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

Lanzaro F *et al.* Metabolic fatty liver in children

Abstract

In 2020, an international group of experts proposed to replace the term of Non-alcoholic fatty liver disease (NAFLD) 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 closely focused 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, since the increasing attention for cardiometabolic risk in childhood. To date, accumulating evidence is available on the feasibility of MAFLD definition in clinical practice, but some data are still contrasting 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. On this ground, 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

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Core Tip: Recently, experts proposed to rename non-alcoholic fatty liver disease (NAFLD) 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 tested the effectiveness of the new definition in real world both 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.

INTRODUCTION

As proposed by an international consensus in 2020[1], the nomenclature of Non-alcoholic fatty liver disease (NAFLD) has been updated as Metabolic dysfunction 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 in Caucasian male subjects and 88 cm in females (or ≥ 90/80 cm in Asian individuals); (2) Blood pressure levels ≥ 130/85 mmHg or specific drug treatment; (3) Triglycerides (TG) levels ≥ 1.70 mmol/L or specific drug treatment; (4) HDL-C < 1.0 mmol/L for male and < 1.3 mmol/L for female; (5) Prediabetes (*i.e.*, fasting glucose levels 5.6 to 6.9 mmol/L, or 2-hour post-load glucose levels 7.8 to 11.0 mmol/L or HbA1c 5.7% to 6.4%; (6) Homeostasis model assessment-insulin resistance (HOMA-IR) score ≥ 2.5; and (7) High-sensitive C-reactive protein (hs-CRP) levels > 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 aimed to strengthened the close association of fatty liver with metabolic dysfunction[2,8-12] to early identify at higher risk subjects 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 MAFLD diagnostic criteria. However, it should be kept in mind that further specific diagnostic criteria for MetS defined 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 old (Table 1). The comparison between MetS and MAFLD criteria (Tables 2 and 3) allowed to identify MetS subjects with fatty liver as MAFLD patients. Although both conditions allowed to identified subjects at higher cardiometabolic risk, the inclusion of fatty liver as MAFLD criteria enhanced the multifactorial pathophysiology of the disease and its close relationship with metabolic derangements as well[16-20]. Given the overall emphasis of this latter association in MAFLD definition (from normal-weight to subjects with obesity), the new term included 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].

Accumulating data explored the Metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO) both in adult and pediatric cohorts[22-24]. MUO individuals have shown a higher cardiovascular risk than their metabolically healthy

counterparts. However, MHO also might predispose overtime 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 clinical marker of IR) represents a crucial first step for the evaluation of these patients.

More, a critical influence for adipose distribution pattern has been supposed for MAFLD development, as demonstrated by the positive correlation of visceral adipose tissue amount 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 has also emerging in pediatric age.

Therefore, we aimed to provide a comprehensive overview by summarizing the most recent evidence on the tangled puzzle of MAFLD both in adults and children.

PATHOPHYSIOLOGY

Fatty liver pathophysiology included 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 the *patatin-like phospholipase domain containing 3 (PNPLA3)*[30-32], *transmembrane 6 superfamily member 2 (TM6SF2)*[33], *membrane-bound O-acyltransferase domain-containing protein 7 (MBOAT7)*[34-36], and *hydroxysteroid 17-beta dehydrogenase 13 (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 down-regulation of the *MBOAT7* gene predisposed to fatty liver development both in children and adults[34,52,53].

On the other hand, 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 SNPs related to fatty liver, this variant has been found also to influence kidney function[56].

More, minor genetic variants affecting IR, oxidative stress, and inflammation pathways have been found to be related to fatty liver development [45,57]. Particularly, a significant association between the rs17618244 G>A variant in the *b-Klotho (KLB)* gene and hepatic fibrosis has been described, being also this gene 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].

Nowadays, the 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 as well[58]. Noteworthy, recent evidence supported 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 13083 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 in MAFLD criteria)[61-62]. Authors found that patients with fatty liver were older, more likely to be male, and with a 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 non-invasive liver fibrosis scores levels. In addition, an increased percentage of metabolic comorbidities

(including diabetes, IR, and hypertension) was reported in these patients[60]. More, subjects in the non-MD-NAFLD group were the youngest and presented with a better metabolic profile than those belonging to MAFLD and NAFLD groups. In this framework, a more accurate identification of patients at higher risk of negative metabolic consequences seemed to be performed 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]. More, 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 Coeliac disease (CD) as 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 than NAFLD in identifying individuals with significant hepatic fibrosis and clarified the influence of mild alcohol consumption (< 20 gms/day) on the degree of the hepatic condition in a large cohort of 765 subjects clustered in two groups as NAFLD and MAFLD. Compared to NAFLD, MAFLD criteria provided a 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, authors also examined its influence on fatty liver severity[67]. Patients with MAFLD and an alcohol intake habit (1-59 g/day) 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 (0 g/day) [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) (OR: 4.798; 95%CI: 2.078–13.935; $P < 0.0001$), and both MAFLD and mild alcohol intake were associated with increased prevalence of significant fibrosis (25.0% *vs* 15.5%; $P\ p = 0.0181$)[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 currently reached on the effect of alcohol in MAFLD context, but some non-invasive 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 progression to malignant transformation into hepatocellular cancer has been not yet evaluated.

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

Owing to the fact that MAFLD definition has been first tested for adult subjects, its clinical utility in pediatric setting is still under investigation, since the fatty liver aetiology at this stage[71-73] and the obesity status[21]. A recent Italian study questioned the usefulness of MAFLD criteria in 954 children with obesity[21]. Authors grouped their cohort as subjects (1) with obesity only; (2) with obesity and NAFLD; and (3) with obesity, NAFLD and metabolic dysregulation. This latter group was significantly older ($P = 0.001$) and

showed higher BMI-SDS ($P < 0.0001$), SBP-SDS ($P < 0.0001$), DBP-SDS ($P = 0.001$), W/Hr ($P < 0.0001$) HOMA-IR ($P < 0.0001$), triglycerides levels ($P < 0.0001$), baseline and 2-h OGTT glycaemia ($P < 0.0001$), and transaminase levels ($P < 0.0001$). More, a higher prevalence of carriers of the *PNPLA3* rare allele was reported in this group compared with others ($P = 0.001$). Taken together, these findings suggested a worse cardiometabolic profile in subjects with obesity, fatty liver, and metabolic dysregulation than 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]. Noteworthy, the *PNPLA3* gene seemed to play 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 wide increase has been mainly linked to obesity epidemic[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 was strongly related to IR severity[75]. As a consequence, data also reported the occurrence of severe complications (including liver transplantation) at this early age. Given that, the pivotal role of the primary care for early detection of pediatric fatty liver is widely recognized, being lifestyle modifications the only valid treatment for the disease[75]. Therefore, redefinition of pediatric MAFLD represents a crucial step for a 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]. Given that, a growing number of studies evaluated different non-invasive biomarkers for MAFLD diagnosis, by identifying also novel attractive therapeutic options for the management of the disease[78-81]. In this context, the gut-liver-axis investigation has reached remarkable 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 strengthened the association of the liver with the gut barrier.

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

More, both dysbiosis and gut barrier changes have been linked to inflammation and metabolic abnormalities in MAFLD subjects. Remarkably, a peculiar association of microbiome alterations with carbohydrates, lipids, and amino acids metabolism in MAFLD has been also described[81], but no consensus has been still reached in this field. Nevertheless, promising preclinical studies[81] have enriched the spectrum of potential MAFLD therapeutic tools such as the fecal microbiota transplantation[82-84].

A similar study on MAFLD adults[84] investigated microbiota-derived metabolites as potential non-invasive 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 micro-RNA-122 (as the major hepatic micro-RNA involved in metabolic diseases) were significantly related to MAFLD progression in subjects with obesity and MAFLD[80]. Therefore, authors suggested their potential prognostic utility for liver disease progression[80].

Although preliminary, some promising evidence has supported the identification of novel potential therapeutic targets for MAFLD[85-88]. In particular, a significant decrease in MAFLD prevalence was 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 underscoring 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 non-invasive markers able to improve the management of MAFLD patients[75]. Noteworthy, 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 define nowadays, but mounting adult evidence has supporting a significant increased cardiovascular risk in view of the concomitant occurrence of metabolic impairments with liver disease.

Therefore, a better knowledge of the intricate MAFLD pathophysiology might pave the way for new insightful therapeutic approaches to significant improve the management of these patients at greater cardiometabolic risk.

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