Nonalcoholic Fatty Liver Disease in Children with Obesity: Narrative Review and Research Gaps

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Keywords

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Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is the leading hepatic disease in children, ranging from steatosis to steatohepatitis and fibrosis. Age, sex, hormonal levels, pubertal stages, genetic risk- and epigenetic factors are among the many influencing factors. Appearing predominantly in children with obesity, but not exclusively, it is the liver's manifestation of the metabolic syndrome but can also exist as an isolated entity. **Summary:** Pediatric NAFLD differs from the adult phenotype. This narrative review on NAFLD in children with obesity provides an overview of the current knowledge on risk factors, screening, and diagnostic methods, as well state-of-the-art treatment. The recent discussion on the proposition of a new nomenclature – Metabolic [Dysfunction-] Associated Liver Disease – is featured, and current gaps of knowledge are discussed. **Key Messages:** Currently, there is no international consensus on screening and monitoring of pediatric NAFLD. With lifestyle interventions being the corner-

stone of treatment, no registered pharmacological treatment for pediatric NAFLD is available. Development and validation of additional noninvasive biomarkers, scores and imaging tools suitable to subcategorize, screen and monitor pediatric patients are necessary. With a variety of upcoming and promising agents, clear recommendations for pediatric nonalcoholic steatohepatitis trials are urgently needed.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a multifactorial disease that has become the most common chronic disease of the liver in children and adults worldwide. Over the last decades, the prevalence of NAFLD has more than doubled [1]. With a pandemic of obesity on the rise, these numbers will further increase [2]. A meta-analysis by Anderson et al. [3] estimated the global prevalence of NAFLD in children with obesity at 34.2% (95% CI: 27.8–41.2%) as compared to the general pediatric population at 7.6% (95% CI: 5.5–10.3%).

NAFLD itself is not a single entity but represents a spectrum, ranging from steatosis to nonalcoholic steatohepatitis (NASH) and fibrosis [4]. Although obesity and its metabolic dysregulations are the main risk factors, a variety of other factors (e.g. genetic, epigenetic, gut-liver axis, DNA-methylation, hormone levels, puberty) add to the pathophysiology of NAFLD. Not only does obesity cause metabolic dysregulation, but it also increases oxidative stress and mitochondrial dysfunction and therefore plays a role in the progression of NAFLD [4–7].

Pediatricians and GPs find themselves confronted with the challenge of diagnosing underlying hepatopathies in children with obesity. There is no uniform consent in how to screen for NAFLD in children with obesity and how to exclude liver disease mimicking NAFLD. In this narrative review, we summarize the current knowledge on risk factors, screening, diagnostic methods and treatment in children with obesity. In addition, the recent discussion on the proposition of a new nomenclature – Metabolic [Dysfunction-] Associated Liver Disease (MAFLD) – is featured and current gaps of knowledge are addressed [8].

Risk Factors

Obesity and Metabolic Aspects

Obesity and its associated metabolic derangements are well established as main risk factors of NAFLD. The disease itself is considered part of a spectrum of the metabolic syndrome, as are other metabolic risk factors like high blood pressure, impaired glucose tolerance, type 2 diabetes (T2D), insulin resistance, dyslipidemia and visceral adiposity as early as during childhood [9]. In keeping with this, Manco et al. [10] showed that at least 1 metabolic risk factor was present in the majority of children with biopsy-proven NAFLD [10, 11]. Moreover, NAFLD was associated with a higher risk for prediabetes and T2D in cross-sectional pediatric studies. In addition, more severe forms of NAFLD seemed to be linked to an even greater risk of developing T2D already in infancy [5, 9, 12–14]. Waist circumference, as a proxy for visceral adiposity, is known to be strongly associated with NAFLD independent of BMI [15]. Other risk factors include obstructive sleep apnea syndrome (OSAS) and polycystic ovary syndrome. OSAS is linked to higher levels of oxidative stress, which in return is known to accelerate the pathogenesis of NAFLD. Polycystic ovary syndrome is associated with increased androgen levels and consecutive insulin resistance [16, 17].

It has to be noted that in spite of the fact that NAFLD mainly occurs in youth with obesity, normal weight does not preclude the diagnosis. The existence of this “lean NASH” indicates the role of a multifactorial pathogenesis (e.g. genetic variants and gut-liver axis) [18, 19].

Lifestyle

A sedentary lifestyle and high caloric diet, especially rich in simple carbohydrates like fructose and glucose, have been shown to be a key factor in developing obesity and NAFLD. Fructose stimulates (hepatic) de novo lipogenesis independent of total caloric intake, reduces hepatic lipid oxidation and increases liver fibrogenesis via fibroblast-growth-factor-21 induction [20–23]. On the other hand, dietary fiber seems to have beneficial effects. Dietary fiber is processed by the intestinal microbiota, resulting in short-chain fatty acids (i.e. n-butyrate, acetate and propionate). These short-chain fatty acids play a role in modulating intestinal inflammation as well as maintaining the integrity of the gut wall [20, 24]. For the development of NAFLD, it has been stated that the type of fat matters more than the consumed amount. Consuming increased amounts of saturated long-chain trans-fatty acids results in elevated oxidative stress and hence inflammation, while Omega-3 fatty acids appear beneficial [4, 20–23].

Gut-Liver Axis

The intestinal microbiome is altered in children with obesity and NAFLD. Dysbiosis (i.e. decreased α -diversity and increased β -diversity) at the root of hepatic inflammation due to bacterial endotoxins and pro-inflammatory cascades has been documented in the development of NASH that is otherwise absent in children with obesity but without NAFLD. Additionally, an intestinal microbiome with an increased number of alcohol-producing bacteria (i.e. *Escherichia coli*) and elevated blood ethanol levels in children with NASH has been observed [25–27].

Gender, Age, Ethnic, and Regional Aspects

Data concerning the association between NAFLD, sex, and glucose metabolism are inconclusive. Some publications describe a male predominance for NAFLD [13, 28, 29]. Koutny et al. [12, 13] demonstrated in 2 articles that girls with advanced NAFLD have been shown to have a two-fold increased risk for T2D than boys and that children with NAFLD and obesity have a doubled risk to progress to a prediabetic state within 10 years. The prevalence of NAFLD in children with obesity increases with age. Explanations include the effects of puberty (e.g. insulin resistance and effect of sex hormones) and recom-

Table 1. Possible causes for asymptomatic pediatric fatty liver disease (modified after [40, 45, 46])

General or systemic	Genetic-metabolic causes	Drugs/chemicals
Obesity	Cystic fibrosis	Ethanol
Metabolic syndrome	Shwachman syndrome	Ecstasy, cocaine, solvents
Obstructive sleep apnea	Wilson's disease	Nifedipine
PCOS	Alpha 1-antitrypsin deficiency	Diltiazem
Diabetes mellitus type 1	Fructosemia	Estrogens
Thyroid disorders (hypothyroidism)	Cholesterol ester storage disease	Corticosteroids
Hypothalamic-pituitary disorders	Glycogen storage disease (type I, VI, and IX)	Methotrexate
Inflammatory bowel disease	Mitochondrial and peroxisomal defects	Prednisolone
Celiac disease	α - and β -oxidation defects	Valproate
Protein calorie malnutrition	Organic acidosis	Vitamin D deficiency
Rapid weight loss	Abeta or hypobetalipoproteinemia	Zidovudine and HIV treatments
Anorexia nervosa	Porphyria cutanea tarda	Solvents (e.g. tri- and tetrachlorethylene, carbon tetrachloride)
Small intestinal bacterial overgrowth	Homocystinuria	Pesticides (e.g. glyphosate, dimethoate, and zineb)
Hepatitis C	Familial hyperlipoproteinemias	
	Bile acids synthesis defects	
	Congenital disorders of glycosylation	
	Citrin deficiency	
	Turner syndrome	

PCOS, polycystic ovary syndrome.

mendations for screening [30, 31]. In addition, ethnicity and geographical region have been shown to influence prevalence, with Hispanic and white adolescents being at higher risk than black youth. The highest prevalence of NAFLD is being reported for adolescents from Central America and the Middle East [32, 33].

Genetic and Epigenetic Factors

A number of genetic risk factors for NAFLD have been identified, with single nucleotide polymorphisms in the patatin-like-phospholipase-domain-containing-protein-3 being most strongly linked to progression to NASH and fibrosis [34–37]. Other genetic risk factors include GCKR (affects monosaccharide uptake and lipid synthesis), MBOAT7 (affects lipid metabolism), MTTP, and TM6SF2 (affects lipid excretion) as well as other single nucleotide polymorphisms affecting mitochondrial function, transmembrane transport of sugars, bile acids and inflammatory pathways [5, 38, 39]. Further, epigenetic risk factors include hyperglycemia in utero and gestational diabetes, maternal obesity and excessive weight gain during pregnancy, caesarian section, low and high birth weight, absence of breastfeeding and early exposure to antibiotics [40, 41].

Diagnosing NAFLD in Children with Obesity

Screening

NAFLD is an exclusion diagnosis and can progress (NASH and fibrosis) if undiagnosed and untreated. Thus, timely diagnosis of NAFLD and ruling out other (treatable) pathologies of the liver is important (see Table 1) [5, 42]. There is no uniform international consent for screening for NAFLD in children with obesity. American Association for the Study of the Liver (AASLD) guidance does not recommend screening for NAFLD in children with obesity due to “paucity of evidence” [43]. In contrast, NASPGHAN recommends screening by alanine aminotransferase (ALT) but does not recommend ultrasound (US) due to low sensitivity, in all children with obesity and overweight with additional risk factors at age 9–11 years [31]. ESPGHAN recommends liver function tests (LFT) and US in all children/adolescents with obesity [2]. Both methods combined seem favorable as ALT might be normal or only slightly elevated and US sensitivity diminishes in children where hepatic fat accumulation remains below 30% [6, 44].

The optimal cutoff value of ALT is still under discussion. NASPGHAN states that elevation above twice the upper norm levels should induce further investigation promptly (upper norm level for males 26 IU/L and 22

IU/L in females) [31]. Studies on different cutoff values were performed by Schwimmer (ALT >52 IU/L for females and >44 IU/L for males) and Radetti (>40 IU/L) with very different results concerning sensitivity (Schwimmer 88% and Radetti 54%) and specificity (Schwimmer 26% and Radetti 100%) for NAFLD [29, 47]. Maffeis et al. [48] performed a study in a group ($n = 56$) of 10-year-old children with obesity. They found mean ALT values of 42.04 IU/L (standard deviation 27.3 IU/L) in children with NAFLD and mean values of 25.11 IU/L (standard deviation 9.55 IU/L) in children without NAFLD. When ALT was combined with waist-to-height ratio and homeostasis model assessment of insulin resistance sensitivity was 89% and specificity 76% to predict NAFLD in children with obesity.

Liver Biopsy

Despite improvements of diagnostic imaging, liver biopsy remains the standard reference. It allows to exclude other pathologies of the liver (e.g. Wilson's disease) as well as grade inflammation and fibrosis [5, 49]. In case of persistent elevation of liver enzymes, in spite of weight reduction and otherwise unexplained, liver biopsy should be performed no later than 12–24 months, according to the AASLD [43]. NASPGHAN recommends liver biopsy if there is risk for NASH or advanced fibrosis, persistent ALT >80 IU/mL, splenomegaly, AST/ALT >1 but does not give a time limit [31]. Although being standard reference, liver biopsy suffers from diagnostic and procedural pitfalls. First, there is a potential sampling error by obtaining only a small sample, which might be unaffected by distribution of steatosis or fibrosis since NASH is non-homogeneously distributed in the liver. Second, interobserver variability in histopathologists has been stated as being high [50, 51].

Histology

NAFLD is defined as the presence of at least 5% of macrovesicular steatosis in hepatocytes and the absence of alcoholic origin or other causes of fatty liver. As previously noted, NAFLD is seen as a pattern that ranges from steatosis to NASH, showing various degrees of fibrosis to cirrhosis. Fibrosis was present in 70% of autopsy studies for children/adolescents with NAFLD, with advanced stages of fibrosis being present in 15–30% [52–54]. Histological patterns for NASH differ in pediatric populations and are commonly distinguished into “type 1” (adult pattern of NASH) and “type 2” (pediatric pattern). In type 1, there is more severe steatosis of the centrilobular area with inflammation and collagen deposition along

the sinusoids of zone 3 as well as hepatocellular ballooning, lobular inflammation, and Mallory-Denk-bodies. Type 2 features no ballooning and is characterized by inflammation of zone 1 and dominant portal-periportal fibrosis. Type 2 is associated with younger age, male gender, a more severe degree of fibrosis and a higher prevalence in youth with Hispanic or Asian descent. While Type 2 pattern is more frequently diagnosed in children, most children show a combination of Type 1 and 2 NASH [52–54].

Noninvasive Diagnostic Measures

Scores and Biomarkers

A number of scores, noninvasive tests and laboratory tests have been suggested to monitor NAFLD, fibrosis, and NASH. The Pediatric NAFLD score was reported to be mediocre and insufficient for clinical use. Scores for NASH are either unvalidated for the pediatric population (NASH predictive index, NASHT test, and HAIR score) or externally unvalidated (Pediatric predictive NASH model) [5]. Most of the predictive fibrosis scores were not developed for children, except for the “Pediatric NAFLD fibrosis index” and the “Pediatric NAFLD fibrosis score.” Both these tests include waist circumference, age, and triglycerides and were reported to be only moderately accurate. However, if combined with the ELF test (enhanced liver fibrosis test), Pediatric NAFLD fibrosis index shows good accuracy in the prediction of fibrosis. In addition, cytokeratin-18 is linked with the severity of NASH (histology and score) in children [5, 6, 55].

Imaging Techniques

Imaging techniques like regular US, transient elastography system, or controlled-attenuation-parameter (CAP) are increasingly in use. US is inaccurate for diagnosing fibrosis and unable to detect inflammation. Transient elastography system has been described as a valid tool for the detection of higher degrees of fibrosis but is unreliable in case of florid inflammation. CAP calculates the attenuation of the shear-wave propagation through the tissue and has proven a good method to detect steatosis in adults, while further pediatric evaluation is still needed. MRI remains the imaging reference standard, proton density fat fraction and magnetic resonance spectroscopy being the most accurate methods to quantify the fat content of the liver. However, due to high costs and limited availability, MRI and its modalities are not for routine use [5, 6, 20, 56].

Treatment

To this date, there is no pharmacological drug registered for the treatment in pediatric NAFLD. Lifestyle modifications with the aim of a low-caloric healthy diet (low in carbohydrates, fructose, saturated fatty acids, and trans-fatty acids) and an active lifestyle are the cornerstones of treatment. Physical exercise has shown to be protective of NAFLD. Reduction of BMI demonstrated histological improvement of NASH and fibrosis [57]. Nobili et al. [58] found that weight loss of >20% in children led to a significant improvement of ALT. However, success is usually modest and drop-out rates are high. A multidisciplinary approach has been suggested as most promising, including recurrent visits and the involvement of dieticians and psychologists [6, 59]. Proposed pharmacological therapies include insulin sensitizers, probiotics, anti-inflammatory agents, lipid-lowering drugs, and vitamins (see Table 2). Noteworthy is d-alpha-tocopherol at 800 IU/day orally administered, as it significantly reduces biopsy-proven NASH in children and adults alike, although long-term safety reports are still lacking. Metformin is currently not recommended in children to treat NAFLD [4, 6, 60, 61]. Table 2 gives an overview of pharmacological substances investigated for treating pediatric NAFLD.

Bariatric surgery is not recommended by the Expert Committee on NAFLD (ECON) and NASPGHAN. Their joint statement declares it may be considered in selected adolescents with BMI ≥ 35 kg/m² who have noncirrhotic NAFLD and other serious comorbidities. These comorbidities include T2D, severe sleep apnea (OSAS), or idiopathic intracranial hypertension [31]. AASLD states that bariatric surgery may be considered in individuals with obesity and NAFLD or NASH [43]. Pediatric studies show that the weight loss after bariatric surgery results in reversion of NASH and fibrosis. Comorbidities of severe obesity (e.g. diabetes dyslipidemia and OSAS) and quality of life are significantly improved [4–6, 63]. As lifestyle modification may fail or its effects are temporary, bariatric surgery may be considered for a few highly selected cases with severe obesity and associated comorbidities. Selection of patients is crucial as bariatric surgery features serious potential complications [5, 63].

Gaps of Knowledge – Research Need

The study of the pediatric phenotype of the disease is crucial for understanding the natural history of NAFLD across the age spectrum. At the time being, there are uncertainties about the pathophysiology of childhood-onset NAFLD, disease subphenotypes, diagnostic tests, along

with lack of knowledge related to long-term benefits and cost-effectiveness of screening and treatment options. Among others, the following aspects of pediatric NAFLD need to be addressed in future work.

Pathophysiology and Natural History

- The natural history of NAFLD in pediatric populations and its onset at different ages influences progression.
- The interaction of genetic and epigenetic factors, enteric microbiota, diet, prepartal maternal influences and growth.

Screening and Monitoring

- Need for uniform screening recommendations for NAFLD, in particular in high-risk groups attending primary care, diabetes- or obesity clinics; this includes the assessment of individual benefit and cost-effectiveness of screening pediatric family members of adult patients with NAFLD on population level.
- Development and validation of additional noninvasive biomarkers including genetic markers, alterations of gut microbiota, metabolism (lipid markers, bile acids, gut metabolites and other variables identified by untargeted and targeted proteomics, etc.), and collagen turnover, scores, and imaging tools suitable to screen and monitor for fibrosis/NASH.

Specific Aspects of Pediatric NAFLD Clinical Trial Design

Recently, the AASLD and the European Association for the Study of the Liver reviewed scientific NAFLD trials, gaps of knowledge and refined guidance, and endpoints for future trials. Pediatric considerations include the following [64]:

- Possible advantages of treatment must be compared to the risks of drug exposure for patients who are not at high risk for progression. Data from pediatric studies should therefore be analyzed to subcategorize and identify patients at risk of liver-related outcomes. As a result, high-risk patients might be prioritized and low-risk patients may avoid unnecessary drug exposure with potential adverse events.
- Potential drawbacks in drug development for children with NASH include logistical barriers such as fear of procedures, ethical barriers, regulatory barriers, and physiological barriers.
- Putting the focus on safety, including the risk of liver biopsy, the acceptance of surrogates for histology appears to be easier as trial endpoints compared with adult patients.

Table 2. Overview on pharmaceutical research on NAFLD

Drug name	Class	Mechanism	(Potential) benefits	Potential side-effects	Comment
<i>Concluded trials/drugs</i>					
Metformin [4–6, 62]	Insulin sensitizer		Improvement in ALT and liver histology	Gastrointestinal, lactate acidosis	No recommendation (not superior to placebo) May be considered in NAFLD with insulin resistance
Pioglitazone [63]	Insulin sensitizer	Upregulation of adiponectin, insulin-sensitizing	Histological NASH improvement	Weight gain	No recommendation
	PPAR	Prevents uptake of fatty acids in organs	Improvement of NAS activity score		Effect resolves after discontinuing pioglitazone
			Resolution of NASH		
			Improving fibrosis		
Vitamin E (D-alpha-tocopherol) [4–6, 62]	Vitamin	Protective against oxidative stress by blocking apoptotic pathway	Histological NASH improvement	Concerns with long-term use (prostate cancer, hemorrhagic stroke)	No recommendation (not superior to placebo)
	Antioxidant		Improvement of NAS activity score and ALT		May be considered in biopsy-proven NASH without diabetes
			Resolution of NASH greater than placebo		
<i>Lactobacillus rhamnosus</i> GG [6, 62]	Probiotic		Improvement in ALT (significant), no change in US		Further studies with larger sample size needed
Prokids probiotic (mixture of 4 probiotic strains) [6]	Probiotic		Improvement in ALT and steatosis in US (significant)		Further studies with larger sample size needed
VSL#3 (mixture of 8 probiotic strains) [6]	Probiotic		Improvement in steatosis in US and BMI (significant)		Further studies with larger sample size needed
			Improvement in ALT		
DHA [4, 6, 62]	PUFA	Beneficial effect on lipid accumulation in the liver	Improvement in ALT, steatosis, and ballooning		No recommendation for NASH, may be used in NAFLD and hypertriglyceridemia
EPA [6, 62]	PUFA	Beneficial effect on lipid accumulation in the liver	Improvement in ALT and US – nonsignificant		No recommendation for NASH, may be used in NAFLD and hypertriglyceridemia

Table 2 (continued)

Drug name	Class	Mechanism	(Potential) benefits	Potential side-effects	Comment
<i>Drugs in development/ongoing trials</i>					
Liraglutide/semaglutide [5]	GLP-1* agonist	Insulin secretion	Resolution of steatosis	Gastrointestinal (e.g., diarrhea)	
		Reduces hepatic glucose production	Improvement of metabolic risk factors (e.g., weight, BMI, HDL-cholesterol, glucose level)		
		Delays gastric emptying (satiety)			
Obeticholic acid [5, 32]	FRX agonist	Modulation of bile acid, lipid, and glucose metabolism	Potential decrease of steatosis, inflammation, and fibrosis Potential increase of insulin sensitivity	Dyslipidemia	Safety and long-term effects missing, other FXR agonists: tropifexor (LJN452) and cilofexor (CS9674)
Elafibranor (NCT03883607) [5, 6, 32]	Dual receptor peroxisome-proliferator-activated alpha/delta agonist	Improves insulin sensitivity and lipid metabolism, reduces inflammation	Improved cardiometabolic risk profile	Increase in creatinine levels	
Empagliflozin (NCT03867487) [6]	SGLT2*** inhibitor, insulin sensitizer				
Losartan (NCT03467217) [5, 6]	Angiotensin II receptor blocker	Reduction of plasminogen-activator-inhibitor-1 production; improvement of insulin sensitivity	Study endpoint for ALT reduction		Evaluation for age 8–17 years and 70–149 kg
Anti-LPS** antibody (NCT03042767) [5, 6]	Monoclonal antibody to LPS	Anti-inflammatory; reduction of LPS-transfer from gut			
Selonsertib [5, 32]	Apoptosis signal-regulating kinase-1 inhibitor	Modification of inflammation	Histologic improvement		Lack of efficiency – placebo effect
			Improvement in fibrosis without worsening of NASH		
Cenicriviroc [5, 32]	CCR2/CCR5 chemokine receptor blocker	Blocks fibrosis caused by recruitment of macrophages and monocytes	Improvement in fibrosis without worsening of NASH	Fatigue, diarrhea	
Aramchol [32]	Synthetic bile acid and a saturated fatty acid	Inhibition of stearyl-CoA desaturase	Downregulation of hepatic steatosis		ARTISAN study planned (adolescents)
CBDR [4–6]	Antioxidant	Increases intracellular glutathione	Improvement in ALT and lobular inflammation – no benefit on fibrosis		No recommendation
					May benefit >13 years old and <65 kg

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; ALT, alanine aminotransferase; US, ultrasound; PPAR, peroxisome-proliferator-activated agonist; PUFA, polyunsaturated fatty acid; DHA, Docosahexaenoic acid; EPA, Eicosapentaenoic acid; FRX, Farnesoid receptor X; CBDR, cysteamine bitartrate. * Glucagon-like-peptide-1. ** Lipopolysaccharide. *** Sodium-glucose cotransporter.

Current Discussion: MAFLD versus NAFLD

Calls to rename NAFLD have been around since the early 2000s but it was the suggestion of an expert group in 2020 that sparked the debate anew. Eslam et al. [65, 66] suggest that the term MAFLD captures the nature of its origin more accurately. Besides a new nomenclature, new criteria for studies and clinical trials were suggested. Clinical diagnosis of MAFLD would therefore be based upon hepatic steatosis (liver biopsy, imaging, or blood biomarker evidence) and at least 1 of 3 criteria (obesity/overweight, T2D, or evidence of at least 2 metabolic abnormalities).

Eslam et al. [65, 66] argued that besides reflecting new knowledge concerning etiology, it would turn MAFLD from an “exclusion diagnosis” towards an “inclusion diagnosis.” This allows coexistence with other pathologies (e.g. viral hepatitis) which would otherwise rule out the diagnosis of NAFLD and thus allowing to target the underlying causes in a better way [65]. Other authors support the change in terminology, stating MAFLD would benefit the patient’s understanding and management of the disease and the new diagnostic criteria are better for identifying significant hepatic diseases (e.g. fibrosis) [67]. However, opposing authors argue that the change is too swift as there is no general consensus on the definition of metabolic health. Furthermore, the new criteria would not include patients without metabolic risk factors, who can still have NAFLD [68]. It also triggers a discussion on the definition of “metabolic.” In addition, the new criteria could jeopardize running clinical and pharmacological studies and confuse nonhepatologists and patients alike [69]. So far, the discussion primarily addressed adult patients and now awaits pediatric contribution.

Conclusion

NAFLD in children with obesity has reached epidemic proportions and today is the leading chronic liver disease in children and adults. Prevention and treatment via an active lifestyle and a healthy diet remain the only real options. However, long-term adherence in children and adolescents is modest. While novel biomarkers and imaging tools for pediatric NAFLD are developed, improved, and validated, liver biopsy remains the standard reference in clinical care. Future studies need to address the plethora of gaps of knowledge to advance our understanding of the distinct features of pediatric NAFLD so that treatment targets children and adolescents at high risk as opposed to those at low risk for long-term morbidity and mortality.

Conflict of Interest Statement

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References

- 1 Marzuillo P, Del Giudice EM, Santoro N. Pediatric non-alcoholic fatty liver disease: new insights and future directions. *World J Hepatol.* 2014;6(4):217–25.
- 2 Vajro P, Lenta S, Socha P, Dhawan A, McKiernan P, Baumann U, et al. Diagnosis of non-alcoholic fatty liver disease in children and adolescents: position paper of the ESPGHAN Hepatology Committee. *J Pediatr Gastroenterol Nutr.* 2012;54(5):700–13.
- 3 Anderson EL, Howe LD, Jones HE, Higgins JP, Lawlor DA, Fraser A. The prevalence of non-alcoholic fatty liver disease in children and adolescents: a systematic review and meta-analysis. *PLoS One.* 2015; 10: e0140908.
- 4 Mann JP, Valenti L, Sciorletti E, Byrne CD, Nobili V. Nonalcoholic fatty liver disease in children. *Semin Liver Dis.* 2018;38(1): 1–13.
- 5 Draijer L, Benninga M, Koot B. Pediatric NAFLD: an overview and recent developments in diagnostics and treatment. *Expert Rev Gastroenterol Hepatol.* 2019;13(5):447–61.
- 6 Goldner D, Lavine JE. Nonalcoholic fatty liver disease in children: unique considerations and challenges. *Gastroenterology.* 2020; 158(7):1967–83.e1.
- 7 Hyun J, Jung Y. DNA methylation in nonalcoholic fatty liver disease. *Int J Mol Sci.* 2020; 21:21.
- 8 Baumann U. Differenzialdiagnostik bei persistierender Erhöhung der Transaminasenkonzentrationen – Klinische Einschätzung und Vorgehen. *Monatsschr Kinderheilkd.* 2015;163:167–78.
- 9 Patton HM, Yates K, Unalp-Arida A, Behling CA, Huang TT, Rosenthal P, et al. Association between metabolic syndrome and liver histology among children with nonalcoholic fatty liver disease. *Am J Gastroenterol.* 2010; 105(9):2093–102.
- 10 Manco M, Marcellini M, Devito R, Comparcola D, Sartorelli MR, Nobili V. Metabolic syndrome and liver histology in paediatric non-alcoholic steatohepatitis. *Int J Obes.* 2008;32(2):381–7.

- 11 Armstrong MJ, Adams LA, Canbay A, Syn WK. Extrahepatic complications of nonalcoholic fatty liver disease. *Hepatology*. 2014; 59(3):1174–97.
- 12 Koutny F, Stein R, Kiess W, Weghuber D, Körner A. Elevated transaminases potentiate the risk for emerging dysglycemia in children with overweight and obesity. *Pediatr Obes*. 2021. Epub ahead of print.
- 13 Koutny F, Weghuber D, Bollow E, Greber-Platzer S, Hartmann K, Körner A, et al. Prevalence of prediabetes and type 2 diabetes in children with obesity and increased transaminases in European German-speaking countries. Analysis of the APV initiative. *Pediatr Obes*. 2020;15(4):e12601.
- 14 Nobili V, Mantovani A, Cianfarani S, Alisi A, Mosca A, Sartorelli MR, et al. Prevalence of prediabetes and diabetes in children and adolescents with biopsy-proven non-alcoholic fatty liver disease. *J Hepatol*. 2019;71(4):802–10.
- 15 Nobili V, Svegliati-Baroni G, Alisi A, Miele L, Valenti L, Vajro P. A 360-degree overview of paediatric NAFLD: recent insights. *J Hepatol*. 2013;58(6):1218–29.
- 16 Benedict M, Zhang X. Non-alcoholic fatty liver disease: an expanded review. *World J Hepatol*. 2017;9(16):715–32.
- 17 Nobili V, Cutrera R, Liccardo D, Pavone M, Devito R, Giorgio V, et al. Obstructive sleep apnea syndrome affects liver histology and inflammatory cell activation in pediatric nonalcoholic fatty liver disease, regardless of obesity/insulin resistance. *Am J Respir Crit Care Med*. 2014;189(1):66–76.
- 18 Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. *J Clin Invest*. 2005;115(5):1343–51.
- 19 Lambert JE, Ramos-Roman MA, Browning JD, Parks EJ. Increased de novo lipogenesis is a distinct characteristic of individuals with nonalcoholic fatty liver disease. *Gastroenterology*. 2014;146(3):726–35.
- 20 Bonsembiante L, Targher G, Maffei C. Non-alcoholic fatty liver disease in obese children and adolescents: a role for nutrition. *Eur J Clin Nutr*. 2021. Epub ahead of print.
- 21 Chakravarthy MV, Waddell T, Banerjee R, Guess N. Nutrition and nonalcoholic fatty liver disease: current perspectives. *Gastroenterol Clin North Am*. 2020;49(1):63–94.
- 22 Schwarz JM, Noworolski SM, Erkin-Cakmak A, Korn NJ, Wen MJ, Tai VW, et al. Effects of dietary fructose restriction on liver fat, de novo lipogenesis, and insulin kinetics in children with obesity. *Gastroenterology*. 2017; 153(3):743–52.
- 23 Vos MB, Lavine JE. Dietary fructose in nonalcoholic fatty liver disease. *Hepatology*. 2013; 57(6):2525–31.
- 24 Zhao L, Zhang F, Ding X, Wu G, Lam YY, Wang X, et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. *Science*. 2018;359(6380):1151–6.
- 25 Schwimmer JB, Johnson JS, Angeles JE, Behling C, Belt PH, Borecki I, et al. Microbiome signatures associated With steatohepatitis and moderate to severe fibrosis in children with nonalcoholic fatty liver disease. *Gastroenterology*. 2019;157(4):1109–22.
- 26 Soderborg TK, Clark SE, Mulligan CE, Janssen RC, Babcock L, Ir D, et al. The gut microbiota in infants of obese mothers increases inflammation and susceptibility to NAFLD. *Nat Commun*. 2018;9(1):4462.
- 27 Zhu L, Baker SS, Gill C, Liu W, Alkhouiri R, Baker RD, et al. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. *Hepatology*. 2013;57(2):601–9.
- 28 Denzer C, Thiere D, Muche R, Koenig W, Mayer H, Kratzer W, et al. Gender-specific prevalences of fatty liver in obese children and adolescents: roles of body fat distribution, sex steroids, and insulin resistance. *J Clin Endocrinol Metab*. 2009;94(10):3872–81.
- 29 Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. *Pediatrics*. 2006;118(4):1388–93.
- 30 Suzuki A, Abdelmalek MF, Schwimmer JB, Lavine JE, Scheimann AO, Unalp-Arida A, et al. Association between puberty and features of nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2012;10(7): 786–94.
- 31 Vos MB, Abrams SH, Barlow SE, Caprio S, Daniels SR, Kohli R, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). *J Pediatr Gastroenterol Nutr*. 2017;64(2):319–34.
- 32 Nobili V, Alisi A, Valenti L, Miele L, Feldstein AE, Alkhouiri N. NAFLD in children: new genes, new diagnostic modalities and new drugs. *Nat Rev Gastroenterol Hepatol*. 2019; 16(9):517–30.
- 33 Tricò D, Caprio S, Rosaria Umano G, Pierpont B, Nouws J, Galderisi A, et al. Metabolic features of nonalcoholic fatty liver (NAFL) in obese adolescents: findings from a multiethnic cohort. *Hepatology*. 2018;68(4):1376–90.
- 34 He S, McPhaul C, Li JZ, Garuti R, Kinch L, Grishin NV, et al. A sequence variation (I148M) in PNPLA3 associated with nonalcoholic fatty liver disease disrupts triglyceride hydrolysis. *J Biol Chem*. 2010;285(9):6706–15.
- 35 Kumari M, Schoiswohl G, Chitruju C, Paar M, Cornaciu I, Rangrez AY, et al. Adiponutrin functions as a nutritionally regulated lysophosphatidic acid acyltransferase. *Cell Metab*. 2012;15(5):691–702.
- 36 Mangge H, Baumgartner BG, Zelzer S, Prüller F, Schnedl WJ, Reininghaus EZ, et al. Patatin-like phospholipase 3 (rs738409) gene polymorphism is associated with increased liver enzymes in obese adolescents and metabolic syndrome in all ages. *Aliment Pharmacol Ther*. 2015;42(1):99–105.
- 37 Uygun A, Ozturk K, Demirci H, Oztuna A, Eren F, Kozan S, et al. The association of non-alcoholic fatty liver disease with genetic polymorphisms: a multicenter study. *Eur J Gastroenterol Hepatol*. 2017;29(4):441–7.
- 38 Dongiovanni P, Valenti L, Rametta R, Daly AK, Nobili V, Mozzi E, et al. Genetic variants regulating insulin receptor signalling are associated with the severity of liver damage in patients with non-alcoholic fatty liver disease. *Gut*. 2010;59(2):267–73.
- 39 Santoro N, Zhang CK, Zhao H, Pakstis AJ, Kim G, Kursawe R, et al. Variant in the glucokinase regulatory protein (GCKR) gene is associated with fatty liver in obese children and adolescents. *Hepatology*. 2012;55(3):781–9.
- 40 Bertrando S, Vajro P. NAFLD at the interface of the mother-infant dyad. *Curr Pharm Des*. 2020;26(10):1119–25.
- 41 Newton KP, Feldman HS, Chambers CD, Wilson L, Behling C, Clark JM, et al. Low and high birth weights are risk factors for nonalcoholic fatty liver disease in children. *J Pediatr*. 2017;187:141–6.e1.
- 42 Vajro P, Maddaluno S, Veropalumbo C. Persistent hypertransaminasemia in asymptomatic children: a stepwise approach. *World J Gastroenterol*. 2013;19(18):2740–51.
- 43 Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67(1):328–57.
- 44 Molleston JP, Schwimmer JB, Yates KP, Murray KF, Cummings OW, Lavine JE, et al. Histological abnormalities in children with non-alcoholic fatty liver disease and normal or mildly elevated alanine aminotransferase levels. *J Pediatr*. 2014;164(4):707–13.e3.
- 45 Lundqvist G, Flodin U, Axelsson O. A case-control study of fatty liver disease and organic solvent exposure. *Am J Ind Med*. 1999 Feb; 35(2):132–6.
- 46 Laothong U. Pesticides and non-alcoholic fatty liver disease. *Thai J Toxicol*. 2016;31:97–107.
- 47 Radetti G, Kleon W, Stuefer J, Pittschieler K. Non-alcoholic fatty liver disease in obese children evaluated by magnetic resonance imaging. *Acta Paediatr*. 2006;95(7):833–7.
- 48 Maffei C, Banzato C, Rigotti F, Nobili V, Valandro S, Manfredi R, et al. Biochemical parameters and anthropometry predict NAFLD in obese children. *J Pediatr Gastroenterol Nutr*. 2011;53(6):590–3.
- 49 Brunt EM, Tiniakos DG. Histopathology of nonalcoholic fatty liver disease. *World J Gastroenterol*. 2010;16(42):5286–96.
- 50 Fukusato T, Fukushima J, Shiga J, Takahashi Y, Nakano T, Maeyama S, et al. Interobserver variation in the histopathological assessment of nonalcoholic steatohepatitis. *Hepatol Res*. 2005;33(2):122–7.

- 51 Ratzl V, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology*. 2005;128(7):1898–906.
- 52 Mann JP, De Vito R, Mosca A, Alisi A, Armstrong MJ, Raponi M, et al. Portal inflammation is independently associated with fibrosis and metabolic syndrome in pediatric nonalcoholic fatty liver disease. *Hepatology*. 2016;63(3):745–53.
- 53 Patton HM, Lavine JE, Van Natta ML, Schwimmer JB, Kleiner D, Molleston J, et al. Clinical correlates of histopathology in pediatric nonalcoholic steatohepatitis. *Gastroenterology*. 2008;135(6):1961–71.e2.
- 54 Schwimmer JB, Behling C, Newbury R, Deutsch R, Nievergelt C, Schork NJ, et al. Histopathology of pediatric nonalcoholic fatty liver disease. *Hepatology*. 2005;42(3):641–9.
- 55 Feldstein AE, Alkhouri N, De Vito R, Alisi A, Lopez R, Nobili V. Serum cytokeratin-18 fragment levels are useful biomarkers for nonalcoholic steatohepatitis in children. *Am J Gastroenterol*. 2013;108(9):1526–31.
- 56 Shaunak M, Byrne CD, Davis N, Afolabi P, Faust SN, Davies JH. Non-alcoholic fatty liver disease and childhood obesity. *Arch Dis Child*. 2021;106(1):3–8.
- 57 Nobili V, Manco M, Devito R, Di Ciommo V, Comparcola D, Sartorelli MR, et al. Lifestyle intervention and antioxidant therapy in children with nonalcoholic fatty liver disease: a randomized, controlled trial. *Hepatology*. 2008;48(1):119–28.
- 58 Nobili V, Manco M, Devito R, Ciampalini P, Piemonte F, Marcellini M. Effect of vitamin E on aminotransferase levels and insulin resistance in children with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2006;24(11–12):1553–61.
- 59 Ramon-Krauel M, Salsberg SL, Ebbeling CB, Voss SD, Mulkern RV, Apura MM, et al. A low-glycemic-load versus low-fat diet in the treatment of fatty liver in obese children. *Child Obes*. 2013;9(3):252–60.
- 60 Lavine JE, Schwimmer JB, Van Natta ML, Molleston JP, Murray KF, Rosenthal P, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. *JAMA*. 2011;305(16):1659–68.
- 61 Younossi ZM, Loomba R, Rinella ME, Bugianesi E, Marchesini G, Neuschwander-Tetri BA, et al. Current and future therapeutic regimens for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Hepatology*. 2018;68(1):361–71.
- 62 Mann JP, Tang GY, Nobili V, Armstrong MJ. Evaluations of lifestyle, dietary, and pharmacologic treatments for pediatric nonalcoholic fatty liver disease: a systematic review. *Clin Gastroenterol Hepatol*. 2019 Jul;17(8):1457–76.e7.
- 63 Leoni S, Tovoli F, Napoli L, Serio I, Ferri S, Bolondi L. Current guidelines for the management of non-alcoholic fatty liver disease: a systematic review with comparative analysis. *World J Gastroenterol*. 2018;24(30):3361–73.
- 64 Rinella ME, Tacke F, Sanyal AJ, Anstee QM; Participants of the AASLD/EASL Workshop. Report on the AASLD/EASL joint workshop on clinical trial endpoints in NAFLD. *Hepatology*. 2019;70(4):1424–36.
- 65 Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. *J Hepatol*. 2020;73(1):202–9.
- 66 Eslam M, Sanyal AJ, George J; International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology*. 2020;158(7):1999–2014.e1.
- 67 Fouad Y, Elwakil R, Elsahhar M, Said E, Ba-zeed S, Ali Gomaa A, et al. The NAFLD-MAFLD debate: eminence vs evidence. *Liver Int*. 2021;41(2):255–60.
- 68 Huang J, Kumar R, Wang M, Zhu Y, Lin S. MAFLD criteria overlooks a number of patients with severe steatosis: is it clinically relevant [letter]. *J Hepatol*. 2020;73(5):1265–7.
- 69 Younossi ZM, Rinella ME, Sanyal AJ, Harrison SA, Brunt EM, Goodman Z, et al. From NAFLD to MAFLD: implications of a premature change in terminology. *Hepatology*. 2021;73(3):1194–8.