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Metabolic-associated fatty liver disease from childhood to adulthood: State of art and future directions

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Abstract

In 2020, an international group of experts proposed to replace the term of nonalcoholic fatty liver disease with metabolic-associated fatty liver disease (MAFLD). This recent proposal reflects the close association of fatty liver with metabolic derangements, as demonstrated by previous robust data. Several factors [including genetics, inflammation, metabolic abnormalities, insulin resistance (IR), obesity, prenatal determinants, and gut-liver axis] have been found to be involved in MAFLD pathophysiology, but this tangled puzzle remains to be clearly understood. In particular, IR has been recognized as a key player in metabolic impairments development in children with fatty liver. On this ground, MAFLD definition focuses on the pathophysiological basis of the disease, by emphasizing the crucial role of metabolic impairments in this condition. Although primarily developed for adults, MAFLD diagnostic criteria have been recently updated with an age-appropriate definition for sex and age percentiles, because of the increasing attention to cardiometabolic risk in childhood. To date, accumulating evidence is available on the feasibility of MAFLD definition in clinical practice, but some data are still conflicting in highly selected populations. Considering the growing prevalence worldwide of fatty liver and its close relationship with metabolic dysfunction both in children and adults with subsequent increased cardiovascular risk, early strategies for MAFLD identification, treatment and prevention are needed. Novel therapeutic insights for MAFLD based on promising innovative biological techniques are also emerging. We aimed to summarize the most recent evidence in this intriguing research area both in children and adults.

Key Words: Metabolic; dysfunction; Fatty; Liver; Pathophysiology; Cardiovascular; Risk; Adults; Children

Core tip: Recently, experts have proposed to rename nonalcoholic fatty liver disease as metabolic-associated fatty liver disease (MAFLD), by emphasizing the close association of fatty liver with the metabolic milieu. Given that, a growing number of studies have tested the effectiveness of the new definition in adults and children, although evidence in this latter population is still limited. However, expanding knowledge about MAFLD and its pathophysiology is crucial for a better identification of subjects at greater metabolic risk.

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INTRODUCTION

As proposed by an international consensus in 2020[1], the nomenclature of nonalcoholic fatty liver disease (NAFLD) has been updated to metabolic-associated fatty liver disease (MAFLD). MAFLD diagnosis is based on histological (biopsy), imaging or blood biomarker evidence of hepatic steatosis, and on the presence of any condition among: (1) Overweight/obesity; (2) diabetes mellitus; or (3) evidence of metabolic dysregulation[1], commonly defined as ≥ 2 of these characteristics: (1) Waist circumference ≥ 102 cm in Caucasian male subjects and 88 cm in women (or $\geq 90/80$ cm in Asian individuals); (2) blood pressure $\geq 130/85$ mmHg or specific drug treatment; (3) triglyceride level ≥ 1.70 mmol/L or specific drug treatment; (4) high-density lipoprotein (HDL)-cholesterol < 1.0 mmol/L for men and < 1.3 mmol/L for women; (5) prediabetes (*i.e.*, fasting glucose levels 5.6–6.9 mmol/L, or 2-h post-load glucose levels 7.8–11.0 mmol/L or hemoglobin A1c 5.7%–6.4%); (6) homeostasis model assessment-insulin resistance (HOMA-IR) score ≥ 2.5 ; and (7) high-sensitive C-reactive protein (hs-CRP) level > 2 mg/L.

Numerous different factors such as inflammation, sex, age, ethnicity, diet, microbiota, hormones, and genetics have been pathogenically linked to NAFLD[2–4], but current knowledge about MAFLD pathophysiology is still limited[5–6].

During the past decades, research focused on the strong association between insulin resistance (IR) and NAFLD[7]. In particular, previous data have largely supported the role of NAFLD as a hepatic manifestation of systemic metabolic disorders[2,3]. Based on these premises, the new nomenclature aims to strengthened the close association of fatty liver with metabolic dysfunction[2,8–12] to identify early subjects at higher risk of long-term metabolic consequences.

As noted for obesity and its related consequences [*e.g.*, metabolic syndrome (MetS) and Type 2 diabetes (T2D)][13–15], a key pathogenic role has been described for the low-grade systemic inflammation in modulating fibrosis development and the overall course of the hepatic disease. As a result, an inflammatory biomarker such as hs-CRP, has been considered as a MAFLD diagnostic criterion. However, it should be kept in mind that further specific diagnostic criteria for MetS define this peculiar cluster of metabolic abnormalities, according to age group[16,18]. In fact, the MetS definition provided for adults and children aged ≥ 10 years by the International Diabetes Federation (IDF)[16,17] was further integrated for subjects aged 2–11 years (Table 1). The comparison between MetS and MAFLD criteria (Tables 2 and 3) allows identification of MetS subjects with fatty liver as MAFLD patients. Although both conditions allow identification of subjects at higher cardiometabolic risk, the inclusion of fatty liver as a MAFLD criterion enhances the multifactorial pathophysiology of the disease and its close relationship with metabolic derangements[16–20]. Given the overall emphasis of this latter association in MAFLD definition (from normal weight to obesity), the new term includes a wide phenotypical range from metabolically unhealthy normal weight to metabolically unhealthy. Nevertheless, an accurate definition of metabolic health is still lacking, especially in patients with obesity[21].

An increasing number of studies have explored metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO) in adult and pediatric cohorts[22–24]. MUO individuals have a higher cardiovascular risk than their metabolically healthy counterparts. However, MHO also might predispose over time to an increased risk of cardiometabolic derangements[25–27]. In light of this, a detailed clinical assessment of the cardiometabolic risk in children (including evaluation of anthropometric measures such as weight, height, waist, and hip circumferences according to age- and gender-specific percentiles and Acanthosis nigricans detection as a clinical marker of IR) represents a crucial first step for the evaluation of these patients.

Table 1 Comparison between metabolic associated fatty liver disease and non-alcoholic fatty liver disease diagnostic criteria

MAFLD criteria[1]	NAFLD criteria[62]
Histological (biopsy), imaging or blood biomarker evidence of hepatic steatosis and the presence of one of these criteria:	Presence of steatosis in > 5% of hepatocytes detected by biopsy
(1) Overweight/obesity	-The proton density fat fraction (providing a rough estimation of the volume fraction of fatty material in the liver) > 5.6% assessed by proton magnetic resonance spectroscopy
(2) Diabetes mellitus	
(3) Evidence of metabolic dysregulation defined as the presence of ≥ 2 of the following conditions:	
(a) Waist circumference ≥ 102 cm in Caucasian men and 88 cm in women (or ≥ 90/80 cm in Asian men and women);	
(b) Blood pressure ≥ 130/85 mmHg or specific drug treatment; (c) triglyceride ≥ 1.70 mmol/L or specific drug treatment;	
(d) High-density lipoprotein cholesterol < 1.0 mmol/L for men and < 1.3 mmol/L for women;	
(e) Prediabetes (<i>i.e.</i> , fasting glucose levels 5.6–6.9 mmol/L, or 2-h postload glucose levels 7.8–11.0 mmol/L or hemoglobin A1c 5.7%–6.4%;	
(f) Homeostasis model assessment-insulin resistance score ≥ 2.5;	
and (g) High sensitive C-reactive protein > 2 mg/L	-Quantitative fat/water selective magnetic resonance imaging
	Exclusion of both secondary causes and a daily alcohol consumption ≥ 30 g for men and 20 g for women

MAFLD: Metabolic associated fatty liver disease; NAFLD: Non-alcoholic fatty liver disease.

Adipose distribution pattern is considered to have a critical influence on MAFLD development, as demonstrated by the positive correlation of amount of visceral adipose tissue with liver inflammation and fibrosis[4].

To date, the clinical feasibility of MAFLD definition has been mostly studied in adults, but a similar growing interest is also emerging in children. Therefore, we aimed to provide a comprehensive overview by summarizing the most recent evidence on the tangled puzzle of MAFLD in adults and children.

PATHOPHYSIOLOGY

Fatty liver pathophysiology includes a well-known spectrum of determinants such as inflammation, IR, genetics and environment[4,28,29]. Genetic determinants commonly implied in NAFLD susceptibility (such as *PNPLA3*[30–32], *TM6SF2*[33], *MBOAT7*[34–36] and *HSD17B13*[37–42] genes) have been also linked to MAFLD pathogenesis[43–45] (Table 2). In particular, the effect of the *PNPLA3* I148M polymorphism as a key genetic factor for NAFLD susceptibility across different ethnicities has been largely recognized both in adults and children[45]. Similarly, robust data have also supported the role of the *TM6SF2* gene in hepatic steatosis development both in adults and children[46–48]. Noteworthy, a pleiotropic effect has been described for both genes because of their extrahepatic role in affecting also kidney function in children with obesity[49,50] and adult with T2D and fatty liver[51]. In addition, robust evidence showed that the downregulation of the *MBOAT7* gene predisposed to fatty liver development both in children and adults[34,52,53]. In contrast, the *HSD17B13* variant has been recognized as a protective factor against liver injury and its progression[38,54,55]. As described for other well-known single nucleotide polymorphisms related to fatty liver, this variant has been found also to influence kidney function[56].

Minor genetic variants affecting IR, oxidative stress and inflammation pathways have been found to be related to fatty liver development[45,57]. In particular, a significant association between the rs17618244 G>A variant in the *KLB* gene and hepatic fibrosis has been described, and this gene is a central player in obesity and lipid and glucose metabolism, as demonstrated by its association with lobular inflammation and cirrhosis in patients clustered according to obesity degree[57].

MAFLD genetic susceptibility is still poorly explored[58,59]. Liu *et al*[59] confirmed the role of the *HSD17B13* region in a cohort of 427 Han Chinese adults as a genetic factor predisposing to MAFLD-related fibrosis and of modulated *PNPLA3* rs738409 polymorphism on fatty liver development[58].

Table 2 Main findings of the studies on MAFLD genetics

Gene	Study design	Population	Gene pathophysiology	Main findings
<i>b-Klotho (KLB) gene</i>	Panera <i>et al</i> [57], Hospital-based retrospective cohort study	1111 adult Italian MAFLD patients from the Metabolic Liver Diseases outpatient service at Fondazione IRCCS Ca'Granda of Milan between January 1999 and December 2019. Patients were stratified according to obesity status: -BMI > 35: 708 subjects -BMI ≤ 35: 403 subjects Inclusion criteria were liver biopsy or severe obesity and availability of DNA samples	The rs17618244 G>A variant in the <i>b-Klotho (KLB)</i> gene encodes for a transmembrane protein which complexes with Fibroblast Growth Factor Receptors to bind the hormones FGF21 and FGF19. Both genes play an important role in lipid and glucose metabolism and in obesity	<i>KLB</i> rs17618244 variant was linked to hepatic fibrosis KLB A allele was associated with lobular inflammation and cirrhosis in patients stratified for obesity status; Hepatic KLB mut expression seemed to be linked to proliferative rate improvement and pro-fibrogenic genes induction
<i>Hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13) gene</i>	Liu <i>et al</i> [59], Cross-sectional analysis	427 Han Chinese from the PERSONS cohort with biopsy confirmed MAFLD; Aged ≥ 18 yr	<i>Hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13)</i> gene encodes a hepatic lipid droplet protein	Data confirmed that the <i>HSD17B13</i> region is a susceptibility locus for MAFLD-related fibrosis An effect of modulated PNPLA3 rs738409 on hepatic steatosis was reported Significant differences in levels of fasting glucose, triglycerides, and high-density lipoprotein cholesterol among subject with <i>HSD17B13</i> - rs72613567 (TA allele) genotypes were observed, but no differences in biochemical parameters among the rs6531975 (A allele) genotypes were found; The minor TA allele was linked to an increased risk of fibrosis, while the minor A allele had a protective effect against liver damage
Membrane-bound O-acetyltransferase domain-containing protein 7 (MBOAT7)	(1) Meroni <i>et al</i> [52], Review: 21 studies: -6 case control studies; -10 case only; -2 metanalysis; -2 GWAS; -1 cohort studies (2) Ismaiel <i>et al</i> [53], Review: 22 studies: -7 case control studies; -3 case only; -5 metanalysis; -7 cohort studies	(1) Age: -4 pediatric studies; -17 adult studies; Ethnicity: -14 Caucasian; -5 multiethnic; -2 Asian (2) A total of 22 studies: -4 pediatric studies with ultrasound (US) diagnosis of fatty liver; -18 adult studies: 17 with fatty liver diagnosis with liver biopsy/ imaging and 1 with US	The MBOAT7 codifies for an enzyme highly expressed in hepatocytes, hepatic stellate cells and hepatic sinusoidal cells; It has been involved in fatty acid metabolism and in hepatic both inflammation and fibrosis	(1) In patients with MAFLD, MBOAT7 might affect liver damage Downregulation of liver expression of MBOAT7 induces changes in phosphoinositide composition pattern with subsequent modified membrane lipid composition and lipid mediator profiles Hyperinsulinemia, is a cofactor for MBOAT impairment; MBOAT7 dysfunction may influence liver disease progression to steatohepatitis and fibrosis and chronic hyperinsulinemia to steatosis development (2) Except for Asian population, studies on European, Hispanic, and African American adults with MAFLD evaluating the rs641738 variant reported a downregulation of the MBOAT7 expression, which increased MAFLD severity, liver fat, NASH progression, advanced fibrosis, and HCC No association with coronary artery disease was found. In children with obesity this variant was associated with increased plasma ALT levels

MAFLD: Metabolic associated fatty liver disease; FGFR: Fibroblast growth factor receptor; ALT: Alanine transaminase; MBOAT7: Membrane-bound O-acetyltransferase domain-containing protein 7; US: Ultrasound; GWAS: genome-

wide association study.

Recent evidence supports an inverse allelic effect of the association of *HSD17B13* variants on liver damage: in particular, hepatic fibrosis risk has been found to be increased by the minor allele TA of the rs72613567 variant, while a protective role against liver damage for the minor A allele of the rs6531975 variant has been demonstrated[59].

EVIDENCE ON MAFLD: FROM ADULTHOOD TO CHILDHOOD

As the renaming of the liver condition, the clinical usefulness of MAFLD definition has been tested in several studies[60-64] (Table 2). Lin *et al*[60] first compared MAFLD and NAFLD criteria in a large cohort of 13 083 subjects grouped as MAFLD (31.24%), NAFLD (33.23%) and non-metabolic-dysfunction-associated NAFLD (non-MD-NAFLD) (4.74%) (*e.g.*, subjects with NAFLD but not covered by MAFLD criteria)[61-62]. Authors found that patients with fatty liver were older, more likely to be male, and have worse cardiometabolic and hepatic profile independently of the used criteria[60].

Compared to NAFLD, MAFLD subjects were older (48.39 ± 15.20 years) and presented with higher body mass index (BMI), liver enzymes, and noninvasive liver fibrosis scores. In addition, an increased percentage of metabolic comorbidities (including diabetes, IR and hypertension) was reported in these patients[60]. Patients in the non-MD-NAFLD group were the youngest and presented with a better metabolic profile than those belonging to the MAFLD and NAFLD groups. In this framework, a more accurate identification of patients at higher risk of negative metabolic consequences seemed to be achieved by MAFLD criteria[60].

Conversely, no significant differences for the main clinical and biochemical variables between NAFLD and MAFLD were found in a large cohort of 780 adult patients with biopsy-proven fatty liver diagnosis [55]. Taking into account the alcohol consumption in MAFLD definition, patients with MAFLD with significant alcohol intake showed a worse hepatic profile (characterized by higher steatosis degree and transaminase levels) compared to those with MAFLD only[55].

The usefulness of MAFLD definition has been also examined by Sun *et al*[65] in a highly selected population such as patients with chronic kidney disease (CKD). Authors demonstrated a better performance of MAFLD diagnostic criteria than NAFLD in identifying patients with CKD[65], as previously found[64]. Of note, a strong and independent relationship of MAFLD and MAFLD with increased liver fibrosis scores with CKD and abnormal albuminuria was described[65].

Recently, differences between NAFLD and MAFLD criteria were tested in a 2-year follow-up Italian study conducted in 221 patients receiving a new diagnosis of celiac disease (CD) as a high-risk condition for fatty liver[66]. Compared to NAFLD, MAFLD definition allowed a better identification of CD patients at risk of disease progression and the coexistence of fibrosis seemed to enhance the occurrence of adverse outcomes in these patients[66].

Yamamura *et al*[67] compared the diagnostic accuracy of MAFLD and NAFLD in identifying individuals with significant hepatic fibrosis and clarified the influence of mild alcohol consumption (< 20 g/d) on the degree of the hepatic disease in a large cohort of 765 subjects clustered in two groups as

Table 3 Metabolic syndrome criteria in adults and children

	Abdominal obesity	Hypertension	Dyslipidemia	Fasting glucose
IDF central obesity + 2 of 4 criteria in adult patients and children aged >10 yr[87-89]	10–15 yr old waist circumference (WC) $\geq 90^{\text{th}}$ percentile for age and sex >15 yr old WC ≥ 94 cm (male) b WC ≥ 80 cm (female)	Systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg	TG ≥ 150 mg/dL or specific treatment HDL < 40 mg/dL (male), HDL < 50 mg/dL (female)	≥ 100 mg/dL or diagnosis of type 2 diabetes mellitus
Panel: IDEFICS definition of metabolic syndrome in children aged 2–11 yr[90] ¹	10–15 yr old WC $\geq 90^{\text{th}}$ percentile for age and sex > 15 yr old adults criteria	Blood pressure: systolic $\geq 90^{\text{th}}$ percentile or diastolic $\geq 90^{\text{th}}$ percentile	TG: $\geq 90^{\text{th}}$ percentile or HDL cholesterol: $\leq 10^{\text{th}}$ percentile	Insulin $\geq 90^{\text{th}}$ percentile or fasting glucose $\geq 90^{\text{th}}$ percentile

¹Children would require close monitoring if three or more of these risk factors exceed the 90th percentile (or $\leq 10^{\text{th}}$ percentile for HDL cholesterol), and an intervention if three or more of these risk factors exceed the 95th percentile (or $\leq 5^{\text{th}}$ percentile for HDL cholesterol).

BP: Blood pressure; HDL: High-density lipoprotein; IDEFICS: Identification and prevention of dietary- and lifestyle-induced health effects in children and infants; IDF: International diabetes federation; TG: Triglycerides; WC: Waist circumference.

NAFLD and MAFLD. Compared to NAFLD, MAFLD criteria provided careful detection of hepatic fibrosis, as reflected by the strong relationship between certain hepatic fibrosis markers and liver stiffness in patients diagnosed with MAFLD[67]. Given that, dysmetabolic patients at high risk of adverse hepatic outcomes were better identified through MAFLD than NAFLD criteria[12,21].

As the well-known relevance of alcohol intake on hepatic fibrosis risk development was not included in MAFLD definition, the authors also examined its influence on fatty liver severity[67]. Patients with MAFLD and alcohol intake of 1–59 g/d were more likely to be male and to have higher fasting blood glucose, serum liver enzymes, creatinine, and uric acid levels than those with MAFLD and no alcohol consumption[67]. Of note, there is no evidence on the potential negative effect of alcohol intake on renal damage risk in MAFLD individuals[67]. Authors concluded that MAFLD presence was an independent risk factor for significant fibrosis (defined by FIB-4 index ≥ 1.3 and liver stiffness ≥ 6.6 kPa using Shear wave elastography), and both MAFLD and mild alcohol intake were associated with increased prevalence of significant fibrosis (25.0% *vs* 15.5%)[67].

Further data examining the role of alcohol intake in this context[60] demonstrated a better metabolic profile but increased transaminase levels in subjects with MAFLD having a greater alcohol intake compared to those with no alcohol consumption. However, no consensus has been reached on the effect of alcohol in MAFLD, but some noninvasive fibrosis scores have been positively associated with MAFLD and alcohol intake[60].

Despite accumulating data on the impact of MAFLD on liver disease severity[60,65,67], its influence on the potential malignant transformation into hepatocellular cancer has been not evaluated.

Unlike adults, pediatric MAFLD data are limited. Because of the widespread distribution of this hepatic condition in childhood, recent epidemiological data reported a worrying increase of pediatric MAFLD prevalence[68-70].

MAFLD definition has been tested first in adult subjects; therefore, its clinical utility in a pediatric setting is still under investigation, since the fatty liver etiology at this stage[71-73] and the obesity status [21]. A recent Italian study investigated the usefulness of MAFLD criteria in 954 children with obesity [21]. The authors grouped their cohort as subjects with (1) obesity only; (2) obesity and NAFLD; and (3) obesity, NAFLD and metabolic dysregulation. The latter group was significantly older and showed higher BMI, systolic blood pressure, diastolic blood pressure, waist/hip ratio, HOMA-IR, triglyceride levels, baseline and 2-h oral glucose tolerance test glycemia, and transaminase levels. A higher prevalence of carriers of the *PNPLA3* rare allele was reported in this group compared with others. Taken together, these findings suggest a worse cardiometabolic profile in subjects with obesity, fatty liver, and metabolic dysregulation than in those belonging to other groups. As a preliminary study, MAFLD diagnosis based on metabolic dysregulation in children with obesity seemed more accurate for cardiometabolic risk stratification in a high-risk population such as children with obesity[21]. *PNPLA3* gene seems to play a role in a wider metabolic milieu beyond NAFLD[21], as previously found in a similar pediatric cohort[50,74].

More recently, an international panel[75] has proposed an age-appropriate MAFLD definition based on sex and age percentiles. Diagnostic criteria for pediatric MAFLD are based on the presence of hepatic steatosis (detected either by liver histology, imaging, blood biomarkers or blood scores) in addition to one of the following conditions: excess adiposity, T2D or prediabetes, or evidence of metabolic dysregulation (defined by the presence of at least two metabolic risk conditions according to sex and age percentiles such as hypertension, increased waist circumference, hypertriglyceridemia, low serum HDL cholesterol levels, triglyceride-to-HDL ratio ≥ 2.25 , and impaired fasting glucose)[75].

Contrary to the adult findings, the natural history of fatty liver in children is still not fully understood but its increase has been mainly linked to obesity[75]. Pediatric fatty liver usually does not occur in children < 3 years and is rare in those aged < 10 years. To date, it has been demonstrated that the entire spectrum of liver disease severity (from simple steatosis to steatohepatitis, fibrosis, and end-stage cirrhosis) might occur also in pediatric patients diagnosed with fatty liver, and that the progression is strongly related to IR severity[75]. As a consequence, the occurrence of severe complications (including liver transplantation) at this early age has also been reported. The pivotal role of primary care for early detection of pediatric fatty liver is widely recognized, and lifestyle modifications are the only valid treatment for the disease[75]. Therefore, redefinition of pediatric MAFLD represents a crucial step for global management improvement, including risk stratification and multidisciplinary care.

MAFLD: NEW INSIGHTS AND FUTURE DIRECTIONS

The tangled and multifactorial physiopathology of MAFLD (including inflammation, sex, age, ethnicity, diet and microbiota, hormones, and genetics) is still poorly defined. Despite the centrality of metabolic dysfunction, diagnosing fatty liver is also essential for MAFLD definition. Liver biopsy represents the common diagnostic gold standard for hepatic fat content assessment, but its invasiveness has limited its clinical utility in children[76,77]. A growing number of studies has evaluated different noninvasive biomarkers for MAFLD diagnosis, by identifying novel attractive therapeutic options for the management of the disease[78-81]. In this context, investigation of the gut-liver axis has attracted scientific attention[81-84]. Considering the relevance of the intestinal barrier in multiple biological mechanisms and the crucial influence of the immune system (located in the liver, intestine and adipose tissue)[84], this term strengthens the association of the liver with the gut barrier.

The association of gut-liver axis changes with MAFLD pathophysiology have recently been explored [78], by pointing out the role of inflammation and release of chemokines and cytokines by liver-infiltrating macrophages as key factors for progressive forms of fatty liver[78].

Dysbiosis and gut barrier changes have both been linked to inflammation and metabolic abnormalities in MAFLD. Remarkably, a peculiar association of microbiome alterations with carbo-hydrates, lipids and amino acids metabolism in MAFLD has also been described[81], but no consensus has been reached in this field. Nevertheless, promising preclinical studies[81] have enriched the spectrum of potential MAFLD therapeutic tools such as fecal microbiota transplantation[82-84]. A similar study on MAFLD adults[84] investigated microbiota-derived metabolites as potential noninvasive biomarkers for MAFLD, by identifying certain metabolites [e.g., phosphatidylcholine (PC), lysoPC, plasma eicosanoic acid or fatty acid 20:1 (FA20:1), PCaaC24:0, xanthine, and triglycerides] as early microbiota-related products involved in liver disease progression[84]. In addition, a significant association of the *PNPLA3* gene with plasma monounsaturated fatty acid FA(20:1) or eicosanoic acid was also demonstrated.

Notably, serum mi-RNA-122 (as the major hepatic mi-RNA involved in metabolic diseases) is significantly related to MAFLD progression in subjects with obesity and MAFLD[80]; therefore suggesting their potential prognostic utility for liver disease progression[80].

Although preliminary, some promising evidence supports the identification of novel potential therapeutic targets for MAFLD[85-88]. In particular, a significant decrease in MAFLD prevalence has been reported in normal-weight adolescents treated with a low-dose combination of spironolactone, pioglitazone and metformin (SPIOMET)[86-90] than those with classical hormone therapy, by underlining the role of SPIOMET treatment as a promising new pathophysiological approach in MAFLD patients[88]. Due to the relevant cardiometabolic burden of MAFLD and the absence of effective pharmacological agents both in children and adults, further studies are needed to identify specific noninvasive markers able to improve the management of MAFLD patients[75]. Several novel therapeutic targets based on molecular pathways are under investigation[78,84], but there are no current licensed MAFLD treatments[75].

CONCLUSIONS

The natural history of pediatric MAFLD remains to be defined, but mounting evidence from adults supports a significant increased cardiovascular risk in view of the concomitant occurrence of metabolic impairments with liver disease. Therefore, better knowledge of the intricate MAFLD pathophysiology might pave the way for new therapeutic approaches to improve the management of these patients at greater cardiometabolic risk.

FOOTNOTES

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