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EDITORIAL

Interplay between metabolic dysfunction-associated fatty liver disease and renal function: An intriguing pediatric perspective

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Abstract

Over recent years, the nomenclature of non-alcoholic fatty liver disease has undergone significant changes. Indeed, in 2020, an expert consensus panel proposed the term "Metabolic (dysfunction) associated fatty liver disease" (MAFLD) to underscore the close association of fatty liver with metabolic abnormalities, thereby highlighting the cardiometabolic risks (such as metabolic syndrome, type 2 diabetes, insulin resistance, and cardiovascular disease) faced by these patients since childhood. More recently, this term has been further replaced with metabolic associated steatotic liver disease. It is worth noting that emerging evidence not only supports a close and independent association of MAFLD with chronic kidney disease in adults but also indicates its interplay with metabolic impairments. However, comparable pediatric data remain limited. Given the progressive and chronic nature of both diseases and their prognostic cardiometabolic implications, this editorial aims to provide a pediatric perspective on the intriguing relationship between MAFLD and renal function in childhood.

Key Words: Metabolic (dysfunction) associated fatty liver disease; Renal; Function; Children; Obesity

Core Tip: Metabolic (dysfunction) associated fatty liver disease (MAFLD) has been closely linked to a wide spectrum of cardiometabolic consequences. Among these, accumulating data demonstrated an association between MAFLD and renal function in children with obesity. Worthy of note, a shared pathophysiology has been reported with a pivotal role of insulin-resistance in this dangerous interplay among obesity, renal hemodynamics, and metabolic derangements. Considering the relevant clinical and prognostic implications of this association, an increased awareness of this growing health concern for clinicians is needed.

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INTRODUCTION

In 2020, an expert panel proposed replacing the nomenclature of non-alcoholic fatty liver disease (NAFLD) with the more inclusive term metabolic (dysfunction) associated fatty liver disease (MAFLD) to underscore the pathogenic link between the disease and metabolic derangements in both adults and children[1,2]. According to the definition[2], the acronym MAFLD was introduced to strengthen the association of pediatric hepatic steatosis (diagnosed by biopsy with histological evaluation, imaging, or blood biomarkers) with at least one of the following criteria: (1) Excess adiposity; (2) Prediabetes or type 2 diabetes (T2D); and (3) Evidence of metabolic dysregulation[2].

Similar to NAFLD, the prevalence of MAFLD has been increasing worldwide in parallel with the obesity epidemic since childhood[1-3]. Current estimates suggest that approximately a quarter of the global adult population presents with MAFLD, while pediatric data indicate a global prevalence of 34% among children and adolescents with obesity in the general population, and 45% among peers in the obesity clinical setting[3]. Given this, MAFLD represents a major health and economic concern.

Indeed, MAFLD has been closely linked to cardiovascular disease (CVD) risk, but recent evidence also supports its role as a predictor of atherosclerosis, heart failure, T2D, and cancer-related mortality[1,3]. Consistent with previous evidence for NAFLD[4,5], a higher incidence of chronic kidney disease (CKD) has also emerged in patients with MAFLD[6-10], underscoring the impact of the disease on cardiometabolic health. Notably, robust adult data document a stronger association of MAFLD with CKD than NAFLD[10,11]. However, similar evidence linking MAFLD to CKD is still limited in childhood[12,13], though the underlying complex interplay among liver, kidney, adiposity, and metabolic dysfunction has been highlighted in these young patients[14-17]. Therefore, in this editorial, we aim to discuss the available evidence in the field to provide a perspective on the relevant clinical and prognostic implications of the interplay between MAFLD and CKD in children with obesity.

THE PATHOPHYSIOLOGICAL COMPLEXITY OF THE INTERPLAY BETWEEN MAFLD AND KIDNEY

Although the interplay of several determinants such as genetics, lifestyle, and environmental factors has been well-documented in the development of MAFLD, its exact pathogenesis remains to be fully elucidated[1-3]. In particular, certain features of MAFLD, such as systemic inflammation, metabolic dysfunction, and vascular dysfunction, have been found to act as mediators in the tangled inter-organ crosstalk underlying the close association of MAFLD with extrahepatic diseases (*e.g.*, CVDs, cognitive impairment, thyroid dysfunction, and CKD)[1,3,6,8]. On this basis, the relationship between MAFLD and renal function is unsurprising given their shared pathogenic factors such as low-grade inflammation, oxidative stress, and insulin resistance (IR)[8,9,18] (Figure 1).

In this complex pathophysiological puzzle, the contribution of genetics has also been well-documented[8,9,19]. The risk variant rs738409 C>G of the Patatin-like phospholipase domain-containing 3 gene represents a major genetic determinant of MAFLD in both adults and children[19-21]. Additionally, other polymorphisms such as the transmembrane 6 superfamily member 2 loss-of-function variant rs58542926[22] and the rs641738 C>T variant in the membrane-bound O-acyltransferase 7 gene[23,24] have been found to increase susceptibility to MAFLD[8,19]. Notably, recent evidence also supports a multifaceted role of these polymorphisms in renal health[21,22,24,25].

Furthermore, a prominent pathogenic role for inflammation needs to be underlined[26], as demonstrated by the inclusion of C-reactive protein among MAFLD diagnostic criteria[1,2]. Indeed, both chronic low-grade inflammation and oxidative stress lead to hepatic fibrosis by exacerbating pro-inflammatory signaling pathway activation[18,26], which in turn promotes endothelial dysfunction[18]. Consequently, this deleterious cycle impairs renal function by increasing glomerular permeability and proteinuria[18,27]. Notably, this increase in systemic inflammation might also affect cardiovascular health[6,8,18].

To complicate matters, IR - as a shared pathophysiological factor - plays a central role in the development of both MAFLD and CKD[28,29]. In fact, certain processes mediated by IR, such as an increased release of free fatty acids and an altered secretion of adipokines, affect both the liver and kidney[18,30-32].

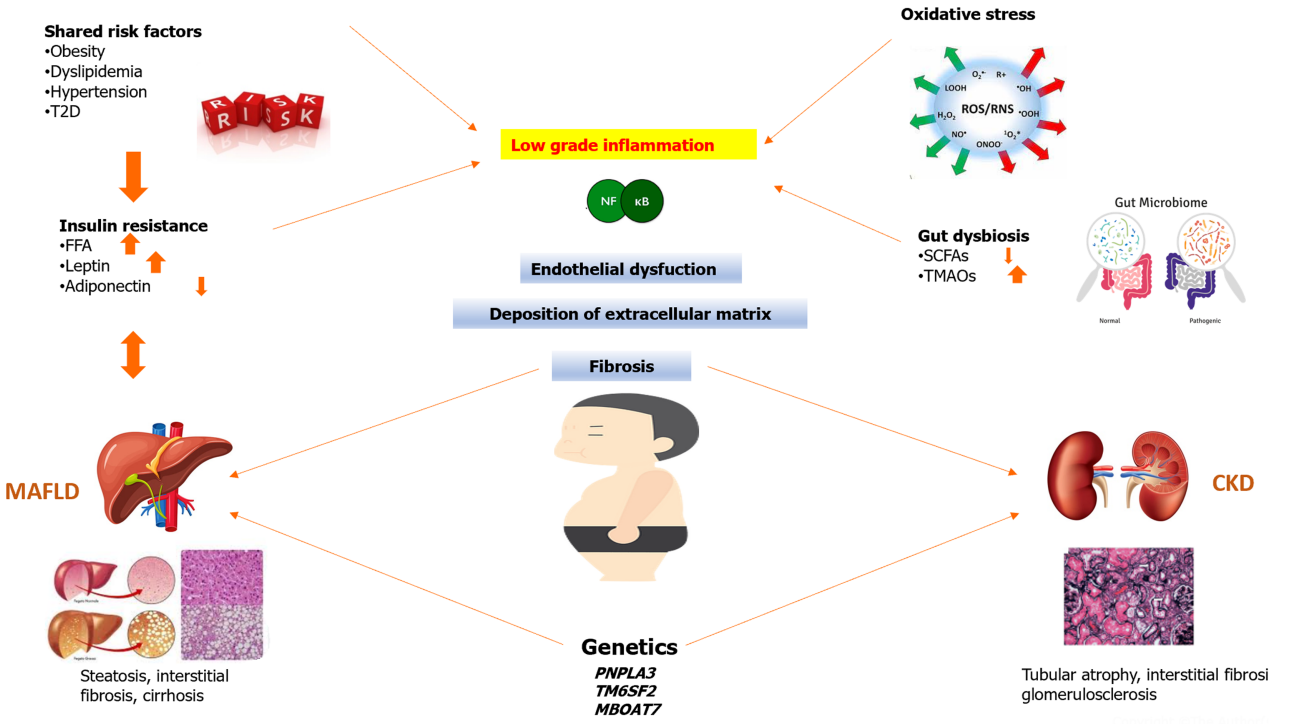

Figure 1 The complex pathophysiological interplay between metabolic (dysfunction) associated fatty liver disease and renal function. T2D: Type 2 diabetes; FFA: Free fatty acids; MAFLD: Metabolic (dysfunction) associated fatty liver disease; CKD: Chronic kidney disease; ROS: Reactive oxygen species; RNS: Reactive nitrogen species; SCFAs: Short chain fatty acids; TMAOs: Trimethylamine-N-oxides; PNPLA3: Patatin-like phospholipase domain-containing 3; TM6SF2: Transmembrane 6 superfamily member 2; MBOAT7: Membrane-bound O-acyltransferase 7.

Interestingly, recent insights into the complex pathogenic interplay between MAFLD and CKD highlight a role for the gut-liver-kidney axis, suggesting an intriguing contribution of gut microbiota to the development and progression of both diseases[18,33,34]. This realizes a vicious circle among dysbiosis, IR, inflammation, and oxidative stress[18,32]. In particular, metabolites derived from the gut microbiota such as trimethylamine-N-oxides[34,35] exert systemic effects impairing both liver[33,34] and renal function[35]. Additionally, the crosstalk between the liver and kidney also affects the production of short-chain fatty acids[36], further amplifying the underlying pathophysiological processes (*e.g.*, inflammation, IR, and oxidative stress) of MAFLD and CKD[36-38].

MAFLD AND CARDIOMETABOLIC HEALTH: THE RENAL PERSPECTIVE

MAFLD has been widely recognized as a strong predictor of all-cause mortality including CVD-related mortality[39-42]. More interestingly, recent data have unveiled an intriguing correlation between MAFLD and renal impairments[43-45], particularly CKD[18,38,40].

Several shared pathophysiological factors such as metabolic abnormalities (*e.g.*, obesity and IR), inflammation, adipokines, gut dysbiosis, and genetics contribute to liver and renal damage development[4,18,19,38]. In particular, IR appears to play a central role in the tangled interplay between MAFLD and CKD through various molecular pathways[6,8,18,38]. This exacerbates not only hypertension and atherogenic dyslipidemia but also activates renin-angiotensin system (RAS), which is closely related to endothelial dysfunction[6,8]. RAS activation further amplifies both proinflammatory and pro-coagulant states by releasing numerous mediators[6,8,18,38].

Moreover, evidence supports not only the intricate link between MAFLD and kidney function[8,43-45] but also the severity of hepatic damage with specific renal parameters in adults[46-48]. Indeed, recent studies have revealed associations between liver fibrosis, assessed *via* transient elastography, and kidney dysfunction parameters such as urinary albumin-to-creatinine ratio and estimated glomerular filtration rate (eGFR)[46-48]. However, research exploring the association between MAFLD and renal damage in pediatric populations remains limited[12,13].

Valentino *et al*[12] examined a cohort of Italian children with MAFLD and CKD during the initial coronavirus disease 2019 pandemic lockdown. After a six-month follow-up, children with MAFLD and CKD exhibited lower eGFR levels and an overall worse cardiometabolic profile compared to those without MAFLD[12]. De Groot *et al*[13] showed that children with a liver fat fraction > 2% and MAFLD presented with a worse cardiometabolic risk profile including higher blood pressure levels (as renal injury expression) compared to both children with a liver fat fraction < 2% and ≥ 2% liver fat without MAFLD. Of note, children with a liver fat fraction > 2% and MAFLD had an increased odds of clustering cardiometabolic risk factor compared to those with liver fat fraction < 2% independently of MAFLD presence (odds ratio = 7.65, 95% confidence interval: 5.04-11.62)[13]. In line with adult findings[42-44], these results underscore an association between MAFLD and renal damage in childhood[12,13]. Nevertheless, further large-scale studies are warranted to

validate this intriguing link comprehensively.

CONCLUSION

Recently, several lines of evidence have supported not only a pathogenic link between renal health and metabolic dysfunction but also its prognostic impact, both in children[12,13,18] and adults[18,40-43]. A complex inter-organ crosstalk sustained by metabolic impairments (*e.g.*, IR, visceral adiposity) has been supposed to be responsible for the relationship of MAFLD with extrahepatic diseases, including CKD[18]. More specifically, an intricate interplay among cardiometabolic risk factors, genetics, lipid nephrotoxicity, and hemodynamic changes has likely been implied in the relationship between MAFLD and renal impairment, but knowledge gaps in its exact pathophysiology still remain[8,18].

Compared to NAFLD, a better diagnostic and prognostic performance in identifying subjects at greater risk of hepatic and extra-hepatic complications has been demonstrated for the more inclusive MAFLD definition[8,18,41,48]. Based on these premises, children with MAFLD should receive more attention from clinicians through a multidisciplinary assessment that takes into account the intriguing MAFLD-associated multi-organ crosstalk.

Given the prognostic implications of the tangled relationship of MAFLD with extra-hepatic diseases[2,40-43], more scientific efforts are needed in this research area for a deeper understanding of the intricate interplay of molecular pathways contributing to hepatic and renal damage. On the other hand, this might also implement strategies for overall MAFLD management (including prevention, diagnosis, and treatment) to optimize patient outcomes since childhood.

FOOTNOTES

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