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The Role of Probiotic Therapy in Pediatric MASLD: Pathophysiological and Clinical Perspectives

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently the most common chronic liver disease in children, with its prevalence steadily increasing alongside the global epidemic of childhood obesity. Despite the growing scale of the problem, effective therapeutic strategies remain limited. Recently, an increasing evidence has highlighted the role of gut dysbiosis and gut-liver axis in the pathogenesis of MASLD, prompting interest in probiotics as a potential treatment. Available date indicate that probiotics may improve liver enzymes and reduce hepatic steatosis, suggesting their potential as an adjunctive therapy. Additional reported benefits include favorable modulation of appetite-regulating hormones (leptin, ghrelin), reductions in anti-peptidoglycan antibodies and increases in incretin hormone GLP-1. However, current date are constrained by substantial limitations, preventing definitive conclusions regarding probiotic efficacy. Therefore, further well-designed studies involving larger sample sizes, longer follow-up periods, and standardized assessment methods are required to fully determine the therapeutic value of probiotics in pediatric MASLD.

Keywords: childhood obesity, MASLD, NAFLD, probiotic

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly referred to as non-alcoholic fatty liver disease (NAFLD), is a commonly occurring metabolic liver disorder in the pediatric population, leading to progressive hepatic injury and dysfunction [1,2]. The prevalence of MASLD among children has increased substantially in recent years and continues to rise, closely mirroring the global epidemic of childhood obesity and the growing incidence of metabolic syndrome [3,4,5]. It currently represents the most common cause of chronic liver disease in children [6,7,8].

Recent meta-analyses estimate that the prevalence of MASLD reaches approximately 12-16% in the general pediatric population and 41-50% among children with overweight or obesity [4,3]. Prevalence varies by sex (general population: girls-10%, boys-15%; obese population: girls-39%, boys-54%) [4] as well as geographical region. Among children with overweight or obesity, the highest prevalence is reported in North America (43.6%), and the lowest in Africa (31.3%) [3]. Methodological differences across studies also significantly influence prevalence estimates, highlighting the need for unified diagnostic criteria [3].

The increasing number of MASLD cases in the pediatric population is of particular concern, as early onset of the disease may lead to severe long-term health consequences, including metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis, and hepatocellular carcinoma [3,9]. These complications extend beyond the liver and include a higher risk of cardiovascular events and metabolic abnormalities, collectively contributing to increased mortality [1,3,10,11].

Equally alarming are the findings of the meta-analysis by Matheus Souza et al., involving 5898 children with biopsy-confirmed MASLD [12]. The study demonstrated that approximately 60% of pediatric patients had MASH, around 30% had significant fibrosis (≥F2), and about 12% showed advanced fibrosis (≥F3). These results indicate that many children present with inflammatory changes and permanent structural liver damage already at the time of diagnosis, suggesting a faster and earlier progression of the disease than previously assumed [12].

The etiology of MASLD is multifactorial and includes hormonal factors, lifestyle and dietary components, as well as metabolic disturbances such as excess adipose tissue, dyslipidemia, insulin resistance, and impaired glucose tolerance [1,10]. In addition, numerous studies have identified several genetic variants that disrupt hepatic lipid metabolism and predispose children to the development of MASLD. The most important and best-studied genetic determinant is PNPLA3 (rs738409; I148M) [13,14]. This variant is associated not only with an increased susceptibility to the disease but also with a more severe clinical course. The G allele has been shown to exacerbate both steatosis and inflammatory features (lobular and portal inflammation), thereby contributing to an elevated risk of progression to MASH and fibrosis [14]. Other genes implicated in the pathogenesis of pediatric MASLD include TM6SF2 (E167K), GCKR (P446L) and MTTP, although their effects are generally weaker compared with PNPLA3 [14,15].

Despite its significant health consequences, MASLD in children is frequently underdiagnosed or diagnosed late. This is primarily due to the lack of reliable, validated, and easily accessible diagnostic tools [1,16,17]. Liver biopsy remains the most accurate method for staging disease severity, however, its use in routine pediatric diagnostics is limited owing to its invasive nature, risk of complications, and procedural costs [1,16].

At present, there are no approved or consistently effective pharmacological therapies for MASLD in either adults or children. Current management focuses on lifestyle modification (dietary intervention [18] and increased physical activity [19]), as well as selected supplements (such as vitamin E [20], probiotics, and omega-3 fatty acids [21]), in addition to targeted obesity treatment [1,6]. The number of clinical trials assessing pharmacotherapy in pediatric MASLD is limited and includes agents such as GLP-1 analogues [2], DPP-4 inhibitors [22], orlistat [23],

and metformin [24]. However, the results remain inconclusive, and their clinical applicability is restricted due to small sample sizes and the lack of long-term data on safety and sustained efficacy [1].

Consequently, lifestyle modification, including a healthy diet and increased physical activity, remains the primary and most widely recommended therapeutic strategy for children with MASLD. This approach is supported by the strong association between MASLD development and excess body weight [1,6].

The aim of this study is to evaluate the effectiveness of probiotic supplementation in the treatment of MASLD in children. MASLD has emerged as a growing public health concern in the pediatric population, with its prevalence increasing in parallel with the rising rates of childhood obesity. The rapid expansion of the population of children with excess body weight suggests that the burden of disease will continue to escalate in the coming years, while current therapeutic options remain limited. Probiotics, through their potential influence on the gut-liver axis, have gained increasing interest as a possible therapeutic strategy. This review summarizes the current state of knowledge regarding their efficacy, limitations, and potential role in the management of pediatric MASLD.

Methods

The literature search strategy was carried out using the PubMed database based on a combination of keywords: childhood obesity, probiotic, MASLD, NAFLD. Additionally, references within selected publications were reviewed to identify related studies. After screening titles and abstracts, incomplete articles and those not directly related to pediatric MASLD or the role of probiotics in its treatment were excluded. The final analysis included 39 publications that met the inclusion criteria. Most of these studies were published within the last five years.

Evolution of terminology: from NAFLD to MASLD

Over recent years, a significant shift has occurred in the nomenclature used to describe this liver disease entity. The original term non-alcoholic fatty liver disease (NAFLD), defined primarily by the exclusion of alcohol-related liver injury, was deemed insufficient due to both the potentially stigmatizing label ,,non-alcoholic" [25] and its failure to acknowledge the central role of metabolic dysfunction in the disease's pathogenesis.

In 2020, the term metabolic-associated fatty liver disease (MAFLD) was proposed, based on inclusion criteria requiring:

-the presence of hepatic steatosis detected by imaging (ultrasound, magnetic resonance imaging (MRI), transient hepatic elastography with controlled attenuation parameter (CAP), histology,

or biochemical markers and derivative scoring systems, and

-coexistence of overweight or obesity, prediabetes, type 2 diabetes, or other metabolic abnormalities [3].

This change emphasized the metabolic basis of the disease, aligned diagnostic criteria more closely with clinical phenotypes and pathological features, and allowed recognition of liver disease driven by overlapping metabolic, alcoholic, and other mechanisms [10].

In 2023, through an international Delphi consensus process, a new taxonomy and diagnostic algorithm were established. The overarching classification criterion is now the presence or absence of hepatic steatosis - steatotic liver disease (SLD). Patients with SLD are subsequently stratified based on the presence of at least one of five cardiometabolic risk factors (CMRF):

1. Elevated adiposity, defined as BMI ≥ 85th percentile for age/sex (BMI z-score ≥ +1) or waist circumference (WC) > 95th percentile
2. Prediabetes or diabetes, defined as fasting plasma glucose (FPG) ≥ 100 mg/dL, hemoglobin A1c (HbA1c) ≥ 5.7%, or a self-reported diagnosis of diabetes and treatment
3. Elevated blood pressure, defined as BP ≥ 95th percentile (age ≤ 12 years) or BP ≥ 130/85 mmHg (age ≥ 13 years), or use of antihypertensive medication
4. Elevated triglycerides, defined as ≥150 mg/dL or use of lipid-lowering treatment
5. Reduced high-density lipoprotein cholesterol, defined as HDL ≤ 40 mg/dL or use of lipid-lowering treatment [26].

Patients meeting these criteria are diagnosed with metabolic dysfunction-associated steatotic liver disease (MASLD). The classification further distinguishes:

-MASH (metabolic dysfunction-associated steatohepatitis) - the inflammatory subtype of MASLD, corresponding to NASH (non-alcoholic steatohepatitis)

-MetALD (metabolic and alcohol-associated liver disease) - diagnosed in individuals who meet MASLD criteria and have moderate alcohol intake (140-350 g/week for females, 210-420 g/week for males)

-Cryptogenic SLD-steatosis without accompanying CMRF or other identifiable causes [25, 26, 27].

The new diagnostic framework allows classification of most liver diseases along multiple parallel axes (such as viral hepatitis+/-, SLD+/-, and CMRF+/-). This approach underscores the role of hepatic steatosis and insulin resistance as key modifiers of liver disease progression, regardless of the primary etiology [26, 25, 27].

As demonstrated by a study conducted in a large cohort of American adolescents (n = 1410, aged 12-19 years), the new MASLD classification substantially overlaps with the previous

diagnosis of NAFLD [26]. Using the EchoSens-recommended controlled attenuation parameter (CAP) cutoff of transient elastography (TE) at 240 dB/m, the diagnostic concordance between MASLD and NAFLD was approximately 85%, indicating that the vast majority of adolescents previously diagnosed with NAFLD would also meet the criteria for MASLD. This concordance increased with higher CAP thresholds and approached nearly 100% at elevated cutoffs, suggesting that the definition of hepatic steatosis plays a crucial role in disease classification. Despite this high level of agreement, at the CAP = 240 dB/m threshold, approximately 15% of adolescents fulfilling NAFLD criteria did not meet MASLD criteria, resulting in ambiguous diagnoses categorized as cryptogenic SLD or possible MASLD. The most concerning finding of the study, however, related to adolescents with MASLD who also had clinically significant liver fibrosis. Only 8.8% of these individuals fulfilled the current NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology and Nutrition) referral criteria: overweight/obesity combined with ALT ≥ 80 U/L. This indicates that more than 90% of adolescents with clinically meaningful fibrosis would remain undetected if relying solely on existing screening recommendations.

Given that the nomenclature change occurred relatively recently, the terminology used throughout this article reflects the original classifications applied in the cited publications. Consequently, different terms may appear in reference to the same disease entity.

Probiotics as a potential therapeutic strategy for MASLD

In recent years, increasing attention has been directed toward the role of the gut microbiota in the pathogenesis of MASLD, particularly through mechanisms involving the gut-*liver axis [28, 29, 30], which has led to growing interest in probiotics as a potential therapy aimed at modulating microbiota composition and inflammatory processes [31].*

Pathophysiological perspective

A meta-analysis incorporating shotgun metagenomic data from nine studies, supplemented by an additional cohort, demonstrated that both α- and β-diversity of the gut microbiota in children with MASLD and MASH were significantly altered compared with obese and healthy controls ($p < 0.001$). This indicates that microbiome disturbances are associated not only with obesity but also specifically with liver disease. Among the taxa most strongly differentiating the groups, *Faecalibacterium prausnitzii* was found to be depleted in MASLD and MASH, whereas *Prevotella copri* abundance increased in parallel with fibrosis severity

($p=0.0082$). Advanced machine-learning models (XGBoost, random forest) trained on gut microbiome profiles successfully distinguished obese children from those with MASLD (AUROC 87%) and MASH from MASLD (AUROC 89%), suggesting that microbiome

alterations intensify with disease progression from MASLD to MASH in pediatric patients. These findings point to the potential utility of the gut microbiome as a non-invasive biomarker of disease severity and underscore the role of diet as a modifiable therapeutic target [28]. The study further demonstrated that machine-learning models distinguished pediatric MASH from adult MASH with high accuracy (AUROC 97%), suggesting that pediatric MASH may represent a biologically distinct entity with different underlying mechanisms compared with the adult form [28].

Available studies, *although limited in number and constrained by methodological variability, indicate that, in both adult and pediatric populations, the presence of NAFLD is associated with increased intestinal permeability (IP), independent of BMI. This increase appears to be more pronounced in children [29]. Moreover, IP has been shown to correlate positively with hepatic steatosis, whereas evidence for its association with lobular inflammation, hepatocyte ballooning, or fibrosis remains inconsistent [29]. Mechanisms underlying elevated IP include gut microbiota dysbiosis, altered production of short-chain fatty acids (SCFAs), and increased endogenous alcohol generation by intestinal bacteria. Differences in microbiome composition between children and adults may explain the distinct patterns of SCFA alterations and varying degrees of IP observed in both groups [29]. Dysbiosis and increased IP facilitate the translocation of bioactive bacterial products into the portal circulation, where they influence hepatic lipid metabolism, immune signaling, and redox homeostasis [30]. These changes promote steatosis, inflammation, and oxidative stress, contributing to the development of MASLD and its progression to MASH and fibrosis [15, 30]. Key bacterial-derived mediators implicated in this process include:*

-lipopolysaccharide (LPS) - activates hepatic TLR4 (toll-like receptor 4) signaling, triggering proinflammatory cascades, oxidative stress, and fibrogenesis.

-SCFAs (e.g., butyrate, propionate) - may promote hepatic lipid accumulation via AMPK (5'AMP-activated protein kinase) inhibition [32, 30].

-secondary bile acids - regulate glucose, lipid, and lipoprotein metabolism through FXR (Farnesoid X Receptor) *signaling and modulate intestinal barrier integrity.*

-choline- and trimethylamine-derived metabolites - contribute to steatosis by impairing the synthesis of very low-density lipoproteins (VLDL).

-aromatic amino acids (AAAs) and their derivatives - some (e.g., phenylacetic acid) exacerbate inflammation, whereas others (e.g., indole metabolites) exert protective effects [30, 15].

Clinical perspective

In children with MASLD, interventions aimed at restoring microbial balance may serve as a valuable adjunct to standard lifestyle modification strategies. The following section summarizes available randomized clinical trials and meta-analyses assessing the efficacy of probiotics in pediatric MASLD, with particular attention to their effects on biochemical parameters (ALT, AST, lipid profile, fasting blood glucose), anthropometric measures (weight, BMI, waist circumference), and ultrasound-based assessment of steatosis.

A meta-analysis conducted by Nikolaos Gkiourtzis and colleagues, including four randomized clinical trials (a total of 238 children with NAFLD), evaluated the efficacy of probiotic supplementation containing various bacterial strains in the treatment of pediatric NAFLD. The analysis demonstrated that probiotic use was associated with a significant reduction in ALT and AST levels, improvements in anthropometric parameters, reductions in total cholesterol and triglyceride concentrations, and measurable improvement in ultrasound-detected hepatic steatosis [33]. The most favorable effects were observed with formulations containing *Lactobacillus acidophilus* combined with *Bifidobacterium* or other *Lactobacillus strains*. However, despite these positive findings, it was not possible to conclusively determine which specific strain was responsible for the observed benefits [33].

Furthermore, a systematic review of four randomized controlled trials investigating the use of probiotics in children with NAFLD reported that probiotic supplementation led to a statistically significant reduction in ALT levels *[34]. Nonetheless, findings related to other hepatic and metabolic parameters were inconsistent, preventing the authors from performing a reliable quantitative synthesis [34]*.

One of the studies included in the above-mentioned review was a randomized clinical trial conducted by Goyal P. and colleagues, involving 106 obese children aged 5-*18 years [35]. This study stood out from the others due to its large sample size, its unique evaluation of combined therapy (probiotic supplementation + lifestyle modification), and because it was the only trial to assess appetite-regulating hormones (leptin and ghrelin) [35]. In contrast to the remaining studies, in which lifestyle modification was recommended to all participants, thereby preventing an isolated assessment of the effects of probiotic therapy, this trial evaluated the efficacy of four therapeutic strategies administered over a 4-month period: VSL#3 plus lifestyle intervention (n = 26), VSL#3 alone (n = 27), lifestyle intervention alone (n = 26), and placebo (n = 27) [35]. The most pronounced improvement across all assessed domains - reduction of hepatic steatosis on ultrasound, improvement in biochemical parameters (ALT, AST, lipid profile, FBG, hsCRP), anthropometric measures (BMI,WC), as well as favorable modulation*

of obesity-related hormones (increased ghrelin and decreased leptin levels) - was observed in the group receiving the combined VSL#3 + lifestyle intervention [35]. This effect was significantly more marked than that achieved with probiotic supplementation alone or lifestyle modification alone, suggesting a synergistic impact of the combined therapeutic approach [35].

Another study included in the above-mentioned review and meta-analysis was a randomized clinical trial conducted by A. Alisi, involving 44 children with NAFLD (22 in the VSL#3 group and 22 in the placebo group). This was the only study among the analyzed trials that evaluated the effect of probiotics on the incretin hormone GLP-1 and its active form. The same multispecies probiotic preparation, VSL#3, as used in the study by Goyal et al., was administered [36]. The results demonstrated that probiotic supplementation led to a significant reduction in the severity of hepatic steatosis assessed by ultrasound [after 4 months, 91% of children receiving VSL#3 presented either no steatosis (21%) or only mild steatosis (70%), compared with 7% in the placebo group]. However, in contrast to the findings of Goyal et al., no significant differences were observed between groups regarding triglycerides, HOMA-IR, or ALT levels [36]. In the probiotic group, a reduction in BMI and a significant increase in both total and active GLP-1 levels were detected [36]. These findings suggest a potential mechanism of action whereby probiotics exert their effects through modulation of the gut-*hormonal axis. As proposed by the authors, restoration of a healthy gut microbiota may reduce intestinal permeability, enhance the production of SCFAs and stimulate intestinal L-cells to secrete gut hormones such as GLP-1 [36]. GLP-1 plays a crucial role in glucose and lipid metabolism, increases insulin sensitivity, and inhibits lipogenesis, indicating its potential contribution to hepatic improvement in patients with NAFLD [36].*

Overall, the results imply that probiotics, by modulating gut microbiota and increasing endogenous GLP-1 secretion, may represent a safe and promising therapeutic approach, potentially synergistic with GLP-1 receptor agonists used in the treatment of obesity and type 2 diabetes mellitus [36].

Another study included in the analyses was a randomized, double-blind pilot trial conducted by Pietro Vajro and colleagues, involving 20 obese children with NAFLD and persistent hypertransaminasemia [37]. A distinguishing feature of this study, compared with the others, was the evaluation of the effect of probiotic therapy on serum peptidoglycan-polysaccharide IgA antibodies (PG-PS IgA), a marker of bacterial antigen translocation and intestinal barrier integrity, and therefore an indirect indicator of small intestinal bacterial overgrowth (SIBO) [37]. Growing evidence suggests that SIBO and the associated dysbiosis may play a key role in the pathogenesis of MASLD. In the course of SIBO, excessive production of bacterial toxins

and hepatotoxic metabolites, such as lipopolysaccharide (LPS) and endogenous ethanol, occurs. These substances, once they cross the impaired intestinal barrier, trigger chronic inflammation, exacerbate insulin resistance and oxidative stress, and promote lipid accumulation in hepatocytes. Additionally, dysbiosis disrupts choline metabolism, which is essential for the synthesis of VLDL, thereby impairing triglyceride export from the liver and contributing to steatosis [38]. The results of this study demonstrated that 8-week supplementation with a probiotic containing *Lactobacillus rhamnosus* GG (12 billion CFU/day) significantly reduced ALT levels and PG-PS IgA concentrations compared with placebo [37]. This effect was independent of changes in BMI z-score and visceral fat mass, indicating a direct action of the probiotic rather than an indirect consequence of weight reduction. No significant improvements were observed in ultrasound parameters or TNF-α levels [37]. This study suggests that modulation of the gut microbiota may influence key mechanisms underlying NAFLD. The reduction in PG-PS IgA levels indicates that probiotics may improve intestinal barrier integrity, decrease translocation of bacterial antigens, and potentially reduce the influx of pro-inflammatory mediators to the liver-factors that play a central role in the pathogenesis of NAFLD [37].

Another study included in the analyses was a randomized, triple-blind clinical trial conducted by Fatemeh Famouri, involving 64 obese pediatric patients with sonographically confirmed NAFLD [39]. This study stands out for its high methodological quality, as it was the only one conducted using a triple-blind design, thereby strengthening the reliability of the findings and minimizing the risk of bias. The intervention consisted of a 12-week supplementation with a multistrain probiotic (containing *Lactobacillus acidophilus* ATCC B3208, 3×10^9 *CFU;* Bifidobacterium lactis *DSMZ 32269, 6* $\times 10^9$ *CFU;* Bifidobacterium bifidum *ATCC SD6576, 2* $\times 10^9$ *CFU; and* Lactobacillus rhamnosus *DSMZ 21690, 2* $\times 10^9$ *CFU) [39]. Supplementation resulted in a significant reduction in ALT and AST levels, improvement of the lipid profile (total cholesterol, LDL-C, triglycerides), and a reduction in waist circumference, with no changes in body weight or BMI [39]. Notably, 53.1% of children in the probiotic group achieved a normal liver ultrasound appearance, compared with only 16.5% in the placebo group, suggesting a beneficial effect of the intervention on the regression of hepatic steatosis [39].*

Despite the promising results, it is important to acknowledge that the available studies have several significant limitations. The sample sizes were relatively small, which reduces the statistical power and limits the generalizability of the findings to broader pediatric populations. The short duration of follow-up in most trials prevents assessment of the long-term sustainability of the therapeutic effects and their impact on disease progression. Moreover, the

studies exhibited substantial heterogeneity in the probiotic formulations used (different strains, doses, and intervention durations) and in diagnostic methods, making comparison between studies difficult and limiting the ability to draw firm conclusions. In most trials, diagnosis and treatment response were assessed primarily using biochemical markers and ultrasound, which are less reliable than MRI-PDFF or liver biopsy. In addition, none of the studies included an analysis of gut microbiota composition or mechanistic endpoints, which prevents confirmation of the probiotic's mechanism of action and its association with modifications in microbial composition.

Summary

The current state of evidence does not allow probiotics to be unequivocally recognized as an effective treatment for pediatric MASLD. Although some studies report encouraging findings, their small sample sizes, short intervention periods, and methodological heterogeneity preclude strong clinical recommendations. Consequently, lifestyle modification, *aimed at weight normalization and regular physical activity, remains the cornerstone of therapy. To determine the true therapeutic potential of probiotics, well-designed studies with larger cohorts, longer follow-up, and standardized, advanced assessment methods, including histological and microbiome analyses, are needed. Only such an approach will allow for a reliable evaluation of probiotic efficacy in pediatric MASLD and for defining the optimal formulation and treatment regimen.*

Disclosure

Author's Contribution

Conceptualization: Natalia Staszko, Kamila Bała

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