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## COMMENTARY

# Critical need for pharmacologic treatment options in NAFLD: A pediatric perspective

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## Abstract

Nonalcoholic fatty liver disease (NAFLD) affects up to 70% of children with obesity and has become the number one etiology for liver transplant in the United States. Early, effective intervention is critical to prevent disease progression into adulthood. Yet, it is seldom achieved through lifestyle modification alone. Thus, children must be included in NAFLD pharmacology trials, which, to date, continue to focus primarily on adult populations. This commentary serves as a call to action.

Three hundred forty million children worldwide are affected by overweight/obesity (<https://www.who.int/end-childhood-obesity/publications/taking-action-childhood-obesity-report/en/>). Without intervention, > 75% of these children will continue to gain excessive weight and become adults with obesity.<sup>1</sup> Alarming, almost all adults with obesity (90%) develop comorbid nonalcoholic fatty liver disease (NAFLD),

the leading etiology for liver transplant in the United States.<sup>2</sup> Thus, effective, early life intervention is critical for children with obesity, up to 70% of whom already have comorbid NAFLD by adolescence.<sup>2</sup>

Lifestyle modifications (e.g., diet and exercise) resulting in weight loss of as little as one kilogram can improve NAFLD in children.<sup>3</sup> However, overall adherence to lifestyle

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modification is low, with the exception of a few pediatric research studies that offer intense follow-up<sup>3,4</sup> or comprehensive in-home services.<sup>4</sup> As such, bariatric surgery is increasingly recognized as an option for weight reduction in children, but it is invasive and there is an unpredictable subset of patients who experience worsening liver fibrosis and NAFLD progression postsurgery.<sup>5</sup> This leaves a critical, unmet need for effective pharmacologic interventions in pediatric NAFLD.

Currently, there are no approved medications for NAFLD; however, the landscape of potential therapeutic agents is evolving rapidly and showing promise, as highlighted in a comprehensive review by Attia *et al.* published in *Clinical and Translational Science*.<sup>6</sup> In addition to the many novel therapeutic agents discussed (e.g., obeticholic acid, fibroblast growth factor 19 and 21 analogues, thyroid hormone receptor- $\beta$  agonists, etc.), the authors briefly mention past therapeutic experiences with medications already on the market for other clinical indications. Although the adult experience with some of these medications was equivocal, it is important to note that some agents show promise for repurposing in pediatric NAFLD.

One example is metformin, a drug already approved for the treatment of type 2 diabetes in children > 10 years of age. In a study of lifestyle modifications combined with either metformin or placebo in children with obesity and insulin resistance  $\pm$  NAFLD, the metformin group demonstrated a significant decrease in NAFLD scores and NAFLD prevalence, whereas the placebo group experienced an increase from baseline for both.<sup>7</sup> Interestingly, when metformin was administered at lower doses in other pediatric trials, it demonstrated isolated improvement in histopathology features (e.g., hepatic ballooning),<sup>8</sup> but not in the overall histopathology NAFLD score, suggesting that metformin's effect on NAFLD may be dose dependent. Therefore, further studies of metformin in the setting of pediatric NAFLD are indicated.

Other drugs already approved for obesity-related comorbidities may also be of interest for repurposing in pediatric NAFLD. Statins, cholesterol-lowering agents prescribed to patients with obesity and hypercholesterolemia, have been shown to significantly improve hepatic function in patients with obesity and NAFLD<sup>9</sup>—presumably through anti-inflammatory mechanisms in the liver. Although no data are available in pediatrics, in adults with NAFLD, statin therapy is well-tolerated, with low frequency of hepatotoxicity similar to placebo,<sup>9</sup> making statins intriguing drug candidates to consider for the treatment of pediatric NAFLD. Secondary analyses of off-target treatment effects of medications already prescribed to children with obesity (e.g., statins and metformin) may be helpful in uncovering important insights into therapeutic options for pediatric NAFLD treatment. Especially while best practices for expanding novel NAFLD therapeutics trials to

pediatrics remain under development, as referenced in a recent draft guidance from the US Food and Drug Administration (<https://www.fda.gov/media/119044/download>).

In our opinion, and the opinion of other experts,<sup>10</sup> inclusion of pediatric populations in adult NAFLD pharmacology trials is important and represents a strategy that has been successfully implemented in oncology trials. Yet, the majority of new NAFLD agents continue to be pursued more aggressively for adults than children. As illustrated in the review by Attia *et al.*,<sup>6</sup> only 2 of the 17 therapeutic trials discussed included children. By excluding children, we are missing a critical opportunity for early intervention to prevent NAFLD progression from simple hepatic steatosis to more advanced disease (i.e., steatohepatitis, fibrosis, cirrhosis, hepatocellular carcinoma, and end-stage liver failure). Our hope is that increased awareness of pediatric NAFLD prevalence, coupled with the National Institutes of Health policy for inclusion of research subjects across the lifespan (<https://grants.nih.gov/policy/inclusion/lifespan.html>), will encourage investigators to include pediatric patients in clinical trials of NAFLD therapeutics.

Inclusion of children in pharmacology trials comes with its own set of unique challenges and nuances (e.g., ontogeny, age-appropriate outcome measures, parental informed consent and informed assent of minors, etc.), beyond the scope of this commentary and as comprehensively reviewed in a pediatric tutorial guide by Shakhnovich *et al.*<sup>11</sup> In addition, to facilitate inclusion of children specifically in pharmacology trials for NAFLD, NAFLD-specific noninvasive biomarkers are urgently needed. The majority of studies reviewed by Attia *et al.*<sup>6</sup> relied on histopathology-based assessment of NAFLD as a therapeutic outcome measure. However, liver biopsy is invasive and histopathology assessment is not always feasible or ethical in children, especially in the context of research. Alanine aminotransferase, the most commonly utilized clinical serum biomarker of liver injury is nonspecific for NAFLD. Therefore, several more-specific biomarkers are currently under investigation; among them, serum bile acids. Total fasting and postprandial bile acids, and the ratios of conjugated and secondary bile acids, are consistently higher in the sera of adults with nonalcoholic hepatic steatosis, compared with healthy controls.<sup>12</sup> Pediatric studies of bile acids lag behind, are sparse and inconsistent, and are needed to establish minimally invasive biomarkers of NAFLD for children.

Recently, noninvasive liver imaging biomarkers have become more widely available, and it is encouraging to see these modalities incorporated into NAFLD therapeutics research, including four trials discussed by Attia *et al.*<sup>6</sup> Both ultrasound elastography and magnetic resonance elastography can quantify liver stiffness as a noninvasive surrogate for liver fibrosis. However, NAFLD presents a challenge to both techniques because elastography values are affected by

both fat and fibrosis. Magnetic resonance proton density fat fraction (MR-PDFF) can directly estimate hepatic fat content and allows clinicians and researchers to separate the individual contributions from fat vs. fibrosis to liver stiffness. However, MR-PDFF is only available in specialized tertiary care centers and is expensive. Ultrasound techniques for fat quantification could offer a cheaper, more readily available alternative to MR-PDFF and these techniques are likely to become widely available in the near future.

Thus, the landscape of therapeutic pharmacology trials for NAFLD is rapidly evolving. The advent of noninvasive biomarkers for monitoring NAFLD treatment response offers promise and opportunity, especially for inclusion of pediatric patients in research. A concerted effort must be made to include children in NAFLD pharmacology trials, as NAFLD affects up to 70% of children with obesity,<sup>2</sup> and early childhood intervention is key to minimize/reverse disease progression to end-stage liver disease in adulthood.

## CONFLICT OF INTEREST

The authors declared no competing interests for this work.

## DISCLAIMER

As an Associate Editor of *Clinical and Translational Science*, Valentina Shakhnovich was not involved in the review or decision process for this paper.

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