR,
- The validation of decisional algorithms for LB submission,
- The identification of methods to obtain healthy lifestyle changes targets,
- The definition of personally-tailored cardiometabolic, hepatologic, and oncologic surveillance strategies

Pediatric NAFLD

Analysis of reports from real-life clinical practice

A survey among American primary pediatric care providers showed that, in obese children with NAFLD, clinicians detected hepatomegaly in only 1.4% and requested LTs in 12.5% of encounters, thus increasing the likelihood of a delayed or omitted diagnosis [15]. An Australian survey described that only 9% of GPs used BMI charts to correctly diagnose childhood obesity and only 30% assessed for fatty liver in overweight/obese children [14].

Another survey among general pediatricians and pediatric endocrinologists and gastroenterologists at two American academic hospitals confirmed the underdiagnosis of obesity and the underscreening for MS and NAFLD in children [16].

Analysis of guidelines

Among adult NAFLD guidelines, only the American one deals with specific aspects of pediatric NAFLD [21]; a single position paper is specifically devoted to diagnosis of NAFLD in children and adolescents [22]. The American guideline and ESPGHAN statement disagree with regard to screening for NAFLD in overweight/obese children. American societies suggest that a formal recommendation cannot be made [21], whereas ESPGHAN states that NAFLD should be suspected in all overweight/obese children and adolescents older than 3 years especially if familiarity for NAFLD is present [22].

According to ESPGHAN, abdominal US and LTs should be the first diagnostic step in suspected NAFLD children, followed by exclusion of other liver diseases [22]. The two guidelines agree that very young or lean children with liver steatosis should be tested for monogenic metabolic disorders as causes of fatty liver [21,22].

Both documents suggest similar indications for LB: to rule out other treatable diseases, in cases of clinically suspected advanced liver disease, before pharmacological/surgical treatment, and as part of a structured intervention protocol or clinical research trial [21,22]. Only the American guideline discusses treatment of pediatric NAFLD. According to AGA-AASLD-ACG, intensive lifestyle modification is recommended as the first-line treatment in pediatric NAFLD. Metformin should be avoided. Vitamin E offers histological benefits to children with NASH, but confirmatory studies are needed before its use can be recommended in clinical practice [21].

Comments

The rising incidence of obesity is paralleled by the increasing recognition of NAFLD also in children and adolescents [123,124]. Due to its potential progressive nature also in childhood [125,126], early diagnosis and treatment are important in all age-groups [127]. Therefore, shared standards to be used by physicians caring pediatric NAFLD are needed. Non-invasive diagnostic strategy represents a key issue in pediatric practice. However, contrasting with adult medicine, relatively scarce data are available in pediatric patients [105,128].

Discussion

Given that NAFLD epidemic poses a heavy health-related costs burden [129], an effort is justified to improve our medical ability in clinical practice. A successful management plan requires a motivated public, competent primary care doctors and specialists, and the implementation of multidisciplinary collaborative networks [130]. However, studies in "real-life" practice have shown that: (1) awareness of NAFLD is low in the general population [13]; (2) knowledge of NAFLD and its complications is not properly diffused among GPs who thus may fail to approach some

Table 4. Open questions and future studies.

Screening	• Which screening/surveillance policies for NAFLD in individuals with a single MRF and incomplete features of the MS (e.g. T2D/obesity/dyslipidemia/hypertension alone or variedly associated)? • What about screening in "NAFLD families"? • What about screening for NAFLD in the setting of liver transplantation and major hepatic surgery? • New lowered aminotransferases ranges?
Initial evaluation	• Which is the appropriate standard anthropometric, biochemical and imaging protocol to be followed to detect NAFLD in clinical practice? • Definition of threshold and duration of alcohol consumption • How to measure IR? Which ranges? • A role for genetics [131]? • A role for gut microbiota [132-134]?
Non-invasive assessment	• NASH and fatty liver: two different entities? • Which diagnostic protocols/algorithms in clinical practice? • A role for novel US scoring systems [83,84]?
Liver biopsy	• Which criteria to restrict the number of individuals to submit to LB through strict pre-biopsy testing? • More liberal use in those undergoing surgery for related conditions: gallstones, T2D, obesity? • Is LB mandatory in clinical trials (when are surrogate indices enough?)?
Management	• Diets: standard criteria *vs.* general suggestions? • Entity and types of physical activity? • Role of psychological support-web-based platforms? • Alcohol intake: pros and cons? • When are drugs indicated? • Iron depletion: when, why and how [135,136]? • Gut microbiota: a role for probiotics/antibiotics?
Follow-up	• Definition of NAFLD natural history in unselected populations • Cost-effective analysis of personally tailored screening/surveillance programs for liver-related, cardiovascular and oncologic complications
Children	• Non-invasive diagnostic strategy of NAFLD in pediatric age • To extend recommendations for NAFLD in adults to children *vs.* specific recommendations for pediatric NAFLD?

aspects of diagnosis and management [8–10,14,15]; (3) specialists other than hepatologists may miss a high proportion of high-risk NAFLD patients and under-appreciate the overlap between NAFLD and other MRFs [11,12,16]; (4) a proportion of hepatologists risk to under-diagnose NALFD due to over-reliance on transaminases [12].

Taken collectively, some data [8–16] support that more attention should be paid to medical education and emphasis be placed in integrated NAFLD management. Indeed, awareness of guidelines and teaching programs consistently improve specific competence of practicing physicians [8,9]. Moreover, increased consistency among guidelines issued by different medical societies might eventually result in improved care of NAFLD in clinical practice [9].

Here we have raised awareness of existing guidelines for NAFLD and provided practical suggestions on the chief controversial topics regarding diagnosis and management of NAFLD in daily practice.

In summary:

(1) A new *positive* definition of NAFLD, in which IR and MRFs are the mainstay, is required. All guidelines agree that patients suspected for NAFLD should undergo, as the initial evaluation, a careful assessment of MRFs, competing causes of liver steatosis (particularly HCV infection, alcohol abuse and other), and co-existent CLD [17–21].

(2) Screening for NAFLD is not recommended in the general population. All but one guideline [21] recommend screening for liver steatosis in patients with MRFs. Features of IR should be considered a major prompt to detect NAFLD. US should be the first-line screening procedure for NAFLD [79,80], whereas transaminases are not a useful tool in clinical practice [85,86].

(3) Non-invasive tests are needed to predict NASH and fibrosis in NAFLD patients in order to restrict LB to selected individuals. NAFLD fibrosis score and FibroScan could be useful to this end [5,105]. LB is universally considered the diagnostic and prognostic standard in NAFLD. However, given its invasiveness and costs, there is full agreement in limiting its use on a case-by-case basis.

(4) All guidelines agree that lifestyle modifications are the first-line approach to manage NAFLD patients [17–21]. Bariatric surgery could be a valid option in morbidly obese NAFLD patients non-responders to lifestyle changes. Pharmacologic therapy should be restricted to clinical trials. Specific drug treatments of MRFs (particularly statins) are not contra-indicated in NAFLD patients.

(5) NAFLD patients should undergo regular follow-up not only for liver-related complications but also for metabolic and cardiovascular diseases. Oncologic screening/surveillance should be considered on individual risk.

(6) Pediatric NAFLD shares the same MRFs as NAFLD in adults. Diagnosis of NAFLD in children requires a thorough work-up and exclusion of age-specific diagnoses.

In conclusion, current guidelines appear to be somewhat heterogeneous, if not contradictory, and fragmentary, suggesting the opportunity to implement global recommendations concerning the conduct to be followed in real-life clinical practice and much

research remains to be done about NAFLD screening, diagnosis, management, and follow-up (Table 4).

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Conflict of interest

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