



# Efficacy of Weight Reduction on Pediatric Nonalcoholic Fatty Liver Disease: Opportunities to Improve Treatment Outcomes Through Pharmacotherapy

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Obesity is the single greatest risk factor for nonalcoholic fatty liver disease (NAFLD). Without intervention, most pediatric patients with NAFLD continue to gain excessive weight, making early, effective weight loss intervention key for disease treatment and prevention of NAFLD progression. Unfortunately, outside of a closely monitored research setting, which is not representative of the real world, lifestyle modification success for weight loss in children is low. Bariatric surgery, though effective, is invasive and can worsen NAFLD postoperatively. Thus, there is an evolving and underutilized role for pharmacotherapy in children, both for weight reduction and NAFLD management. In this perspective article, we provide an overview of the efficacy of weight reduction on pediatric NAFLD treatment, discuss the pros and cons of currently approved pharmacotherapy options, as well as drugs commonly used off-label for weight reduction in children and adolescents. We also highlight gaps in, and opportunities for, streamlining obesity trials to include NAFLD assessment as a valuable, secondary, therapeutic outcome measure, which may aid drug repurposing. Finally, we describe the already available, and emerging, minimally-invasive biomarkers of NAFLD that could offer a safe and convenient alternative to liver biopsy in pediatric obesity and NAFLD trials.

**Keywords:** NAFLD, pediatric, weight losing effect, pharmacotherapy, pediatric trials, pediatric NAFLD, weight loss efficacy

## INTRODUCTION

With 340 million children worldwide affected by obesity (1), the rate of nonalcoholic fatty liver disease (NAFLD) is expected to rise because obesity remains the single most significant risk factor for NAFLD (2). The pathophysiology of NAFLD in obesity is complex and likely involves the interplay and dysregulation of multiple mechanisms beyond the scope of this publication

(e.g., insulin resistance, cytokine signaling, gut microbiota) (3); however, continued abnormal weight gain is a common culprit in fueling the disease. NAFLD affects up to 70% of children and up to 90% of adults with obesity (2), and has become a leading indication for liver transplant in the United States (4). Without intervention, more than 75% of children with obesity will continue to gain excessive weight and become adults with obesity (5). Therefore, in addition to effective childhood weight management strategies, readily available non-invasive diagnostic and monitoring modalities are needed for NAFLD management, in order to prevent obesity-associated NAFLD progression from simple hepatic steatosis to steatohepatitis, fibrosis, cirrhosis, hepatocellular carcinoma, and end-stage liver failure in adulthood.

Weight reduction through lifestyle modification remains the first-line treatment approach for NAFLD (6). The present work aims to review the efficacy of weight reduction on pediatric NAFLD and to illustrate opportunities for improving NAFLD diagnosis, monitoring, and treatment outcomes through pharmacologic interventions.

## LIFESTYLE MODIFICATIONS FOR WEIGHT REDUCTION

Lifestyle modification for weight reduction and lasting improvement in health outcomes requires change in multiple areas, including diet and exercise (7). Weight loss of as little as one kilogram has been shown to improve clinical serum biomarkers of NAFLD in children (8), and biopsy-proven NAFLD if weight is subsequently maintained for 24 months (9). Consequently, many dietary interventions have been explored in pediatrics, including portion controlled, reduced glycemic load, low carbohydrate, meal replacement, and time restricted eating, as well as very low calorie diets and protein sparing modified fasting for more severe obesity (10–14). Similar to findings in adults (15), the most effective diet for pediatric weight management is the one that can be sustained successfully over time, with generally less adherence observed for low carbohydrate diets and better adherence to portion control and reduced glycemic load (10). These dietary changes are the recommended first step for NAFLD management, in combination with regular moderate to high intensity exercise (2, 6). Although there is currently insufficient evidence to recommend one type of exercise program over another for NAFLD (16), there is some evidence to suggest that a diet low in free sugar (17) and the Mediterranean diet specifically may have added benefit in treating NAFLD, independent of weight loss (18). Although adherence to these two diets was exceptionally high in some pediatric studies (8–10), this is atypical of most other research studies (19), and likely attributable to intense follow-up (8–10) and in-home interventions (10) that are not available, nor practical in the clinical setting. Dietary recommendations for weight loss and NAFLD are summarized in **Figure 1**, and are generally recommended in conjunction with exercise (>150 minutes/week moderate intensity, or >75 minutes/week high intensity) (16), or moderate to vigorous physical

activity daily for at least 20 minutes (with a goal of 60 minutes) (7).

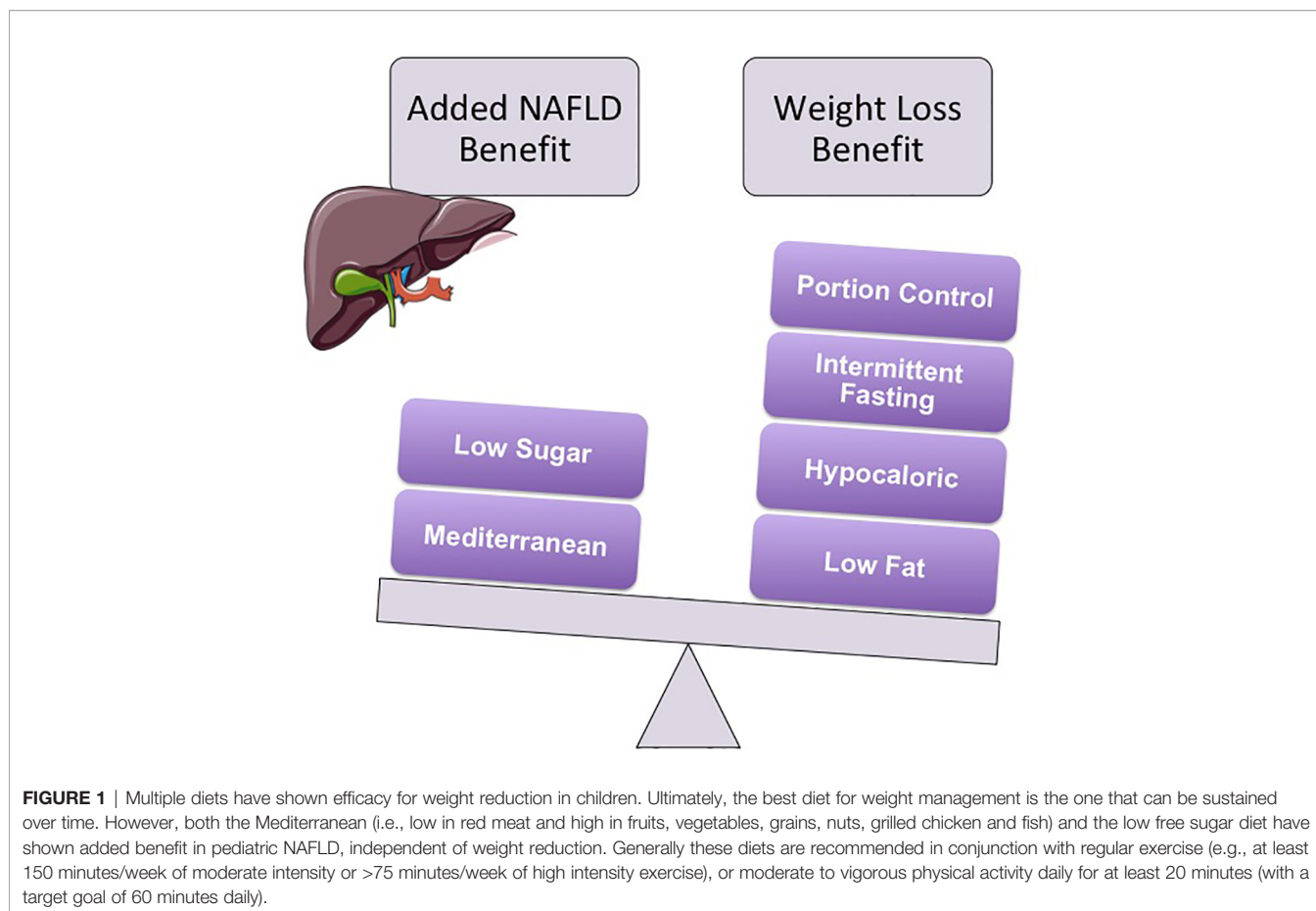
In clinical practice, these lifestyle modifications show heterogeneity in patient adherence and treatment response (20). In pediatrics, obesity is defined by body mass index (BMI) at or above the 95<sup>th</sup> percentile for age and sex, and treatment response assessed using the change in the percent of the 95<sup>th</sup> percentile (%BMI<sub>p95</sub>) (21, 22). In a large national prospective registry of children participating in non-surgical, multicomponent, intensive behavioral clinical treatment for obesity (n=6,454), the mean change in %BMI<sub>p95</sub> after lifestyle modification was -1.88% at 4 to 6 months, -2.5% at 7 to 9 months, and -2.86% at >12 months – showing a modest decline in weight loss over time. Only those patients who achieved -5.2% change in %BMI<sub>p95</sub> showed improvement in alanine aminotransferase (ALT), a clinical biomarker of liver injury (23). Whereas, those patients who experienced a change from normal to abnormal ALT had an increase in %BMI<sub>p95</sub> of 0.48% (23), highlighting heterogeneity in treatment success.

Upon closer examination of the experience of a single program in this registry, only one third of the 769 participants achieved a >5% decrease in %BMI<sub>p95</sub>—the amount of BMI change associated with improvement in ALT and liver health (20). Increased number of clinical follow-up visits and days of physical activity were associated with greater odds of successful weight loss, defined as achieving >5% decrease in %BMI<sub>p95</sub> (23). To illustrate the close clinical contact necessary for weight loss program success, guidance for moderately intense lifestyle modification therapy from the United States Preventative Services Task Force (USPSTF) recommends 26-75 patient contact hours over a 6-12 month period (24). However, in our experience, children with NAFLD are typically seen in clinic for approximately one hour every 2-3 months, falling short of the USPSTF-recommended contact hour target for weight management.

## SURGERY FOR WEIGHT REDUCTION

Bariatric surgery (e.g., laparoscopic sleeve gastrectomy) is an effective intervention for weight reduction (25), with post-surgical weight loss of approximately 20% total body weight in both adults (26) and children (27). Although less common in pediatrics, bariatric surgery is becoming an increasingly recognized option for children greater than 10 to 12 years of age with BMI >120% of the 95<sup>th</sup> percentile (or BMI of 35 kg/m<sup>2</sup>) and comorbid NAFLD (26, 28). Recent investigations in adolescents suggest that bariatric surgery results in a four-fold reduction in hepatic fat fraction, with resolution of hepatic steatosis at 6 months post-surgery on imaging (29, 30), and 100% resolution of steatosis and 90% resolution of fibrosis on liver biopsy at 12 months post-surgery (27).

Despite its promise in treating pediatric obesity and NAFLD, bariatric surgery also appears to worsen NAFLD in a subset of patients. Although no pediatric data are available, in a large meta-analysis of 32 adult studies on bariatric surgery, 19 reported worsening or new NAFLD features, including steatosis,



inflammation, and fibrosis in approximately 12% of patients postoperatively (25). Alarming, no apparent risk factors could be identified for this serious postoperative complication (25). Thus, the risks of bariatric surgery should be balanced against the potential for advantageous surgical outcomes for both obesity and NAFLD, and pharmacologic agents discussed as treatment adjuncts and/or alternative options.

## PHARMACOTHERAPY FOR WEIGHT REDUCTION

Currently, two pharmaceutical agents have approval from the United States Food and Drug Administration (FDA) for weight loss indications in children >12 years (orlistat and liraglutide), and one additional agent for adolescents >16 years (phentermine) (31, 32). Of these agents, orlistat's use is somewhat limited by its gastrointestinal side-effect profile (e.g., diarrhea, bloating) (33); although, it was found to be moderately effective in decreasing BMI from 0.55 up to 4.2 kg/m<sup>2</sup> (34–37). Phentermine is a stimulant and a Class IV controlled substance, necessitating increased consideration when prescribing in children. Additional screening and monitoring is necessary in children with congenital heart disease, cardiovascular disease, and thyroid abnormalities similar to protocols used when

prescribing stimulants for other indications common in pediatrics (32). Phentermine also does not appear to be as effective in achieving weight loss in adolescents as in adults (31). As such, liglutide—a GLP1 agonist newly approved by the FDA in December 2020 for the treatment of pediatric obesity—may soon emerge as the frontrunner. After somewhat disappointing BMI reduction results in an earlier trial in children with type II diabetes (38), results from a more recent, randomized, controlled trial demonstrate a decrease in BMI by 1.58 kg/m<sup>2</sup> compared to placebo, when liraglutide was administered to children with obesity along with lifestyle modifications (39). Although therapeutic end-points for NAFLD were not included in this trial, greater than 5% reduction in BMI, previously associated with improvement in NAFLD (20), was achieved in almost half (43%) of liraglutide-treated participants, versus 19% of participants receiving lifestyle modification therapy alone (39). Additional GLP1 agonists are under investigation and it is our opinion that NAFLD assessment ought to be considered as a secondary treatment outcome in these trials, particularly as minimally-invasive biomarkers of NAFLD become more readily available and mitigate the need for liver biopsy.

The overall efficacy of GLP1 agonists appears comparable to other medications already labeled for pediatric indications and being used off-label for weight loss in children. For example,

metformin, a first-line treatment for pediatric type II diabetes mellitus, has been associated with a modest BMI reduction in children (40). Recent studies looking at metformin demonstrated a decrease of  $-1.07$  and  $-1.3$  kg/m<sup>2</sup> over 6 months (41), with a wide range of success (i.e.,  $+0.38$  to  $-2.52$  kg/m<sup>2</sup> BMI change) noted in some studies (40). Although the observed variability in treatment response may, in part, be related to variability in adherence to concomitant lifestyle modifications, we believe it is also related to variability in systemic drug exposure (i.e., pharmacokinetics) achieved from a given metformin dose administered to an individual child (42). Additional research is ongoing into potential sources of inter-individual variability (e.g., genetics) in metformin pharmacokinetics and pharmacodynamics (i.e., drug efficacy). Meanwhile, the GLP1 agonist exenatide appears to show efficacy comparable to metformin, with placebo-subtracted reduction of  $1.3$  kg/m<sup>2</sup> (approximately  $-2.7\%$  BMI) over 3 months, and  $-4\%$  BMI over 6 months, in pediatrics (41). A small clinical study of topiramate, an anti-epilepsy drug already approved for pediatric use, also shows a 6-month decrease in BMI similar to exenatide ( $-4.6\%$ ), in 48 pediatric patients with severe obesity (43). Thus, medications currently indicated for pediatric weight reduction, as well as those approved for pediatric indications and administered off-label for the purpose of weight reduction, may have a role in weight management for pediatric patients. However, currently available data suggest that the range of weight loss achieved with pharmacotherapy may be only marginally greater than lifestyle modifications alone.

In randomized controlled trials, the mean weight change for lifestyle modification therapy was  $-1.8\%$  BMI, compared to  $-2.8\%$  BMI when therapy was combined with liraglutide or topiramate (44). Similarly, the mean pooled reduction in BMI in response to metformin therapy in children with obesity was  $-0.86$  kg/m<sup>2</sup>, and fell within the BMI reduction ranges from lifestyle modifications alone ( $-0.02$  to  $-1.10$  kg/m<sup>2</sup>) (45). Importantly, on average, none of these weight management approaches achieved a reliable  $>5\%$  reduction in BMI, deemed necessary for NAFLD improvement (20). Thus, though weight-reduction is an important first-line treatment for children with NAFLD, and may be achieved through lifestyle modifications, bariatric surgery or pharmacotherapy, each approach is associated with substantial variability in treatment response. This leaves a gap in universally effective treatments for pediatric NAFLD, and a potential role for precision therapeutics and pharmacotherapy.

## PHARMACOTHERAPY FOR NAFLD

Currently, there are no FDA-approved medications for pediatric NAFLD. However, the landscape of potential therapeutic agents for NAFLD is evolving rapidly and showing promise, as highlighted in recently published reviews (26, 46) beyond the scope of this publication. In addition to novel therapeutic agents (e.g., obeticholic acid, fibroblast growth factor 19 & 21 analogs, thyroid hormone receptor- $\beta$  agonists), there is also interest in repurposing existing drugs—already approved for pediatric

obesity or obesity comorbidities—for the treatment of pediatric NAFLD (47).

One example is the lipid-lowering drug class statins. In addition to improving cardiovascular disease outcomes, statins have demonstrated significant improvement in hepatic function for patients with obesity and NAFLD (48, 49), likely through secondary anti-inflammatory effects. In adults with NAFLD, statin therapy is well-tolerated and has a similar, low frequency of hepatotoxicity comparable to placebo (48, 50), making it a potential candidate for NAFLD management. However, efficacy data remain equivocal (50) and genotype-stratified investigations may be necessary to identify therapeutic target ranges appropriate for NAFLD treatment indications.

It would be remiss not to mention oxidative stress as a potential therapeutic target in NAFLD management. Anti-oxidants (e.g. vitamin E, omega-3 fatty acids) have been used both for the treatment of pediatric weight reduction and NAFLD, with mixed results (8, 51–53). In one longitudinal, randomized, placebo-controlled trial, vitamin E did not demonstrate advantage over weight reduction through lifestyle modifications for NAFLD or obesity (8). In another longitudinal, placebo-controlled trial of vitamin E vs. metformin, neither agent resulted in sustained ALT reduction (51). However, resolution of steatohepatitis was significantly higher with vitamin E compared to placebo, even though BMI reduction was equivocal (51). Conversely, in a trial of omega-3 fatty acids, children treated with omega-3s were more likely to have BMI reduction compared to placebo, but reduction in ALT was equivocal (52, 53). Collectively, these studies indicate equipoise in anti-oxidant efficacy for NAFLD and highlight the need for further study.

Many other agents, already being used on and off-label for weight reduction, have been proposed to have therapeutic benefit for NAFLD (54), though few have been evaluated in children. These include orlistat; GLP1 agonists, such as liraglutide, semaglutide, and exenatide; and SGLT2 inhibitors. While some pediatric studies of orlistat have shown select improvement in serum liver injury markers (55), the majority of studies have not examined the effect of orlistat on liver adiposity or histopathology. Available data to date demonstrate no clear improvement in liver pathology that is independent of orlistat-induced weight loss (54), making orlistat a questionable drug candidate for primary NAFLD indications in children (56). To our knowledge, liraglutide and other GLP1 agonists have not been evaluated as pharmacotherapy for pediatric NAFLD; however, multiple studies in adults demonstrate promising improvement in hepatic steatosis and liver injury markers associated with GLP1 agonist treatment (54, 57). It is unclear whether this effect on NAFLD is independent of weight-loss, a caveat that extends to SGLT2 inhibitors, which also demonstrate some benefit for NAFLD treatment in adults (58). Parallel studies in pediatrics are indicated, particularly now that liraglutide is approved for weight loss indications in children, and more agents may be on the horizon soon.

Metformin, a drug already FDA-approved for type II diabetes in children and used off-label for pediatric weight loss (40, 41),

has also shown some promise for repurposing in pediatric NAFLD. In a study of lifestyle modifications combined with either metformin or placebo in children with obesity and insulin resistance +/- NAFLD, the metformin group demonstrated a significant decrease in NAFLD scores and NAFLD prevalence, while the placebo group experienced an increase in both (59). Other studies in pediatrics using metformin at lower doses demonstrated isolated improvement in hepatic ballooning (51) or lobular inflammation (9) on histopathology, but failed to show an overall improvement in steatosis or NAFLD scores, suggesting that the effects of metformin on NAFLD may be dose-dependent. Improvement in serum ALT has been equivocal between studies, with 2 out of 4 pediatric studies demonstrating improvement in ALT (59, 60). However, this is likely because ALT, along with other currently available clinical markers of liver injury, lacks specificity for NAFLD (25).

## MINIMALLY-INVASIVE BIOMARKERS OF NAFLD

The diagnostic gold standard for NAFLD in children is liver biopsy. However, liver biopsy is invasive and not practical for

recurrent monitoring of NAFLD. Instead, serum ALT is the most commonly used biomarker of NAFLD, but it is non-specific and can be normal in >80% of patients with NAFLD (25). Therefore, minimally-invasive and highly-specific biomarkers are urgently needed to diagnose and monitor NAFLD.

In the past decade, several new, potential biomarkers of NAFLD have been identified by serum proteomics/metabolomics analyses (61, 62). Based on their origin, these markers can be grouped into hepatokines, adipokines, and other cytokines. Although detailed review of these novel biomarker candidates is beyond the scope of this publication, the most promising biomarkers are summarized in **Table 1**. In addition, serum bile acids (BAs) are highlighted as another emerging class of biomarkers.

BAs are synthesized in the liver, excreted into the bile, metabolized by the intestinal microbiome, and undergo several enterohepatic recirculations. Therefore, changes in the BA metabolome could be pathognomonic for various stages of NAFLD. The ratio of the primary BAs, cholic acid and chenodeoxycholic acid, is higher in patients with simple steatosis, as well as more advanced NAFLD (90). Compared to healthy controls, total fasting and postprandial primary BAs, and the ratios of taurine- and glycine-conjugated BAs, are consistently higher in the sera of adults with nonalcoholic

**TABLE 1** | Potential Biomarkers for Nonalcoholic Fatty Liver Disease.

Biomarkers & biomarker candidates	Type/origin	Changes in NAFLD steatosis	Correlations and changes in other NAFLD-related conditions	References
<b>Adiponectin</b>	Adipokine	↓	↓ in inflammation ↓ in fibrosis	(63)
<b>Chemerin</b>	Adipokine	↑	–	(64, 65)
<b>Leptin</b>	Adipokine	↑	↑ in inflammation ↑ in fibrosis	(66)
<b>Resistin</b>	Adipokine	(↑)	(↑) in inflammation (↑) in fibrosis	(67)
<b>Visfatin</b>	Adipokine	↑	(↑) in inflammation (↑) in fibrosis	(68, 69)
<b>Leptin/adiponectin ratio</b>	Adipokine	↑ NAFLD > obese children	positively correlates with triglyceride	(70)
<b>Irsin</b>	Adipokine	↑	(↑) in inflammation (↑) in fibrosis	(71, 72)
<b>Fetuin- A, α2-HS-glycoprotein (AHSG)</b>	Hepatokine	↑	positively correlates with HOMA-IR (insulin resistance index)	(73, 74)
<b>Fibroblast growth factor 21 (FGF-21)</b>	Hepatokine	↑	positively correlates with hepatic fat fraction and hepatic triglycerides	(75–77)
<b>Selenoprotein P (SeP)</b>	Hepatokine	↑ in children ↓ in adults	negatively correlates with adiponectin	(77–79)
<b>Sex hormone-binding globulin (SHBG)</b>	Hepatokine	↓	–	(77)
<b>Leukocyte derived chemotaxin 2 (LECT2)</b>	Hepatokine	↑	↑ in insulin resistance	(80, 81)
<b>Cathepsin D (CatD)</b>	Hepatokine	↓	↓ in inflammation	(82)
<b>Adropin</b>	Hepatokine	↓	–	(83)
<b>Retinol-binding protein 4 (RBP4)</b>	Hepatokine, Adipokine	↓	↓ in insulin resistance & T2DM	(84)
<b>Tumor necrosis factor alpha (TNF-α)</b>	Inflammatory cytokine	↑	↑ in inflammation ↑ in fibrosis	(85, 86)
<b>Zonulin</b>	Intestinal peptide	↑ NAFLD > obese children	↑ in inflammation & NASH	(87, 88)
<b>Interleukin-18 (IL-18)</b>	cytokine	↑ NAFLD > obese children	–	(89)

↑ indicates marker increase; ↓ indicates marker decrease. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; T2DM, type II diabetes mellitus; HOMA-IR, homeostatic model assessment for insulin resistance.

steatohepatitis (NASH) (91). However, the role of secondary BAs as potential biomarkers remains debated, as the two studies above showed different results. Puri et al. observed lower total secondary BAs in adults with NASH compared to controls (90), whereas Ferslew et al. observed higher secondary BAs (91). In pediatrics, BAs study results are sparse and inconsistent, but could offer a valuable, minimally-invasive modality for NAFLD monitoring during treatment trials. Significantly lower total serum BA concentrations were found in one pediatric study of hepatic steatosis (92), but not in others (93, 94). Notably, two of these studies demonstrated decreased concentrations of glycine- and taurine-conjugated deoxycholic acid in children with NAFLD steatosis and/or NASH, compared to healthy controls (92, 93). The third study also found serum concentrations of glycine conjugated deoxycholic acid to be lower in children with NAFLD, but not in children with NASH (94). Together, these observations suggest that bile acid homeostasis in pediatric NAFLD may be distinct from the adult disease phenotype. Therefore, BAs results should not be extrapolated from adults to children, and further investigation in pediatric patients is warranted.

While serum biomarkers of NAFLD remain under investigation, several liver imaging biomarkers have become available. Magnetic resonance proton density fat fraction (MR-PDF) is a non-invasive technique that quantifies the percentage of fat within a given volume of tissue. It correlates closely with steatosis grade on liver biopsy in children (95) and accurately captures longitudinal changes in pediatric NAFLD over time (96). However, it is only available in specialized tertiary care centers and is expensive. Ultrasound techniques for fat quantification are not yet widely available, but could offer a cheaper, more accessible alternative to magnetic resonance fat quantification, and facilitate more consistent and better quality disease monitoring for pediatric obesity and NAFLD trials.

For those imaging biomarkers that *are* widely available, one consistent shortcoming is that they perform best for tracking more severe stages of NAFLD/NASH, typical of adult disease. Grayscale ultrasound has been used for many years as a *qualitative* estimate of hepatic fat content. However, this technique is unreliable and non-specific for hepatic fat quantification, due to overlap in appearance between fatty and fibrotic liver (97, 98). Similarly, although both ultrasound and magnetic resonance elastography can quantify liver stiffness as a surrogate for fibrosis, NAFLD presents a challenge because measurement values are affected by both fat and fibrosis (99). Therefore, an ideal pediatric imaging surveillance program would incorporate *quantitative* imaging measurements that could discriminate fat and fibrosis.

## DISCUSSION

Obesity is the single greatest risk factor for NAFLD in adults and children (2). Although weight loss of as little as 1 kilogram can improve NAFLD in children (8), consistent implementation and maintenance of intensive lifestyle modifications necessary to

induce and sustain such weight loss are low (19, 20). Bariatric surgery is becoming increasingly recognized as an option for weight reduction in children (26), but it is invasive, and there is an unpredictable subset of patients who experience worsening liver fibrosis and NAFLD progression after surgery (25). This leaves room for pharmacologic interventions to aid with weight loss in pediatric obesity to treat and prevent NAFLD.

Without intervention, most pediatric patients with NAFLD continue to gain excessive weight (5) and become adults with NAFLD. Thus, inclusion of children and adolescents in pharmacology trials of novel weight-loss and NAFLD treatments is paramount. Repurposing drugs already labeled for pediatric use in comorbidities associated with obesity may be a complementary strategy to expand pediatric NAFLD treatment options beyond lifestyle modifications or bariatric surgery. Importantly, incorporation of NAFLD treatment end-points into obesity trials up-front would streamline efforts to assess a given drug's efficacy for pediatric NAFLD, as well as obesity, and potentially help discriminate drug effect from weight-loss effect on NAFLD.

Regardless of the treatment approach selected, to streamline and facilitate treatment trials in pediatrics, minimally-invasive, highly-specific biomarkers of NAFLD are urgently needed to augment advanced imaging techniques that offer an alternative to liver biopsy, but are expensive and inaccessible in most clinical settings. A concerted effort must be made to include children in NAFLD biomarkers and therapeutics trials in order to intervene early and effectively in disease progression that is fueled by continued excessive weight gain from childhood into adulthood. Best strategies for including children in NAFLD trials are under development, as referenced in a draft guidance for industry from the FDA (100), and additional tips for optimal patient selection and age-appropriate therapeutic end-points can be found in a recent review by Alkhoury et al. (101).

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## AUTHOR CONTRIBUTIONS

VS and CF conceived the idea for the manuscript. VS, CH-C, SC, IC, JW, BS, and JF provided expert opinion. All authors contributed to the article and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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