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# Metabolic dysfunction-associated steatotic liver disease (MASLD) in children with obesity: An Obesity Medicine Association (OMA) and expert joint perspective 2025

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ABSTRACT

*Introduction:* This Obesity Medicine Association (OMA) Expert Joint Perspective examines steatotic liver disease (SLD), which is composed of metabolic dysfunction-associated steatotic liver disease (MASLD), and metabolic dysfunction-associated steatohepatitis (MASH) in children with obesity. The prevalence of obesity is increasing,

*List of Abbreviations:* AAP, American Academy of Pediatrics; AASLD, American Association for the Study of Liver Diseases; ADHD, Attention Deficit Hyperactivity Disorder; ALD, Alcohol-Associated Liver Disease; ALT, Alanine Aminotransferase; AOM, Anti-Obesity Medicine; AST, Aspartate Aminotransferase; BBS, Bardet-Biedl Syndrome; BMI, Body sMass Index; CAP, Controlled Attenuation Parameter; CMRFs, Cardiometabolic Risk Factors; CPS, Clinical Practice Statement; DILI, Drug-Induced Liver Injury; DPP-4, Dipeptidyl Peptidase-4; ESPGHAN, European Society for Paediatric Gastroenterology Hepatology and Nutrition; ESRD, End-Stage Renal Disease; FDA, Food and Drug Administration; Fib4, Fibrosis-4 Index; FXR, Farnesoid X Receptor; GGT, Gamma-Glutamyl Transferase; GLP-1RA, Glucagon-Like Peptide-1 Receptor Agonist; HCC, Hepatocellular Carcinoma; HCV, Hepatitis C Virus; IBD, Inflammatory Bowel Disease; IF, Intermittent Fasting; ILD, Inborn Errors of Lipid Metabolism; LSM, Liver Stiffness Measurement; MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; MASH, Metabolic Dysfunction-Associated Steatohepatitis; MBS, Metabolic Bariatric Surgery; MEN, Multiple Endocrine Neoplasia; MetALD, Metabolic Alcohol-Associated Liver Disease; MRE, Magnetic Resonance Elastography; MRI, Magnetic Resonance Imaging; MRI-PDFF, Magnetic Resonance Imaging-Proton Density Fat Fraction; NAS, NAFLD Activity Score; NASPGHAN, North American Society for Pediatric Gastroenterology Hepatology and Nutrition; NASH, Non-Alcoholic Steatohepatitis; NAFLD, Non-Alcoholic Fatty Liver Disease; NITs, Non-Invasive Tests; OMA, Obesity Medicine Association; PCOS, Polycystic Ovary Syndrome; PCP, Primary Care Provider; PDFF, Proton Density Fat Fraction; PNPLA3, Patatin-Like Phospholipase Domain-Containing Protein 3; PPAR, Peroxisome Proliferator-Activated Receptor; RCT, Randomized Controlled Trial; RYGB, Roux-en-Y Gastric Bypass; SLD, Steatotic Liver Disease; T2DM, Type 2 Diabetes Mellitus; TE, Transient Elastography; TNF, Tumor Necrosis Factor; UNOS, United Network of Organ Sharing; US, Ultrasound; VLDL, Very Low-Density Lipoprotein; VUS, Variant of Unknown Significance; WHO, World Health Organization.

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rates have tripled since 1963 from 5 % to now 19 % of US children affected in 2018. MASLD, is the most common liver disease seen in children, can be a precursor to the development of Type 2 Diabetes (T2DM) and is the primary reason for liver transplant listing in young adults. We must be vigilant in prevention and treatment of MASLD in childhood to prevent further progression.

*Methods:* This joint clinical perspective is based upon scientific evidence, peer and clinical expertise. The medical literature was reviewed via PubMed search and appropriate articles were included in this review. This work was formulated from the collaboration of eight hepatologists/gastroenterologists with MASLD expertise and two physicians from the OMA.

*Results:* The authors who are experts in the field, determined sentinel questions often asked by clinicians regarding MASLD in children with obesity. They created a consensus and clinical guideline for clinicians on the screening, diagnosis, and treatment of MASLD associated with obesity in children.

*Conclusions:* Obesity and the comorbidity of MASLD is increasing in children, and this is a medical problem that needs to be addressed urgently. It is well known that children with metabolic associated chronic disease often continue to have these chronic diseases as adults, which leads to reduced life expectancy, quality of life, and increasing healthcare needs and financial burden. The authors of this paper recommend healthy weight reduction not only through lifestyle modification but through obesity pharmacotherapy and bariatric surgery. Therefore, this guidance reviews available therapies to achieve healthy weight reduction and reverse MASLD to prevent progressive liver fibrosis, and metabolic disease.

## 1. Introduction

The rates of obesity in children have tripled since the 1960's from 5 % to close to 19 % [1]. This increase is occurring in all age groups, but most significantly in the adolescent population, and estimated to be around 20.6 % [1]. This correlates to an increase in the weight related comorbidities in children including hypertension, prediabetes, hyperlipidemia, as well as MASLD. Detecting and treating MASLD as a comorbidity of obesity early can help prevent or alter the course of the metabolic disease such as seen in T2DM [2]. Managing MASLD remains challenging, even with expert recommendations and guidance. The cornerstone of MASLD treatment has been lifestyle interventions, focusing on a healthful diet and regular physical activity. However, despite these efforts, the prevalence of both MASLD and obesity continues to rise. This challenge is multifaceted and cannot be attributed solely to diet, motivation, or physical activity levels. A range of factors—including genetic, epigenetic, environmental, societal, financial, psychological, and endocrinological influences—contribute to the complexity of achieving sustained weight reduction and effectively managing MASLD.

Traditionally, the management of MASLD in children has focused on ruling out other causes of elevated liver enzymes and hepatic steatosis, alongside promoting lifestyle interventions. Sustained weight reduction is particularly difficult to achieve, necessitating other therapeutic options including anti-obesity medicine (AOM) and bariatric surgery. In a recent international survey Pediatric Gastroenterologists recognize the potential benefits of AOM but there is hesitancy due to the lack of pediatric-specific guidelines and uncertainties surrounding long-term side effects [3]. These gaps highlight the urgent need for enhanced education and resources, as over 90 % of surveyed providers have expressed interest in further training and guidance on managing obesity in MASLD [3]. Additionally, access to pediatric bariatric surgery programs is often limited. Therefore, this expert panel recognized these gaps and selected 9 common clinical questions that were answered in this review.

The authors of this paper advocate for a comprehensive approach to achieving healthy weight reduction in children, emphasizing not only the importance of diet and lifestyle changes but also considering the role of emerging AOM and bariatric surgery in select patients. While traditional strategies focused solely on lifestyle changes have shown limited success in curbing MASLD, this guidance explores a broader range of therapies aimed at promoting sustainable weight reduction, reversing MASLD, and preventing the progression to liver fibrosis. This OMA Expert Joint Perspective created with the input from hepatologists/gastroenterologists with MASLD expertise, examines SLD secondary to obesity in children, which is composed of MASLD and MASH, and the current updates in treatment.

## 2. Methods

In 2022, the OMA published a Clinical Practice Statement (CPS) entitled: "Nonalcoholic Fatty Liver Disease and Obesity" which was coauthored by OMA members [4]. Since that publication, there have been advances in the treatment of MASLD and obesity in children. This joint perspective is an update and follow-up that focuses on sentinel questions often asked by clinicians regarding MASLD and MASH, specifically in children with obesity. The scientific information is based upon published scientific citations, clinical perspectives of the OMA authors, and other experts in hepatology who have interest in MASLD. The medical literature was reviewed via PubMed search and appropriate articles were included in this review. The literature review includes articles published when the terminology of MASLD was referred to as NAFLD (Nonalcoholic fatty liver disease). This work was formulated from the collaboration of eight pediatric hepatologists/gastroenterologists, two physicians who are hepatologists and are part of OMA, and two physicians (one a pediatric endocrinologist, and one is a general pediatrician) from the OMA. Nine clinical questions were identified, and the experts reviewed the medical literature and gave their current recommendations based on evidence in the medical literature to assist in clinical practice of MASLD and obesity in children [Table 1].

## 3. Question 1: what are the new definitions and nomenclature of MASLD and MASH?

In 2024, Rinella et al. created a multi-society consensus statement about the definition and nomenclature of fatty liver disease [5]. The group removed the word fatty and alcoholic from the terminology to assure an affirmative and non-stigmatizing disease nomenclature. These updates were then submitted to a committee of five pediatric hepatologists who adapted the adult nomenclature and definition to the pediatric population. The committee created the overarching terminology of SLD that includes MASLD and MASH. SLD also covers alcohol-associated liver disease (ALD), metabolic ALD (MetALD), and other steatotic liver diseases like drug induced liver injury (DILI), monogenic inborn errors of metabolism, and cryptogenic SLD [5]. MetALD represent a group of patients with MASLD that consumes alcohol, approximately 140−350 g/wk for females and 210−420 g/wk for males [5].

MASLD has replaced the old terminology NAFLD (non-alcoholic fatty liver disease) and is defined as the presence of $\geq$ 5 % hepato-steatosis without hepatocellular injury (i.e., without ballooning of hepatocyte, inflammation, or fibrosis) [6]. MASH has replaced the old terminology of NASH (non-alcoholic steatohepatitis) and is defined as the presence of

≥ 5 % hepato-steatosis and hepatocyte "ballooning" (inflammation with hepatocyte injury and cell liver death) with or without fibrosis [5,6] [Table 2].

Once a patient has SLD identified by imaging or biopsy, the next consideration is to screen the patient for cardio metabolic disease, where patients need one of the five cardio metabolic criteria to be fulfill the diagnosis of MASLD [Table 3]. If there is one cardio metabolic criteria without other medically explainable sources of steatosis, the child will then be diagnosed with MASLD. It is important to recognize that MASLD can coexist with other liver diseases, creating an overlap. This underscores the necessity of thoroughly evaluating and ruling out other common liver conditions, even when MASLD criteria are met, to ensure an accurate diagnosis and appropriate management.

## 4. Question 2: what is the prevalence and prognosis of untreated MASLD in children?

### *4.1. What is the prevalence of MASLD/MASH and obesity in children?*

The prevalence of pediatric MASLD continues to rise in parallel to the rise of obesity in the United States and globally. While the estimated prevalence in the general population with pediatric MASLD is 5–11 %, this rate increases to 30–50% in children and adolescents with obesity [7–10]. In addition to obesity and waist circumference, other factors such as age, sex, race, and ethnicity play a significant role in the prevalence of MASLD [8–10]. Adolescents, males, Mexican Americans, and those with high waist circumference and BMI greater than 85th percentile are more likely to have MASLD [9]. Of the children with MASLD, various studies report the prevalence rate of steatohepatitis (MASH) to be between 23 and 84 % [7,11].

It is important to note that previous prevalence studies have relied on the clinical definition of NAFLD, using various diagnostic methods such as imaging, alanine aminotransferase (ALT) measurements, and limited histological data. With the transition to the updated MASLD nomenclature, there is a need for future research to generate prevalence data using these revised definitions and criteria. This will provide a more accurate representation of the disease burden and enhance our understanding of MASLD in diverse populations.

**Table 2**
Updated nomenclature and definition of fatty liver diseases that may occur in children.

| New Nomenclature | Previous Nomenclature | Definition |
|---|---|---|
| Metabolic dysfunction-associated steatotic liver disease (MASLD) | Nonalcoholic fatty liver disease (NAFLD) | Presence of ≥ 5 % hepato-steatosis without hepatocellular injury (i.e., without ballooning of hepatocyte or fibrosis) |
| Metabolic dysfunction-associated steatohepatitis (MASH) | Nonalcoholic steatohepatitis (NASH) | Presence of ≥ 5 % hepato-steatosis and hepatocyte "ballooning" (inflammation with hepatocyte injury and death) inflammation with or without fibrosis |

### *4.2. What are the pathophysiological and other differences between pediatric and adult MASLD/MASH?*

Although there are similarities between pediatric and adult MASLD, onset of disease at an earlier age can result in more severe disease progression. Histologically, lobular inflammation with hepatocyte ballooning in zone 3 is typical of adult MASLD (type 1 MASH); on the

**Table 1**
List of the 9 most common questions regarding MASLD secondary to obesity in children.

| Nine Common Clinical Questions Regarding MASLD as a Comorbidity of Obesity |
|---|
| 1. What are the new definitions and nomenclature of MASLD and MASH? |
| 2 What is the prevalence and prognosis of untreated MASLD?<br>a What is the prevalence of MASLD/MASH and obesity in children?<br>b What are the pathophysiological and other differences between pediatric and adult MASLD/MASH?<br>c. What are the long-term outcomes for children and adolescents with untreated MASLD/MASH? |
| 3 How does adiposity and weight affect MASLD?<br>a How does fat weight gain contribute to MASLD/MASH in children?<br>b. How much weight loss is needed to help resolve steatosis, MASH, and fibrosis in MASLD in children (Can decrease in BMI be sufficient in improvement of MASLD)? |
| 4 What other conditions besides obesity may contribute to the development of hepatic steatosis?<br>a Alcohol-related liver disease<br>b. Other liver diseases<br>c. Genetic factors and hereditary conditions<br>d. Nutritional deficiencies<br>e. Medications and drug-induced liver injury (DILI)<br>f. Gut Microbiota and intestinal permeability<br>g. Endocrine disorders |
| 5. What are spreferred diagnostic tests to evaluate for MASLD in children? |
| 6 How effective is nutrition and physical activity in reducing liver steatosis and/or reversing liver fibrosis in children?<br>a How does nutrition interventions work in managing MASLD/MASH in children and adolescents?<br>b. How effective is physical activity in reducing liver steatosis and/or reversing liver fibrosis in children? |
| 7 Are there medications for MASLD?<br>a What are the current medications that could be considered in the treatment of MASLD?<br>b. What are the implications of mediation discontinuation, contraindications, emerging long-term safety, and efficacy data?<br>c. How should side effects be monitored and managed?<br>d. Nutritional considerations with GLP-1RA use<br>e. Endoscopic and anesthesia considerations with GLP-1RA use |
| 8 Should bariatric surgery be considered in patients with MASLD/MASH and obesity?<br>a Review of adult data<br>b. Pediatric considerations<br>c. Effectiveness of bariatric surgery in reducing liver fat and reversing fibrosis in children<br>d. Nutritional management in bariatric surgery: pre and post operative considerations |
| 9. What is the cost-effectiveness and accessibility issues related to obesity pharmacotherapy and bariatric surgery for children and adolescents with obesity and MASLD/MASH? |

**Table 3**
Cardiometabolic criteria in children. Patients need 1 of 5 of these criteria to be at risk for MASLD. Adapted from Rinella et al. updates in nomenclature.

| Pediatric Cardiometabolic Criteria | | | |
|---|---|---|---|
| At least 1 out of 5: | | | |
| Weight | Glucose | Blood pressure | Lipids |
| BMI> 85th percentile for age/sex [BMI z score ≥ + 1] | Fasting serum glucose > 5.6 mmol/L [≥100 mg/dl] | Blood pressure age < 13 y, BP≥95th percentile | Plasma triglycerides <10y,≥1.15 mmol/L [≥100 mg/dL]; age≥10y,≥1.7 mmol/L [≥150 mg/dL] |
| WC > 95th percentile | Serum glucose≥11.1 mmol/L [≥200 mg/dl] | ≥ 130/80 mmHg (whichever is lower); age≥13 y, 130/85 mmHg | Plasma HDL-cholesterol≤1.0 mmol/L [≤40 mg/dL] |
| Ethnicity adjusted equivalent | 2-hr. post-load glucose levels≥7.8 mmol [140 mg/dl] | Specific antihypertensive drug treatment | Lipid lowering treatment |
| | HbA1c≥5.7 [39 mmol/L] | | |
| | Already diagnosed/ treated type 2 diabetes | | |
| | Treatment for type 2 diabetes | | |

other hand, portal inflammation and steatosis in zone 1 (Type 2 MASH) or zone 3 can be seen in children with this condition. If fibrosis is present, portal or periportal involvement occurs in pediatric MASLD as opposed to pericellular fibrosis in adults [12]. The reasons behind the distinct histological features observed in pediatric MASH remain unclear. It is uncertain whether these differences represent a progression from type 2 to type 1 or if they signify an entirely separate phenotype. Further research is needed to explore these possibilities and to better understand the underlying mechanisms and implications for disease progression.

Most of what is known about the pathophysiology of MASLD in children is derived from knowledge based on adult MASLD. The reason for this is because there are limited studies on the pathophysiology in children and animal models that fully recapitulate pediatric MASLD/MASH. The "multiple hit" hypothesis is the most favored explanation for the pathophysiology of both pediatric and adult-onset MASLD. Fig. 1 illustrates how hypercaloric diet (especially, high in carbohydrates), genetic susceptibility, dysbiosis, insulin resistance, and sedentary lifestyle lead to fat accumulation and development of hepatic steatohepatitis and fibrosis [13,14].

The role of genetic susceptibility continues to be explored in pediatric MASLD. The I148 M allele of PNPLA3, is associated with MASLD in both children and adults [12]. This mutation is linked to higher prevalence of MASLD in Hispanic population. Other genes that have been more studied in the adult population, TM6SF2 (E167K variant) and MBOAT7, need to be further explored in pediatric MASLD/MASH [12,13,15]. While the role of the gut microbiome is not fully understood in the development and progression of pediatric MASLD, it is worth mentioning that alterations in the gut microbiome can influence genes involved in lipogenesis within the liver [16]. In studies conducted in children with steatotic liver disease (defined by elevation in ALT and/or abnormal MRI hepatic fat fraction), increase in serum ethanol, greater Paraprevotella, and lower α-diversity were common findings [17]. The effects of estrogen and androgen levels in adults have been widely studied, but there are limited studies in children. In a cross-sectional study by Mueller et al., children ≤ 18 years of age with liver-biopsy proven steatotic liver disease were less likely to have severe portal inflammation in those with higher estrone, estradiol, or testosterone levels [18]. Moreover, males with higher testosterone level had a lower

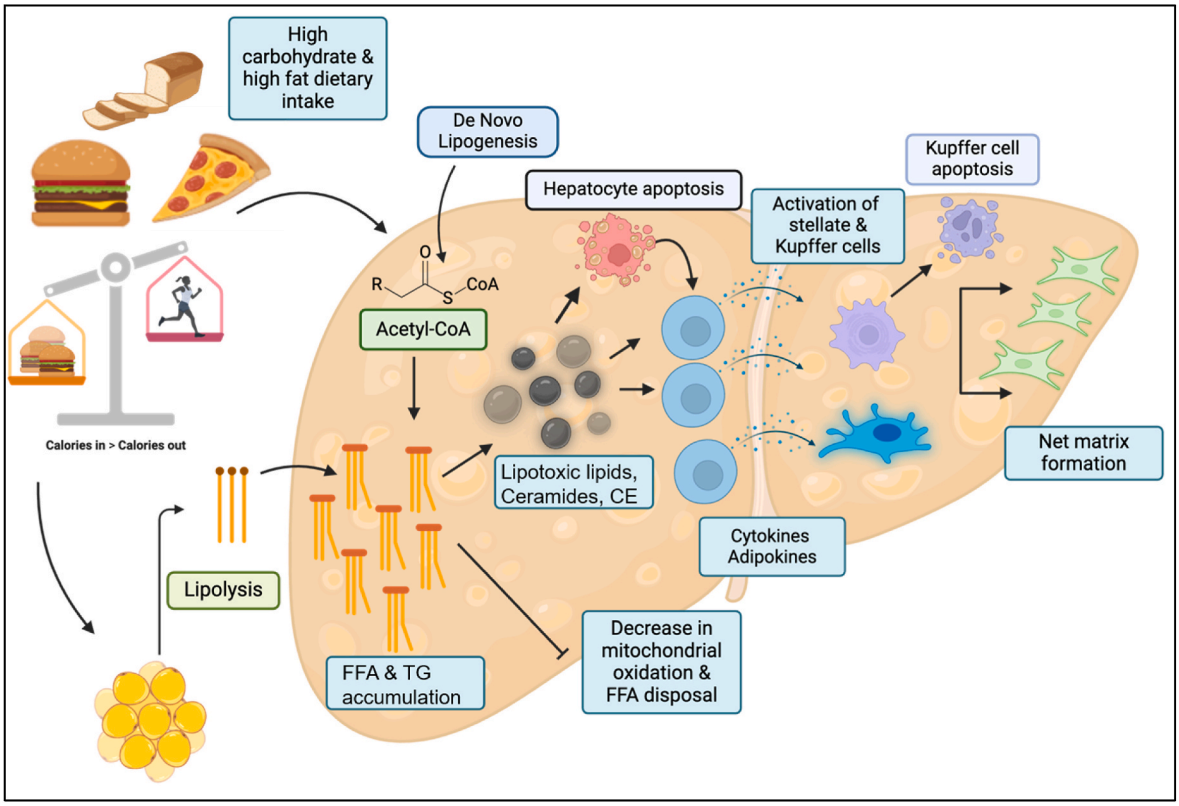


**Fig. 1.** Pathophysiology of MASLD showing high carbohydrates and high fat diet, genetic susceptibility, insulin resistance, and sedentary lifestyle lead to hepatic steatosis and development of steatohepatitis and fibrosis. Created in BioRender. Ramirez, C. (2025) https://BioRender.com/j87d221.

degree of fibrosis. This finding was not observed in females, and increased severity of steatosis was seen in females with higher testosterone [18]. The results of this study agree with the meta-analysis in the adult population [19].

Socioeconomic factors such as poverty, income, education, public assistance, housing and insurance status, measured as Community Deprivation Index (CDI), has been shown to result in earlier clinical presentation of children with MASLD. However, the severity of MASLD is not affected by CDI [20]. Food insecurity is also associated with earlier presentation of MASLD in children and occurs in higher prevalence [21].

### *4.3. What are the long-term outcomes for children and adolescents with untreated MASLD/MASH?*

The lack of long-term natural history studies on pediatric MASLD has created a significant gap in understanding the disease's progression over time. This absence of data makes it challenging to identify predictors of severe disease, underscoring the urgent need for comprehensive longitudinal research in this population. Available evidence suggests that untreated metabolic dysfunction in children can lead to worsening liver injury, inflammation, and fibrosis, paralleling the disease trajectory observed in adults [Fig. 2]. Without appropriate intervention, there is a considerable risk of progression to MASH with fibrosis, which may further advance to cirrhosis during late adolescence or adulthood. When the hepatic steatosis progresses to MASH, patients often remain asymptomatic, but changes in blood work can be seen, such as elevation in ALT, gamma-glutamyl transferase (GGT), and findings suggestive of fibrosis on ultrasound (US) based shear wave or vibration controlled-elastography (VCTE) or MR-elastography (MRE). One-third of children with MASLD who received placebo and standard of care lifestyle advice in 2 double-blind, randomized clinical trials within the MASH showed histologic features of progression within 2 years, in association with increasing body weight and serum levels of aminotransferases and loss of glucose homeostasis [22].

In a randomized controlled multicenter study, at the time of enrollment, in the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK)-sponsored NASH Clinical Research Network, ~30 % of the cohort had definite NASH and ~70 % had some degree of fibrosis [22]. According to a study by Benzinover et al., using the United Network of Organ Sharing (UNOS) database, of all liver transplants performed in adolescents and young adults between 2015 and 2020, the indication in 7 % of the transplants was MASH/Cryptogenic Cirrhosis [23]. MASLD can still reverse the damage before significant fibrosis forms, and therefore treatment should be encouraged early in the course of the disease. In a Swedish cohort study spanning 1966–2017, 718 pediatric and young adult patients with biopsy-confirmed NAFLD faced elevated risks of overall, cancer-, liver-, and cardio metabolic-specific mortality compared to matched controls [24].

## 5. Question 3: how does adiposity and the patient's weight affect MASLD?

### *5.1. How does weight gain contribute to MASLD/MASH in children?*

It is well established that having overweight or obesity contribute to a higher risk of MASLD/MASH in the pediatric population [8]. In particular, visceral adipose tissue increases the risk of MASLD/MASH in children and adolescents [25–27]. White adipose tissue uptakes free fatty acids from circulating lipoprotein complexes and stores energy in the form of triglycerides. At times of energy demand, triglycerides can be hydrolyzed by hormone sensitive lipase resulting in a release of free fatty acids into the bloodstream. This homeostasis is hormonally regulated [28]. In fed states, higher insulin serum levels promote lipogenesis in adipose tissue, whereas catecholamines induce lipolysis during fasting or exercise. However, with worsening obesity, adipose tissue becomes insulin resistant, which inhibits lipolysis and formation of free fatty acids, which themselves travel to the liver where they are stored as triglycerides and worsen MASLD [29,30]. Other hormones, released from adipose tissue and hence called adipokines, play a role in development of obesity and MASLD. The two best studied adipokines are leptin and adiponectin [28].

Leptin suppresses appetite and promotes energy expenditure, and in a select group of leptin-deficient patients with severe lipodystrophy, therapy with leptin can improve hepatic steatosis [31]. However, leptin serum levels are chronically increased in individuals with obesity, resulting in leptin resistance similar to insulin resistance also observed in obesity, which can result in a loss of its antisteatotic effects [32]. Leptin is proinflammatory and profibrotic, as it induces hepatic Kupffer cells to release inflammatory cytokines including tumor necrosis factor (TNF)-alpha as well as profibrogenic cytokines such as transforming growth factor (TGF)-beta, which induce a profibrogenic cascade in hepatic stellate cells [33]. Leptin can thereby contribute to MASLD and

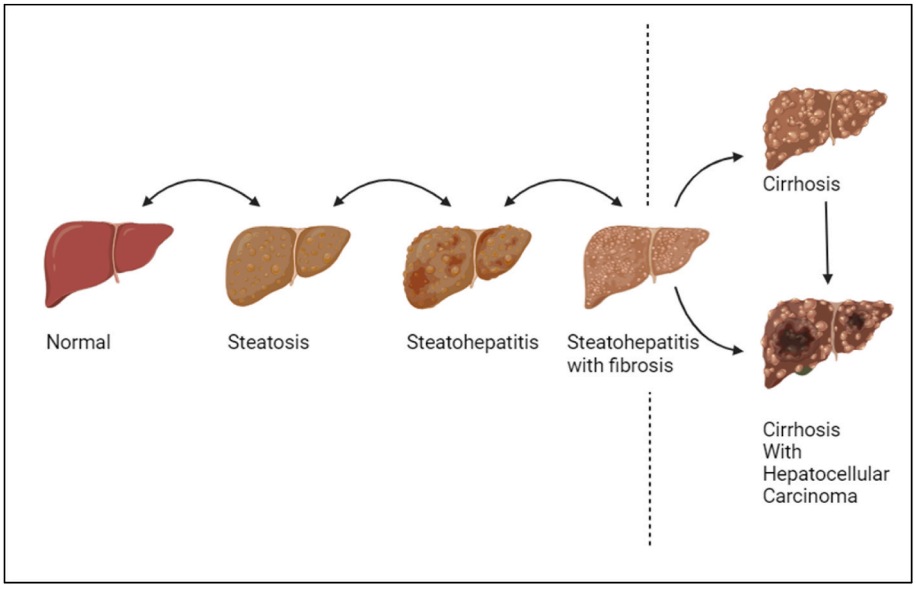


**Fig. 2.** Progression of hepatic steatosis to fibrosis, cirrhosis, and then hepatocellular carcinoma, if untreated. Created in BioRender. Ramirez, C. (2025) https://BioRender.com/p72s900.

MASH.

Adiponectin on the other hand increases insulin sensitivity, decreases oxidative stress and inflammation in the liver, and protects against fibrosis. However, since its serum levels are reduced in children with obesity, it thereby facilitates the development and worsening of MASLD. Children with obesity and hepatic steatosis were found to have even lower serum adiponectin levels than children with obesity alone [34–36]. Further, the adipokine omentin-1 increases insulin sensitivity and decreases hepatic inflammation; its low levels in obesity and in particular in MASH might therefore contribute to the pathogenesis of MASLD [37]. Other adipokines including chemerin, visfatin, resistin, and retinol binding protein are increased in pediatric MASLD and might contribute to MASLD via similar pathophysiological mechanisms [36].

### *5.2. How much weight reduction is needed to help resolve steatosis, MASH, and fibrosis in MASLD in children (Can a decrease in BMI be sufficient for an improvement of MASLD)?*

Adult studies indicate that 65 % of patients who achieve 5–6.99 % weight reduction exhibit steatosis improvement on biopsy, and some completely resolve any steatosis [38,39]. An adult landmark study defined MASH resolution as absence of definite steatohepatitis, ballooning, and fibrosis on biopsy, and found that 26 %, 64 %, and 90 % of patients demonstrated MASH resolution if they lost 5–6.99 %, 7–9.99 %, or ≥10 % of weight, respectively [39]. Further, ≥10 % of weight reduction ameliorated steatosis and lobular inflammation in all patients and ballooning in 90 % of patients [39]. In addition, ≥10 % of weight reduction resolved any steatosis on biopsy in 97 % of adult patients [38]. Fibrosis also improves with weight reduction, with 7–9.99 % or ≥10 % of weight reduction after 52 weeks of lifestyle intervention resulting in 50 % or 81 % of fibrosis regression, respectively, without any fibrosis worsening in adult patients with MASLD and baseline fibrosis on biopsy [39].

Similarly, pediatric studies report that a decrease in BMI and waist circumference is associated with resolution of MASH [22]. Unfortunately, there is a paucity of biopsy-based pediatric MASLD studies, impeding an exact prescription of how much weight reduction should be achieved for histologic improvement in pediatric MASLD. Weight reduction due to intensive lifestyle modifications improves controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) per transient elastography (TE) in pediatric MASLD [40]. Median weight reduction of 25.6 % over 12 months resolved steatosis in 78.2 % of pediatric patients (per US/CAP) and resolved significant fibrosis in 85.7 % (per TE) [40]. Although this study was not biopsy based and relied on US measures, it still indicates that significant weight reduction can result in significant improvement in MASLD in the pediatric population similar to adults. However, even smaller changes in BMI and BMI percentiles can result in improved MASLD measures. In a study investigating the natural progression of pediatric MASLD, 122 children from placebo-treated groups from RCTs over 52 or 96 weeks were evaluated [22]. Their mean BMI at the start was 32.3 kg/m$^2$ and the mean BMI percentile for sex and age was the 98.1st percentile. Despite an increase in BMI by 1.35 kg/m$^2$ and only a small BMI percentile decrease by 0.4 percentiles over the study period, noticeable changes in MASLD parameters, such as the NAFLD Activity Score (NAS), occurred [22]. The NAS is a histological scoring system for MASH, ranging from 0 to 8, with scores 5 and greater correlating highly with MASH [41]. The NAS decreased by 0.7 points (NAS 4.6 at start), the proton density fat fraction (PDFF) by 2.6 % (21.5 % at start), and the ALT levels by 19.9 U/L (112.4 U/L at start) [22]. Of note, there was significantly higher resolution of MASH (40 % vs 17 %), significantly less frequent progression to fibrosis or definite MASH (25 % vs 49 %), and more beneficial change in NAS (−0.9 vs 1.7, $p = 0.16$) in 8–12-year-olds vs 13–17-year-olds with MASLD despite a similar BMI increase during the treatment period (1.32 kg/m$^2$ vs 1.38 kg/m$^2$) [22]. Although the most recent pediatric obesity guidelines by the American Academy of Pediatrics (AAP) do not recommend specific weekly or monthly weight reduction goals, the AAP Institute for Healthy Childhood Weight recommends slow, consistent weight reduction, so children with obesity aged 2–5 years should not lose more than 1 lb per month, whereas older children and adolescents with obesity should not lose more than 2 lbs per week on average [1,42]. Larger randomized control trials (RCTs) in pediatric MASLD are required to obtain better evidence and provide higher quality recommendations.

## 6. Question 4: what other conditions besides obesity may contribute to the development of hepatic steatosis?

While obesity and metabolic syndrome are primary risk factors for steatosis, other factors—including alcohol consumption, genetic predisposition, nutritional deficiencies, certain medications, gut microbiota alterations, and endocrine disorders—also play significant roles in disease development. Identifying these risk factors is essential for comprehensive management of patients with steatosis [1,3]. [Table 4]

### *6.1. Alcohol-related liver disease (ALD)*

Chronic alcohol consumption is a well-established cause of hepatic steatosis that acts independently of obesity. Alcohol intake promotes fatty acid synthesis, decreases fatty acid oxidation, and impairs the secretion of very low-density lipoprotein (VLDL), resulting in fat accumulation within the liver. Additionally, toxic metabolites such as acetaldehyde and reactive oxygen species (ROS), produced during alcohol metabolism, induce oxidative stress and mitochondrial damage, further exacerbating liver injury [1,43]. The American Association for the Study of Liver Diseases (AASLD) defines ALD as hepatic steatosis in individuals with a daily alcohol intake exceeding 50 g for women or 60 g for men [43]. Alcohol consumption, particularly when combined with having obesity, significantly increases the risk of liver injury, cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality [3]. Patients with hepatic steatosis who consume alcohol and also have cardiometabolic risk factors (CMRFs) are classified as having MetALD. MetALD is not consistently assessed for in most pediatric MASLD clinics and maybe underappreciated. Thus, standardized screening measures in our pediatric patients so that lifestyle modifications, including reduced alcohol intake and improved management of metabolic risk factors, may be implemented earlier is necessary to optimize liver health [2,3].

### *6.2. Other liver diseases*

Chronic Hepatitis C Virus (HCV) infection particularly genotype 3, is associated with hepatic steatosis, and successful antiviral therapy has been shown to improve steatosis in affected individuals [4]. Autoimmune hepatitis, although rare (prevalence: 3 per 100,000 cases), can also present with hepatic steatosis and should be considered in the differential diagnosis for pediatric patients [5]. Low titers of serum autoantibodies, such as antinuclear antibodies (ANA) and anti-smooth muscle antibodies (SMA), are commonly observed in MASLD (34 %) often as incidental findings without clinical significance [6]. A NASH Clinical research network study of 864 MASLD patients found significant autoantibody elevations (ANA >1:160, SMA >1:40) in 21 %, though these were not linked to advanced disease or atypical histology [43,78]. Wilson's disease, an autosomal recessive disorder caused by mutations in the ATP7B gene leading to copper accumulation, and alpha-1 antitrypsin (A1AT) deficiency, linked to mutations in the SERPINA1 gene, are significant contributors to hepatic steatosis [3,9]. The c.1096G > A (p.E366K = p.E342K, rs28929474, MAF = 0.0184) variant, which encodes the PiZ protein, is found in 2–4% of Europeans but is present in up to 20 % of patients with MASLD. Heterozygosity for the PiZ and PiS variants has been linked to an increased risk of advanced liver disease. Strnad et al. revealed that individuals carrying the A1AT PiZ variant in a heterozygous state face a more than sevenfold higher risk of developing

**Table 4**
Secondary causes of hepatic steatosis and diagnostic criteria.

| Cause | Subcategory | Diagnostic Criteria |
|---|---|---|
| **Alcohol Use** | | Assessment of alcohol consumption history |
| **Other Liver Diseases** | | |
| | Hepatitis B, Hepatitis C, EBV, CMV | Viral hepatitis serologies (IgG/IgM) |
| | Wilson's Disease | Low ceruloplasmin, elevated 24-h urinary copper excretion, high hepatic copper content, ATP7B mutation |
| | Autoimmune Hepatitis | Serum IgG, ANA, anti-smooth muscle antibody, anti-liver kidney microsomal antibody, liver biopsy |
| | Alpha-1 Antitrypsin Deficiency | Serum A1AT levels, Pi*Z or PiS* phenotype, SERPINA1 mutation |
| | Hereditary Hemochromatosis | Hepatic iron overload, HFE gene mutation |
| **Medications and Environmental Toxins** | | |
| | Amiodarone, Tamoxifen, Corticosteroids, Methotrexate, Valproate, HAART | Medication history |
| | Metals: Arsenic, Cadmium, Mercury, Lead | Environmental exposure history |
| | Chloroalkenes: Vinyl Chloride, Trichloroethylene, Perchloroethylene | Environmental exposure history |
| | Herbicides, Pesticides | Environmental exposure history |
| **Nutritional Causes** | | |
| | Total Parenteral Nutrition (TPN) | History of TPN use, short bowel syndrome, surgical history |
| | Malnutrition/Kwashiorkor | Clinical assessment |
| | Acute Weight Loss (e.g., bariatric surgery, prolonged fasting) | Surgical and dietary history |
| **Intestinal/Gastrointestinal Causes** | | |
| | Intestinal Failure | Clinical history of malabsorption or TPN |
| | Small Intestinal Bacterial Overgrowth (SIBO) | Glucose breath test |
| | Celiac Disease | TTG IgA/IgG, endomysial antibody, serum IgA, duodenal biopsy |
| **Endocrine Causes** | | |
| | Panhypopituitarism | Assessment of cortisol and growth hormone (IGF-1) levels |
| | Hypothyroidism | TSH and free T4 testing |
| | Polycystic Ovary Syndrome (PCOS) | Clinical assessment and testosterone levels |
| | Growth Hormone Deficiency | IGF-1 testing |
| **Liver Disease of Pregnancy** | | |
| | Acute Fatty Liver of Pregnancy | Clinical evaluation and laboratory testing |
| | HELLP Syndrome (Hemolysis, Elevated Liver Enzymes, Low Platelets) | Clinical and laboratory criteria |

A1AT: Alpha-1 Antitrypsin, ANA: Antinuclear Antibody, CMV: Cytomegalovirus, EBV: Epstein-Barr Virus, HAART: Highly Active Antiretroviral Therapy, IgG/IgM: Immunoglobulin G/M, TPN: Total Parenteral Nutrition, TSH: Thyroid Stimulating Hormone, TTG: Tissue Transglutaminase.

cirrhosis in MASLD. Additionally, Z phenotypes are disproportionately represented among MASLD patients undergoing liver transplantation in Ireland, underscoring their clinical significance. However, further pediatric studies are needed to clarify these associations [10–12].

### 6.3. Genetic factors and hereditary conditions

Hepatic steatosis can develop in individuals with a body mass index (BMI) $< 25$ kg/m$^2$, referred to as lean steatotic liver disease. However, its relationship with metabolic syndrome and whether it can be classified as lean MASLD remains under investigation. Emerging studies suggest that lean individuals with steatosis may exhibit unique genetic, metabolic, and environmental factors contributing to disease progression, but further research is needed to clarify these associations and refine diagnostic criteria [16]. PNPLA3 p.I148 M variant is strongly associated with increased susceptibility to the full spectrum of hepatic damage in MASLD as earlier described irrespective of metabolic dysfunction. Similarly, the TM6SF2 E167K variant is linked to a higher risk of progression from simple steatosis to more severe stages such as steatohepatitis and cirrhosis. [14]Variants in other genes, including APOC3, GCKR, and MBOAT7, disrupt lipid metabolism, leading to hepatic fat accumulation even in individuals without obesity.[15.] Inborn errors of lipid metabolism, including congenital lipodystrophy, abetalipoproteinemia, familial hypobetalipoproteinemia, and lysosomal acid lipase deficiency, can also present as hepatic steatosis. Management in these cases focuses on dietary modifications [17]. Table 5 outlines the genetic mutations and key clinical features associated with selected metabolic and genetic disorders.

### 6.4. Nutritional deficiencies

Both over-nutrition and undernutrition contribute significantly to hepatic steatosis. Vitamins, minerals, and essential nutrients are integral to the development and progression of MASLD. Imbalances or deficiencies in these nutrients can adversely impact liver function and worsen disease outcomes. Vitamin D deficiency is linked to increased MASLD risk, as it exacerbates insulin resistance and inflammation, promoting hepatic steatosis [18]. Vitamin E, a powerful antioxidant, has been shown in some studies to reduces oxidative stress, improve liver function and decrease steatosis in MASLD patients [19]. However, evidence remains mixed, and further research is necessary to confirm its long-term efficacy in this population. Similarly, vitamin C protects liver cells from oxidative damage, with preliminary evidence suggesting its supplementation may improve glucose metabolism and overall liver health. Further studies are warranted to validate these findings. Deficiencies in B vitamins, such as B3 (niacin) and B12 (cobalamin), impair energy metabolism and exacerbate liver fat accumulation, increasing the risk of disease progression. Zinc supports immune function and antioxidant defenses, and its deficiency, common in liver diseases, is associated with increased fibrosis and liver damage. Magnesium plays a crucial role in glucose metabolism and insulin sensitivity, with low levels linked to a higher risk of MASLD. Selenium, another essential antioxidant, protects against cellular damage, with supplementation potentially slowing MASLD progression [18].

Essential fatty acids, particularly omega-3 fatty acids, support lipid metabolism and reduce hepatic fat storage through their anti-inflammatory effects and ability to promote fatty acid oxidation in the liver. Additionally, choline deficiency, often observed in restrictive dietary plans, disrupts VLDL production and triglyceride export, contributing to fat accumulation in the liver [1].

Addressing these deficiencies through appropriate dietary intake or supplementation may offer therapeutic benefits in MASLD management. However, further research is needed to establish clear guidelines for their role in disease prevention and treatment.

### 6.5. Medications and drug-induced liver injury (DILI)

Certain medications have been linked to hepatic steatosis as side effects. Common examples include corticosteroids, tamoxifen, amiodarone, and methotrexate, which may disrupt lipid metabolism or increase oxidative stress [5]. Additionally, antipsychotic medications, such as olanzapine and clozapine, are increasingly recognized as contributors to hepatic steatosis, particularly in children and adolescents. These medications are commonly used in the management of psychiatric conditions and are associated with significant metabolic side effects, including weight gain, insulin resistance, and dyslipidemia, which can exacerbate the risk of MASLD. Environmental toxins, such as metals, herbicides, and pesticides, may also contribute. The risk of drug-induced

**Table 5**
Genetic mutations and key clinical features of selected metabolic and genetic disorders.

| Category | Genetic Mutation | Key Clinical Features |
|---|---|---|
| Disorders of Lipid Metabolism | | |
| Abetalipoproteinemia | MTTP (Microsomal triglyceride transfer protein) | Infancy: growth issues, intellectual disability, low LDL and TG, fat malabsorption, failure to thrive, steatorrhea, spinocerebellar ataxia |
| Hypobetalipoproteinemia | APOB-100 | Similar features as abetalipoproteinemia |
| Familial Combined Hyperlipidemia | | Dyslipidemia with elevated LDL and TG levels |
| **Glycogen Storage Diseases** | PHKA2, PHKB | Infancy: growth retardation, lactic acidosis, developmental delay |
| **Syndromic Disorders** | | |
| Weber–Christian Syndrome | Unknown | Childhood: fever, arthralgias, myalgias, skin lesions, painful subcutaneous nodules |
| Prader-Willi Syndrome | Unknown | Developmental and behavioral disorders, often associated with obesity |
| Turner Syndrome | Unknown | Short stature, developmental delays |
| **Congenital Lipodystrophy** | AGPAT2, BSCL2 | Infancy: severe fat loss, voracious appetite, accelerated growth, advanced bone age |
| **Lysosomal Acid Lipase Deficiency** | LIPA gene, enzyme assay | Elevated LDL-C, low HDL-C, high TG, xanthelasma, hypersplenism, early fibrosis, portal hypertension |
| **Urea Cycle Defects** | OTC, CPS1, ASS1, ARG1 | Hyperammonemia, neonatal acute liver failure, neurological symptoms |
| **Carbohydrate Metabolism Disorders** | | |
| Glycogen Storage Disorders (Types I, III, IV, VI, IX, XI) | Multiple subtypes (e.g., Glucose-6-phosphatase deficiency and other enzymes involved in the glycogenesis pathway) | Hepatomegaly, dyslipidemia, hypoglycemia, lactic acidosis, failure to thrive, cardiac or muscular involvement |
| Hereditary Fructose Intolerance | ALDOB | Hepatomegaly, aversion to sweets, Fanconi syndrome |
| Galactosemia | GALT | Hypoglycemia, acute liver failure, gram-negative sepsis |
| **Amino Acid Metabolism Disorders** | | |
| Citrullinemia Type II | SLC25A13 | Neonatal intrahepatic cholestasis; adults: hyperammonemia |
| Tyrosinemia | FAH | Neonatal liver failure, cirrhosis, hepatocellular carcinoma (HCC), Fanconi anemia |
| **Lipid Storage and Transport Disorders** | | |
| Niemann-Pick Disease Type C | NPC1, NPC2 | Multisystem involvement, liver disease, neurological symptoms |
| **Congenital Disorders of Glycosylation** | Various genes | Variable liver disease with multisystem involvement |
| **Inborn Errors of Bile Acid Synthesis** | HSD3B7, AKR1D1, CYP27A1 | Normal GGT cholestasis in infants; older patients: neurological symptoms |

A1AT: Alpha-1 Antitrypsin, GGT: Gamma-Glutamyl Transferase, HCC: Hepatocellular Carcinoma, HDL-C: High-Density Lipoprotein Cholesterol, LDL: Low-Density Lipoprotein, LDL-C: Low-Density Lipoprotein Cholesterol, MTTP: Microsomal Triglyceride Transfer Protein, TG: Triglycerides.

hepatic steatosis is often dose-dependent and may increase in individuals with pre-existing metabolic conditions [20]. Table 6 highlights the drugs and toxins implicated in hepatic steatosis, along with their mechanisms and associated liver injury types.

### 6.6. Gut microbiota and intestinal permeability

The gut-liver axis plays a significant role in the development of hepatic steatosis. Dysbiosis, or alterations in the gut microbiota, can increase intestinal permeability, allowing bacterial endotoxins to enter the bloodstream and trigger an inflammatory response in the liver, promoting fat accumulation [16]. Conditions such as celiac disease, intestinal failure, and prolonged parenteral nutrition are associated with an increased risk of hepatic steatosis due to factors like enhanced intestinal permeability and low choline levels. Fat accumulation in the liver may also occur following bariatric surgery, although this is often reversible with weight reduction [9].

### 6.7. Endocrine disorders

Endocrine disorders, including hypothyroidism, Cushing's syndrome, panhypopituitarism, and polycystic ovary syndrome (PCOS), are associated with hepatic steatosis. Hypothyroidism affects lipid metabolism, leading to fat accumulation in the liver, while Cushing's

**Table 6**
Mechanisms and types of liver injury associated with drugs and toxicants.

| Drug/Toxicant | Mechanism | Type of Liver Injury |
|---|---|---|
| Corticosteroids | Increases insulin resistance, mobilizes fatty acids, promotes triglyceride accumulation in hepatocytes | Macrovesicular steatosis |
| Tamoxifen | Alters estrogen receptor signaling, interferes with lipid metabolism | Steatosis, possible steatohepatitis |
| Amiodarone | Causes mitochondrial toxicity, leading to phospholipid accumulation and oxidative stress | Steatohepatitis, fibrosis |
| Methotrexate | Induces oxidative stress, disrupts mitochondrial function, affects lipid metabolism | Steatosis, potential progression to fibrosis |
| Valproic Acid | Impairs mitochondrial beta-oxidation, leading to fat accumulation | Microvesicular steatosis |
| Tetracycline | Mitochondrial dysfunction, inhibits fatty acid oxidation | Microvesicular steatosis |
| Antiretrovirals (e.g., Zidovudine) | Causes mitochondrial toxicity, interferes with DNA polymerase gamma | Steatosis due to mitochondrial dysfunction |
| NSAIDs | Induces oxidative stress, may cause mitochondrial injury | Steatosis, variable severity |
| Estrogen/Hormonal Agents | Alters lipid metabolism, promotes fat deposition in hepatocytes | Steatosis, potential progression to steatohepatitis |
| Acetaminophen | Causes oxidative stress and hepatocyte injury at high doses | Steatohepatitis, risk of acute liver failure |
| Heavy Metals (e.g., Lead, Cadmium) | Increases ROS, inhibits beta-oxidation, disrupts autophagy, induces mitochondrial dysfunction | Increases hepatic lipid accumulation, inflammation |
| Pesticides (e.g., Dieldrin, Fipronil) | Alters glucose/lipid metabolism, increases oxidative stress, disrupts gut flora | Hepatic lipid overload, inflammation |
| Air Pollutants (e.g., Diesel exhaust particles) | Increases hepatic lipid overload, serum triglycerides, and inflammation | Hepatic inflammation, glucose metabolism alteration |
| Chemical Toxicants (e.g., Bisphenol A) | Disrupts lipid homeostasis, promotes oxidative stress, causes microbiota dysbiosis | Hepatic triglyceride accumulation, lipid dysregulation |

syndrome promotes insulin resistance and increases lipid mobilization. Growth hormone deficiencies associated with panhypopituitarism, along with insulin resistance and androgen excess in PCOS, further contribute to the development of fatty liver disease [17]. A randomized, double-blind multicenter trial evaluated tesamorelin, a synthetic growth hormone-releasing hormone, in HIV-infected individuals with MASLD. Over 12 months, participants received daily 2 mg subcutaneous injections. Tesamorelin significantly reduced hepatic fat fraction, as measured by magnetic resonance spectroscopy, and prevented liver fibrosis progression compared to placebo [21].

## 7. Question 5: what are the preferred diagnostic tests to evaluate for MASLD in children?

The diagnostic approach for pediatric MASLD involves a multifaceted strategy, combining clinical evaluation, imaging studies, and laboratory assessments [Table 7]. MASLD often progresses silently, with many children asymptomatic and the condition discovered incidentally during routine exams. When symptoms are present, they tend to be vague, such as fatigue and abdominal discomfort. Hepatomegaly may not always be detectable on physical examination, making the identification of metabolic risk factors, such as obesity and insulin resistance, crucial. While routine blood tests, particularly liver enzyme tests, can serve as initial indicators, normal levels do not exclude MASLD; advanced fibrosis can occur even with normal ALT levels [44].

Imaging techniques like US can detect hepatic steatosis but are often used incidentally when conducted for other reasons. However, US have limitations in assessing the presence of MASH or fibrosis, and the long-term natural history of simple steatosis in children remains unclear [45]. Advanced diagnostic modalities, including VCTE (TE), MRI proton density fat fraction (MRI-PDFF), MRE and, and liver biopsy are also essential for a comprehensive understanding of the disease spectrum and guide tailored management strategies and are done in specialized centers [46–49]. In the future if MR technology becomes less costly and widely available, it may be the less invasive and preferred modality to evaluate for MASLD and MASH due to its superior imaging of fibrosis and steatosis compared to other imaging modalities. Liver biopsy remains the gold standard for diagnosing MASLD, grading hepatic steatosis, and staging disease severity, but its invasiveness and potential complications, like pain and internal bleeding, limit its use. Despite these challenges, liver biopsy is recommended for patients at high risk of MASH and advanced fibrosis, especially those with persistent elevation of the ALT with lifestyle intervention, splenomegaly, high GGT or an AST/ALT ratio >1 [49].

The North American Society for Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) guidelines recommend MASLD screening for children aged 9 to 11 who have obesity or are overweight with additional risk factors [49]. High-risk patients, such as those with severe obesity or pan hypopituitarism, should be screened earlier. ALT is the preferred screening test, with sex-specific upper limits (22 U/L for females, 26 U/L for males). An ALT level twice the upper limit (≥50 for boys, ≥ 44 for girls) in children aged 10 or older with overweight or obesity has a sensitivity of 57 % and a specificity of 71 % [50]. ALT is 80–90 % sensitive 70–80 % specific in identifying Pediatric MASLD with AUROC of 0.80 in response to treatment [51,52].Routine US is discouraged as a screening test due to its inadequate sensitivity and specificity, especially when liver fat is less than 30 % or in cases where BMI exceeds 40 kg/m$^2$ [53]. Despite its limitations, US is often performed before specialist referral and can help diagnose MASLD in children with normal ALT levels. The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommends using US alongside ALT for diagnosing MASLD [49]. Historically, the AASLD refrained from issuing formal recommendations on screening in children with obesity for MASLD due to limited evidence on long-term benefits [6,54]. However, the most recent AASLD pediatric MASLD guidelines, presented at the 2024 Liver Meeting and awaiting publication, recommend ALT as a screening method for children 10 yo of age or earlier in the presence of cardiometabolic risk factors, family history or severe obesity with consideration of ultrasound as initial imaging to support the diagnosis of MASLD.

Due to the high prevalence of MASLD, many children are diagnosed by primary care providers (PCPs), who play a crucial role in identifying risk factors, initiating evaluations (rule out other conditions), and performing preliminary assessments [Table 8]. PCPs also oversee ongoing monitoring and lifestyle interventions. Tables 3 and 4 shows suggested initial work up and some common MASLD mimics in children with clinical, lab peculiarities.

For complex cases, PCPs can refer patients to specialists, such as hepatologists, who conduct more detailed assessments and provide specialized care to evaluate for other causes of steatosis and elevated liver enzymes as previously reviewed. Unlike in adults, pediatric MASLD lacks well-established clinical pathways. In adults, tools like Fibrosis-4 (Fib4) and Fibro-Scan are commonly used to assess liver fibrosis and disease progression, but similar protocols for children are not yet validated [6]. This gap in established protocols and the lack of awareness among PCPs contribute to low screening rates. A recent study using the Canadian Primary Care Sentinel Surveillance Network found that only 8.7 % of children with obesity were screened for MASLD in the past year, and 23.6 % had ever been screened [55]. This highlights the need for improved screening, diagnostic strategies, and defined pathways for pediatric MASLD.

MASLD presents a significant healthcare and economic burden, with costs for adult patients nearly twice as high due to frequent testing, ongoing monitoring, and hospitalizations [56,57]. Addressing these challenges in pediatric populations requires developing and evaluating cost-effective pathways and strategies to mitigate the economic impact and improve patient outcomes. The collaborative approach between PCPs and Pediatric gastroenterologist and hepatologists ensures comprehensive care, with PCPs managing initial diagnosis and routine care, while specialist handle more complex cases and advanced disease management. With the rising prevalence of MASLD and new treatments on the horizon, establishing clear clinical pathways for pediatric management is essential to ensure accurate diagnosis, effective care, and readiness for emerging therapies, ultimately improving patient outcomes. Fig. 4 outlines a clinical algorithm for the screening, evaluation, and management of pediatric MASLD, emphasizing the role of ALT thresholds, imaging modalities, and lifestyle modifications, as well as criteria for GI referral and consideration of liver biopsy.

**Table 7**
Suggested initial workup for patients with MASLD.

| Condition | Workup |
|---|---|
| Viral Hepatitis | HBsAg, Anti HCV |
| Metabolic liver disease | A1AT, Ceruloplasmin levels |
| Autoimmune Liver disease<br>Celiac disease | IgG/ANA/ALKM/ASMA, TTG/IgA |
| Metabolic dysfunction | Fasting Insulin, glucose, lipid profile, HbA1c, TSH |
| Liver panel | Liver panel (CBC, INR, Albumin, Bilirubin/AST/ALT/GGT/ALP) |
| Renal panel | Creatinine |

A1AT: Alpha-1 Antitrypsin, ALKM: Anti-Liver Kidney Microsomal Antibody, ALP: Alkaline Phosphatase, ALT: Alanine Aminotransferase, ANA: Antinuclear Antibody, AST: Aspartate Aminotransferase, CBC: Complete Blood Count, GGT: Gamma-Glutamyl Transferase, HbA1c: Hemoglobin A1c, HBsAg: Hepatitis B Surface Antigen, HCV: Hepatitis C Virus, IgA: Immunoglobulin A, IgG: Immunoglobulin G, INR: International Normalized Ratio, TSH: Thyroid-Stimulating Hormone, TTG: Tissue Transglutaminase.

**Table 8**
Differential diagnosis of MASLD: Clinical, laboratory, and further workup considerations for common mimics.

| Condition mimics | Clinical Peculiarities | Labs Peculiarities | Further work up |
|---|---|---|---|
| Wilson Disease | • Over 5yr of age<br>• Neuropsychiatric symptoms<br>• Family History | • Low ALP<br>• Hemolytic Anemia- Non immune | • Ceruloplasmin level<br>• 24hr Urinary copper<br>• KF ring |
| LAL deficiency | • Xanthomas, splenomegaly<br>• Features of advanced liver disease<br>• Hepatosplenomegaly | • Elevated LDL-C, low HDL-C, High Triglyceride | • Enzymes assay<br>• Liver biopsy- Micro vesicular steatosis |
| Celiac disease | • Family history<br>• Iron deficiency<br>• GI symptoms | • Anemia<br>• Vitamin Deficiencies | • TTG (IgA)<br>• IgA<br>• Duodenal Biopsy |
| Hepatitis C | • High risk behavior | | • Anti HCV antibody<br>• HCV RNA |
| Autoimmune hepatitis | • Female<br>• Associated autoimmune conditions | • High liver enzymes | • IgG<br>• ANA/ASMA/LKM<br>• Liver biopsy |
| Hypobetalipoproteinemia | • GI symptoms of Malabsorption | • Low LDL<br>• Low Triglycerides | • ApoB levels<br>• Genetic test |
| Mitochondrial dysfunction | • Younger age<br>• CNS and Musculoskeletal involvement | | • Lactate levels<br>• Genetic testing |

ALP: Alkaline Phosphatase, ANA: Antinuclear Antibody, ApoB: Apolipoprotein B, ASMA: Anti-Smooth Muscle Antibody, CNS: Central Nervous System, HCV: Hepatitis C Virus, HDL-C: High-Density Lipoprotein Cholesterol, IgA: Immunoglobulin A, IgG: Immunoglobulin G, KF: Kayser-Fleischer, LAL: Lysosomal Acid Lipase, LDL-C: Low-Density Lipoprotein Cholesterol, LKM: Liver Kidney Microsomal antibody, RNA: Ribonucleic Acid, TTG: Tissue Transglutaminase.

## 8. Question 6: how effective is nutrition and physical activity in reducing liver steatosis and/or reversing liver fibrosis in children?

### *8.1. How does nutrition interventions work in managing MASLD/MASH in children and adolescents?*

Several nutritional patterns have been investigated for the treatment of MASLD including the anti-inflammatory diet, the plant-based diet, the Mediterranean diet, the ketogenic diet, the carbohydrate reduced diet, and intermittent fasting. As previously reviewed, weight reduction can help improve MASLD/MASH significantly. When considering weight reduction, low to moderate weight reduction can be seen in the anti-inflammatory, plant-based, or Mediterranean diet [58–61]. The ketogenic diet, carbohydrate reduced diet, and intermittent fasting have more significant weight reduction [61–74]. However, the ketogenic diet, very low carbohydrate diets, and intermittent fasting carry a risk of malnutrition and need to be monitored by a nutritionist and patients need to be supplemented with multivitamins to prevent deficiencies [61, 75,76].

Clearly there are many metabolic derangements in MASLD and obesity. Therefore, nutrition can target and improve different inflammatory and metabolic pathways. The Mediterranean, the anti-inflammatory, plant-based diet has a dietary structure that helps reduce inflammation, replenish micronutrients, promote good microbiota, and help with insulin resistance [77–79]. Avoidance of sugar-sweetened beverages has been shown to decrease adiposity in children and may benefit children with overweight or obesity who have MASLD [80,81]. One open-label, randomized trial in a cohort of 40 adolescent males, predominantly Hispanic showed greater reduction in hepatic fat on a low free sugar diet for eight weeks compared with usual diet (adjusted mean difference −6.23%. [65]Specifically, it has been documented to improve vascular function, glucose/lipid metabolism, oxidative stress, inflammation (↓IL-6 & ↓TNF-alpha), and lipogenesis [82]. There are several adult RCT that show improved intrahepatic fat, liver stiffness, liver enzymes, both on TE and US [83–87].

Nutritional patterns like the low carbohydrate diet and ketogenic diet can target reduction of de novo lipogenesis and increase fatty acid oxidation that will eventually help insulin resistance downstream [62, 67,70,88,89]. However significant carbohydrate restriction is needed to see these metabolic effects. The data is limited for ketogenic diet in children, but some adult studies have shown improvement of steatosis, while others did not show significant improvement [68,90–93]. The low carbohydrate diet has been studied in children and has been shown to improve hepatic steatosis [65,94].

Intermittent fasting similarly helps utilize fatty acids over glucose for energy when liver glycogen stores are reduced, promoting increased lipolysis, increased hepatic free fatty acid oxidation, decreased lipogenesis, and production of ketone bodies [95–98]. Repetitive fasting improved insulin, antioxidant defenses, DNA repair, mitochondrial function, and ultimately metabolism [99]. There are no medical studies looking at the effects of IF in children. However, several adult studies are showing that IF may lead to significant reduction of steatosis, liver enzymes and fibrosis when assessed by MRI, for liver elastography or Fibroscan [100–107]. Therefore, IF has a metabolic effect far surpassing the effects of weight reduction.

Based on the review of all the diets, they all may have a role in MASLD, and they work by different metabolic mechanisms. The diet needs to be tailored to the patient, their lifestyle, and the metabolic derangements. If one diet plan is not working for the patient, with the help of a nutritionist or dietician, can trial other plans to try to achieve weight reduction. Close monitoring for nutritional deficiencies is highly recommended.

### *8.2. How effective physical activity in reducing liver steatosis and/or reversing liver fibrosis in children?*

The World Health Organization (WHO) and American Academy of Pediatrics (AAP) recommends at least 60 min of moderate- to vigorous-intensity daily for children 5–17 years old. In addition to aerobic activities the addition of resistance strength training to help strengthen muscle and bone should be considered to help ameliorate muscular strength and bone health in children and adolescents [108–110].These WHO guidelines are further endorsed by NASPGHAN with further emphasis on integration of regular physical activity into children's baseline routines.

Studies have shown that exercise affects MASLD through various pathways that regulate triglyceride turnover and, indirectly, liver fat, independent of weight reduction [111–113]. Improved peripheral insulin resistance achieved through exercise reduces the excess delivery of free fatty acids and glucose for free fatty acid synthesis to the liver [112, 113]. While in the liver, exercise increases fatty acid oxidation, decreases fatty acid synthesis, prevents mitochondrial and hepatocellular damage by suppressing reactive oxygen species via up-regulation of several antioxidant enzymes and reduction of the release of damage-associated molecular pathways [112–114].

Physical activity programs in adults which include aerobic exercise with or without resistance training, have shown sufficient evidence to ameliorate intrahepatic fat, improve markers of MASH such as ALT levels, and lead to MASH resolution in adults without weight reduction [115–117].

There have been different clinical trials conducted on patients with obesity demonstrating the beneficial effect of exercise on metabolic risk factors and liver characteristics. Despite this there are very limited studies specifically looking at the direct effect of exercise in pediatric patients with MASLD [118–121]. A meta-analysis demonstrated that physical exercise programs improve hepatic steatosis in pediatric patients with obesity [121]. A systematic review and meta-analysis of supervised-exercise training interventions in children and adolescents showed that both aerobic and resistance exercise, at vigorous or moderate-to-vigorous intensities, with a volume of ≥60 min/session and a frequency of ≥3 sessions/week, aiming to improve cardiorespiratory fitness and muscular strength had benefits on hepatic fat content reduction in youth [122]. A combination of lifestyle modifications with healthful diet and increased physical activity appears effective, despite limited evidence in pediatrics, evidence is strong in adult studies and should be recommended for all pediatric patients with MASLD as a foundation for their therapy [49]. However, larger RCTs are required in pediatric MASLD comparing the type of physical exercise, are required to help guide management better.

Knowing different exercises preferences and patient barriers specifically in children are important for success. A multicenter survey was conducted in children 8–18 years of age with MASLD, in pediatric gastroenterology clinics, included 408 children with MASLD and approximately 52.5 % of participants had physical education classes at school as the primary source of activity averaging 3.7 days per week [123]. Barrier like time constrain were identified and outside of school, walking was their preferred choice of exercise. As such using steps as a marker of activity goals, to meet the recommended daily amount of moderate-vigorous physical activity for children for at least 60 min, this would equate to 13,000–15,000 steps per day for boys and 11,000–12,000 steps per day for girls [124]. While the ideal goal includes moderate-to high-intensity exercise incorporating both aerobic activity and resistance training on most days of the week, individualized exercise plans are often more effective in building confidence and ensuring long-term adherence, particularly for pediatric MASLD [49]. AASLD guidance for treatment of MASLD strongly encourages patients with MASLD to increase their activity level to the extent possible [6]. Thus, any volume or intensity of physical activity from baseline is important compared with the time spent sedentary and should be encouraged [111].

## 9. Question 7: are there medications for MASLD?

### *9.1. What are the current medications that could be considered in the treatment of MASLD?*

MASLD requires a multifaceted treatment strategy that targets both liver pathology and associated metabolic dysfunctions. While lifestyle changes remain the cornerstone of management, they are often insufficient to achieve desired outcomes, necessitating additional therapeutic interventions like AOM [Table 9]. One of the most significant breakthroughs in MASLD and MASH targeted therapies is Resmetirom, an Food and Drug Administration (FDA)-approved agent for adults with noncirrhotic MASH with moderate to advanced fibrosis in conjunction to lifestyle therapy. This liver directed thyroid hormone receptor-β agonist modulates hepatic glucose and lipid metabolism by promoting mitochondrial biogenesis and mitophagy, thereby enhancing hepatic fatty acid β-oxidation and mitigating the deleterious effects of lipotoxic lipids [125]. In clinical trials including MAESTRO-NASH, Resmetirom reduced hepatic fat content (as measured by MRI-PDFF), lowered liver enzyme values, improved noninvasive markers of liver fibrogenesis, and decreased liver stiffness [125,126]. Resmetirom treatment for 52 weeks met the primary endpoints of MASH resolution and/or fibrosis improvement. MASH resolution was achieved in 25.9 % of patients receiving 80 mg and 29.9 % of patients receiving 100 mg, compared to 9.9 % of patients receiving placebo ($p < 0.0001$ vs. placebo for both). Fibrosis improvement was observed in 24.2 % (80 mg) and 25.9 % (100 mg) of Resmetirom-treated patients versus 14.2 % of placebo-treated patients ($p = 0.0002$ and $p < 0.0001$ vs. placebo, respectively) [125,126].

The recommended daily dose of Resmetirom is 80 mg for individuals weighing less than 100 kg and 100 mg for those weighing 100 kg or more [127–129]. While it is generally well-tolerated, common side effects include diarrhea, nausea, pruritus, and vomiting. Individuals receiving Resmetirom should be monitored for gastrointestinal side effects and thyroid hormone function [129]. Resmetirom is not approved for patients with cirrhosis. Though it shows histological benefits in liver disease, Resmetirom is weight-neutral, distinguishing it from weight-loss-focused therapies. This drug has not been tested in clinical trials involving children and is not currently approved for pediatric use. The long-term potential of combining Resmetirom with weight-loss agents like glucagon-like peptide-1 receptor agonists (GLP-1RAs) could provide a more comprehensive treatment strategy, particularly for adults and children dealing with both obesity and MASLD [130].

Other steatohepatitis targeted therapies that have been investigated include vitamin E supplementation, farnesoid X receptor (FXR) agonist and peroxisome proliferator activated receptor (PPAR) agonists. Vitamin E can be prescribed as an adjunct for pediatric and adult patients with MASH in the absence of type 2 diabetes as 400 mg IU twice daily or 800 mg IU daily to improve steatosis [6]. There is no proven improvement in fibrosis [131,132]. Treatment duration is limited to 2 years in pediatrics as inferred from the TONIC trial. It is also limited in adults due to its reported increased risk in mortality. Obeticholic acid (OCA), a selective farnesoid X receptor (FXR) agonist, had demonstrated potential for improving hepatic fibrosis, but was associated with pruritus and potential hepatotoxicity [125]. OCA failed to meet endpoints in the REGENER-ATE trial, such as MASH resolution, and the trial has been discontinued for MASH treatment [125,133]. Pioglitazone, a PPAR gamma agonist which can be used in adult patients with MASH and type 2 diabetes is associated with improved hepatic histology, including hepatic steatosis, ballooning necrosis, and inflammation however, it is considered as weight positive and may lead to weight gain and worsening BMI [6,134]. Lanifibranor, a pan-PPAR agonist, demonstrated promising results in a phase 2 study for MASH patients. Both 1200 mg and 800 mg doses were superior to placebo in resolving MASH and improving fibrosis [125]. Elafibranor, a dual PPAR α/δ agonist, initially showed promise in resolving MASH in a phase 2b analysis. While adverse events were comparable between the drug and placebo groups, primarily consisting of nausea, headache, diarrhea, and fatigue, the phase 3 trial failed to meet its primary endpoint of MASH resolution [125]. Most employed pharmacotherapies in the pediatric age group aside from vitamin E are geared toward achieving sustainable and clinically significant weight reduction.

GLP-1RAs are encouraging therapies for both managing MASLD and improving metabolic dysfunction. These agents work by promoting weight reduction, reducing appetite, delaying gastric emptying, and improving glycemic control thereby improving hepatic dysfunction. Modifications to the incretin glucagon like peptide-1 (GLP-1), including dipeptidyl peptidase-4 (DPP-4) inhibition and amino acid additions, have extended its half-life from minutes to hours. These changes have resulted in short-acting (exenatide) and long-acting (dulaglutide, exenatide once-weekly, liraglutide, semaglutide, etc.) GLP-1RAs for various administration routes [135].

In a 72-week, double blinded phase 2 trial of 320 adult patients with biopsy-proven steatohepatitis revealed rates of MASH resolution without fibrosis progression on semaglutide of 40 % in the 0.1-mg group, 36 % in the 0.2-mg group, and 59 % in the 0.4-mg group,

**Table 9**
Overview of Anti-Obesity Medications: Indications, Dosing, current data, adverse effects, and Efficacy in MASLD.

| GLP-1 RA (Glucagon-Like Peptide 1 Receptor Agonist) | Indications<br>Dosing<br>Monitoring | Pediatric Studies & Reported Weight loss/BMI/ BMI % reduction | Adult and Pediatric Studies on Efficacy in Treatment of MASLD | Adverse Effects (AE)<br>Contraindications<br>Caution/Drug Interactions |
|---|---|---|---|---|
| **Liraglutide**<br>**Trade Name:** Saxenda (Obesity), Victoza (T2DM)<br>**Class:** GLP 1 RA (Glucagon-Like Peptide 1 Receptor Agonist) | **Indications:**<br>**Saxenda-** FDA approved for weight management in adolescents aged ≥ 12 yo<br>**Victoza-** FDA approved for T2DM in adolescents ≥10 years of age<br>Starting dose: 0.6 mg/**day** subcutaneous (SQ)<br>**Dose Titration:** increase dose by 0.6 mg at weekly intervals (1.2, 1.8, 2.4, 3 mg) to a goal of 3 mg daily<br>If increased dose is not tolerated, consider delaying dose escalation by 1 week or decreasing back to previous dosing | Meta-analysis of randomized clinical trials: mean difference in BMI −1.58 (−2.42 to −0.7) and in body weight −1.51 kg (−2.85 to −0.17 kg)<br>Trial in adolescents 12-18yo: −4.3 % Placebo: +0.4 % Difference: −4.6 % with 3 mg SQ at 56 wk.<br>Fox et al. with the SCALE Kids trial group, at week 56, the mean percentage change from baseline in BMI was −5.8 % with liraglutide plus lifestyle interventions and 1.6 % with placebo, representing an estimated difference of −7.4% points (P < 0.001) in children 6–11 years of age with obesity. | **Adult Studies:**<br>**LEAN trial:** Multicenter, double-blind, randomized, placebo-controlled phase 2 study: 26 liraglutide versus placebo<br>39 % had resolution of MASH vs. 9 placebos; 2 versus 8 had progression of fibrosis (placebo)<br>**Pediatric Studies:**<br>Case Series: Improvement in hepatic fat fraction as measured by PDFF by 13 % and ALT improvement > 50 % from baseline, with GGT and AST normalization on liraglutide 1.8 mg daily with lifestyle changes with weight loss of 7.4 kg and BMI z-score improvement of 0.37<br>**Additional Benefits:**<br>Randomized clinical trial: decrease in HbA1c by 0.64 % after 26 wk of liraglutide + metformin relative to increase by 0.42 % for those on placebo and metformin | **AE:** Gastrointestinal disturbance (nausea, diarrhea, vomiting) Less common, hypoglycemia, elevated transaminases, cholelithiasis and pancreatitis<br>Worsening or emergence of suicidal ideation<br>**CI:** Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2<br>Pregnancy<br>Hypersensitivity or anaphylaxis to any component of formulation<br>**Black box warning:** Risk of thyroid c-cell tumors (seen in animal models at clinically relevant doses) |
| **Semaglutide**<br>**Trade name:**<br>Wegovy (Obesity)<br>Ozempic (T2DM)<br>**Class:** GLP 1 RA (Glucagon-Like Peptide 1 Receptor Agonist) | **Indications:**<br>**Wegovy-** FDA approved for weight management in adolescents aged ≥ 12 yr<br>**Adult indication:** Reduces risk for major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight<br>**Ozempic-** FDA approved for adults with T2DM<br>**Dosing:**<br>Once weekly at 0.25–2.4 mg SQ injection<br>**Dose titration:**<br>Starting dose: 0.25 mg weekly subcutaneous for 4 wk.<br>The increase to 0.5 mg weekly for 4 wk, 1 mg weekly for 4 wk, 1.7 mg weekly for 4 wk, then 2.4 mg weekly | **STEP-TEENS Study:** Double-blind, randomized controlled trial in adolescents 12-18yo: mean BMI reduction by 16.1 % from baseline relative to 0.6 % reduction in placebo group, Treatment Difference: −16.7 % with 2.4 mg SQ weekly at 68 wk.<br>16.1 % mean change in BMI from baseline to week 68 with semaglutide versus 0.6 % with placebo (P < 0.001) | **Adult Studies:**<br>72-week, double-blind phase 2 trial in adults with biopsy-confirmed MASH and fibrosis MASH resolution was achieved with no worsening of fibrosis:<br>40 % in the 0.1-mg group<br>36 % in the 0.2-mg group<br>59 % in the 0.4-mg group<br>17 % in the placebo group (P < 0.001)<br>Improvement in fibrosis stage:<br>43 % 0.4 mg SQ daily x 72weeks<br>33 % of the patients in the placebo group (P = 0.48).<br>13 % mean weight loss in the 0.4-mg group and 1 %<br>72week phase 3 ESSENCE trial, semaglutide 2.4 mg vs. placebo in adults with biopsy-defined MASH and fibrosis stage 2 or 3<br>62.9 % resolution of steatohepatitis with no worsening of liver fibrosis compared to 34.1 % on placebo<br>37.0 % achieved improvements in liver fibrosis with no worsening of steatohepatitis compared to 22.5 % on placebo.<br>**STEP-TEENS Study:**<br>In adolescents 12-18yo Percent change in ALT by −18.3 compared to baseline versus −4.9 placebo or −14.1 % at Week 68<br>Single-center retrospective study evaluated the effectiveness of GLP-1RA in treating pediatric MASLD. 111 patients with mean reduction in ALT by 23 U/L at 6 months | **AE:** Nausea, vomiting, decreased appetite, indigestion, diarrhea, constipation, hypoglycemia<br>**CI:** Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2, hypersensitivity or anaphylaxis to any component of the formulation |

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**Table 9** (*continued*)

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| | | | and by 18 U/L overall (P = 0.02) | |
| **Dulaglutide**<br>**Trade Name:** Trulicity<br>**Class:** GLP 1 RA (Glucagon-Like Peptide 1 Receptor Agonist) | **Indications:**<br>FDA approved for children aged ≥10 y with T2DM<br>**Dosing:** 0.75 mg–1.5 mg once weekly ≥10 y<br>Max dose in pediatrics: 1.5 mg weekly<br>Max dose in adults: 4.5 mg<br>**Dose Titration:** 0.75 mg SQ weekly can increase to 1.5 mg weekly after at least 4 weeks on the previous dose | No differences in change in BMI status in treatment vs placebo group | **Adult Studies:**<br>Adults with T2DM and MRI-derived proton density fat fraction-assessed LFC ≥ 6.0 % at baseline; Improvement in liver function compensatory content (LFC) −3.5 compared to placebo on 0.75 mg SQ weekly for 4 weeks, then 1.5 mg weekly for 20 weeks with nonsignificant reductions in PFC, liver stiffness, serum AST, and serum ALT levels<br>**Additional Benefits:**<br>Randomized clinical trial: decrease in HbA1c by 0.6 % with 0.75 mg and by 0.9 % with 1.5 mg after 26 wk relative to increase by 0.6 | **AE:** Nausea, vomiting, decreased appetite, indigestion, diarrhea, fatigue |
| **Exenatide Extended Release**<br>**Trade Name**: Bydureon BCise<br>**Class:** GLP 1 RA (Glucagon-Like Peptide 1 Receptor Agonist) | **Indications:**<br>FDA approved for children aged ≥10 y with T2DM + lifestyle<br>**Dosing:** Initial: 5 mcg SQ BID, increase to 10 mcg BID in 4 weeks if needed | Meta-analysis of randomized clinical trials: mean difference in BMI −1.11 (−1.67 to −0.55) and in body weight −2.02 kg (−4.54 to 0.49 kg) | **Adult Studies:**<br>Adults with obesity, MASLD, and T2DM,<br>Significant reduction in body weight, ALT, AST and GGT, pro-peptide of type III collagen level, fibrosis-4 index, and MASLD fibrosis score with 54 weeks of 300 μg SQ daily<br>Randomized clinical trial: decrease in HbA1c from baseline by 0.36 % relative to increase by 0.49 % in placebo group | **AE:** Nausea<br>**CI:** Anaphylaxis and angioedema with medication |
| **Dual Agonist- 2G's**<br>**GIPR/GLP-1RA** | **Indications**<br>**Dosing**<br>**Monitoring** | **Pediatric Studies & Reported Weight loss/BMI/ BMI % reduction** | **Adult and Pediatric Studies on Efficacy in Treatment of MASLD** | **Adverse Effects (AE)**<br>**Contraindications**<br>**Caution/Drug Interactions** |
| **Tirzepatide**<br>**Trade name:** Zepbound (Obesity) Mounjaro (T2DM)<br>Dual agonist "2G" gastric inhibitory peptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor co-agonist<br>**MOA:** is a long-acting glucose dependent insulinotropic polypeptide that activates both the GLP-1 and GIP (gastric inhibitory polypeptide) receptors | **Indications:**<br>**Mounjaro:**<br>FDA approved to treat T2DM > 18 years old<br>**Zepbound:**<br>FDA approved for weight management in adults with obesity or overweight with at least one weight-related comorbid condition<br>FDA approved to treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity<br>**Dosing:** 2.5 mg weekly SQ weekly<br>**Dose Titration:** Increase dosage in 2.5 mg SQ weekly increments after at least 4 weeks to goal, Maximum dose of 15 mg weekly<br>**Maintenance dose:** are 5 mg, 10 mg, or 15 mg SQ once weekly | Reports up to 17.8 % body weight change<br>In adults - weight loss 20.9 % weight loss at the maximum dose of 15 mg compared to a 3.1 % weight loss with placebo | **Adult Studies:**<br>Phase 2 trial in adults with MASH and moderate or severe fibrosis, treatment with tirzepatide for 52 weeks was more effective than placebo with respect to resolution of MASH without worsening of fibrosis<br>Resolution of MASH without worsening of fibrosis was 10 % placebo group, 44 % on 5 mg 56 % on 10-mg 62 % in the 15-mg tirzepatide group (P < 0.001 for all three comparisons)<br>Significantly greater reduction in ALT (tirzepatide 1,5, 10, 15 mg), Procollagen III (tirzepatide 15 mg), keratin-18 (tirzepatide 5, 10, 15 mg) compared to placebo | **AE:** Nausea, vomiting, decreased appetite, indigestion, diarrhea, constipation, hypoglycemia<br>**CI:** Personal or family history of medullary thyroid cancer or multiple endocrine neoplasias type 2, anaphylaxis, and angioedema to Tirzepatide |
| **Triple Agonist-3G's**<br>**GcgR/GIPR/GLP-1RA** | **Indications**<br>**Dosing**<br>**Monitoring** | **Pediatric Studies & Reported Weight loss/BMI/ BMI % reduction** | **Adult and Pediatric Studies on Efficacy in Treatment of MASLD** | **Adverse Effects (AE)**<br>**Contraindications**<br>**Caution/Drug Interactions** |
| **Retatrutide**<br>Triple agonist "3G"<br>Triple hormone receptor agonist of GLP1, GIP and GCGR receptors (G-protein-coupled receptor (GPCR) – glucagon receptor in islet β cells and liver | **Indications:**<br>Adults with BMI ≥ 30 or ≥27 kg/m2 and ≥1 weight-related condition<br>**Dosing:** 1–12 mg SQ once weekly | Reports up to 22.1 % body weight | **Adult Studies:**<br>Phase 2 treated with retatrutide 8 and 12 mg for 48 weeks experienced weight reductions of 22.8 % and 24.2 %, respectively<br>**No Pediatric Studies** | **AE:** nausea, vomiting, diarrhea, and acid reflux<br>Less common side effects include pancreatitis, gallbladder disease, and worsening of diabetic eye disease<br>**CI:** Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2 |

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**Table 9** (*continued*)

| Partial agonist of Thyroid hormone receptor Beta (THR-β)[a]<br>Indications<br>Dosing<br>Monitoring | Pediatric Studies & Reported Weight loss/BMI/ BMI % reduction | Adult and Pediatric Studies on Efficacy in Treatment of MASLD | Adverse Effects (AE)<br>Contraindications<br>Caution/Drug Interactions |
|---|---|---|---|
| **Resmetirom**<br>**Trade:** Rezdiffra<br>Partial agonist of Thyroid hormone receptor Beta (THR-β)[a]<br>**MOA:** Activating THR-β modulates genes that promote uptake of free fatty acids from both external sources (CPT1), increased production and uptake of internal free fatty acids from de novo lipogenesis (ACC1, FAS) and lipophagy | **Indications:**<br>**Only FDA Approved Medication for MASH with moderate to advanced liver fibrosis** in **ADULTS** (consistent with stages F2 to F3 fibrosis) to be used in conjunction with lifestyle intervention<br>FDA indication is approved under accelerated approval only in adults<br>**Dosing:**<br>≤100 kg: 80 mg tablet once a day<br>≥100 kg: 100 mg tablet once a day | **WEIGHT NEUTRAL** | **Adult Studies:**<br>MASTRO 3 TRIAL:<br>**MASH Resolution:**<br>25.9 % on 80 mg<br>29.9 % on 100 mg<br>Fibrosis Improvement at least 1 stage:<br>24.2 % on 80 mg<br>25.9 % on 100 mg<br>Compared to 14.2 % on placebo<br>**No Pediatric Studies** | **AE:** reported in ≥ 5 % of patients and higher compared to placebo are: diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain, and dizziness<br>Increase in ALT and AST levels were observed in the first 4 weeks after initiating treatment<br>The mean elevation in ALT and AST values was less than 1.5 times baseline at 4 weeks<br>Values returned to baseline around 8 weeks after initiating treatment |
| **Other Medications** | **Indications**<br>**Dosing**<br>**Monitoring** | **Pediatric Studies & Reported Weight loss/BMI/ BMI % reduction** | **Adult and Pediatric Studies on Efficacy in Treatment of MASLD** | **Adverse Effects (AE)**<br>**Contraindications**<br>**Caution/Drug Interactions** |
| **Metformin** | **Indications:**<br>FDA approved in children aged ≥10 yr with T2DM<br>**Dosing:** start 500 mg daily with dinner, and titrate slowly up to 2000 mg daily as needed and if tolerated | Systematic review: decrease in BMI by 1.16 after 6 mo. | **Pediatric Studies:**<br>Multicenter trial described metformin (1000 mg daily) was no more effective than placebo for outcomes of ALT elevation or histologic features of MASLD | **AE:** gas, diarrhea, abdominal discomfort, headache<br>Lactic acidosis- rare<br>Consider if: psychotropic medications, PCOS, insulin resistance, pre-diabetes<br>Take with food |
| **Phentermine**<br>**Trade Name:**<br>Adipex- P, Suprenza (ODT)<br>Lomaira (8 mg)<br>**MOA:** Sympathomimetic amine, Stimulates norepinephrine release from hypothalamic neurons | **Indications:**<br>FDA approved for weight management for adolescents aged >16 y for short-term treatment<br>FDA: only approves for ≤ 12 weeks, after considered off label<br>**Dosing:**<br>8 mg–37.5 mg PO every am (consider starting with 7.5 mg)<br>8 mg tablet has shorter half-life, can be given minutes before meal 2–3 times per day<br>**Dose Titration:** 15 mg in the morning 1 h before breakfast, can increase up to 37.5 mg daily | On 15 mg × 6 months BMI decreased by 4.1 % at 6 months compared to lifestyle modifications alone | **No Pediatric Studies** | **AE:** Dry mouth, insomnia, irritability increased heart rate, blood pressure, constipation, anxiety<br>**CI:** hyperthyroidism, glaucoma, pregnancy, uncontrolled hypertension, and cardiac disease, MAOI use within 14 days<br>Avoid intake of caffeine, energy drinks, decongestants |
| **Topiramate**<br>**Trade name:** Topamax<br>**MOA:** GABA receptor modulation in hypothalamus<br>Carbonic anhydrase inhibition<br>Glutamate antagonism<br>Blocks neuronal voltage dependent sodium channels | **Indications:**<br>FDA approved ≥ 2yo for epilepsy and ≥ 12 yr for migraines<br>Used off label for weight management<br>**Consider:** binge eating, emotional eating, psychotropic medication induced weight gain, uncontrolled migraines<br>**Dosing and Titration:**<br>1st wk: 25 mg PO daily<br>Increase to 50 mg/day; then 50 mg BID; May increase by 25 mg per dose | 4.9 % on topiramate 75 mg daily for at least 3 months | **Pediatric Studies:**<br>Pediatric Case report: AST normalized, ALT significantly improved from 159 to 47 with normal hepatic fat- PDFF based on MR elastography, 14 months after initiation of topiramate 50 mg BID in conjunction with lifestyle management<br>Total weight loss of 9.1 kg with improvement in BMI z-score of 0.25<br>Multicenter retrospective cohort study of 32 children with Pediatric MASLD and obesity received topiramate alongside lifestyle changes. Significant decreases in BMI z-score and serum transaminase levels after 3–6 months, with 43 % achieving liver disease regression, defined as ALT normalization, or reduction of ALT by at least 50 % from baseline | **AE:** Paresthesia, Dysgeusia, fatigue, Difficulty with concentration/attention and memory, metabolic acidosis<br>**CI:** Acute myopia; secondary angle closure, glaucoma; suicidal behavior/ideation; metabolic acidosis<br>Avoid alcohol or sleeping medications |
| **Phentermine/Topiramate**<br>extended release 7.5 mg/46 mg (mid-dose) or 15 mg/92 mg (high dose) (once daily oral)<br>**Trade Name:** Qsymia | **Indications:**<br>FDA approved for weight management in adolescents aged ≥ 12y and BMI ≥95th percentile | ~10.4–11 % BWL<br>Randomized, double-blind clinical trial: Mid dose (phentermine 7.5 mg phentermine/46 mg | **Pediatric Studies:**<br>Treatment (15/92 mg): −7.1 %<br>Placebo: +3.3 % Difference: −10.4 % with 15 mg/92 mg at 56 wk. | **AE:** Cognitive dysfunction, teratogenicity, metabolic acidosis, renal stones, palpitations, hypertension, insomnia, anxiety, dry mouth, increased suicidal |

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| **MOA:**<br>Phentermine (PHEN): stimulates norepinephrine release from hypothalamic neurons<br>Topiramate (TPM): GABA receptor modulation in hypothalamus | **Dosing:**<br>Starting dose: 3.75 mg/23 mg daily for 14 days<br>Titration: 7.5 mg/46 mg daily for 12 wk.<br>**Dose Titration:**<br>If BMI has not decreased by 3 % from baseline, increase to 11.25 mg/69 mg daily for 14 d, then 15 mg/92 mg daily<br>Take after breakfast, avoid late evening administration due to insomnia, not affected by meals | topiramate): percentage change in BMI after 56-wk difference from placebo −8.11 % point (−11.92 to −4.31; P < 0.001). High dose (15 mg/92 mg) −10.44 (−13.89 to −6.99; P < 0.001) | 20 % decrease in triglycerides and about 10 % increase in HDL cholesterol with both doses | ideation<br>**CI:** hyperthyroidism, pregnancy, glaucoma, and cardiac disease<br>Should not be used within 2 wk of MAO inhibitor use<br>Incidence ≥4 % and greater than placebo: depression, dizziness, arthralgia, influenza, and ligament sprain |
| **Naltrexone/Bupropion**<br>**Trade name:** Contrave<br>**MOA:**<br>Bupropion –<br>Stimulates pro-opiomelanocortin (POMC) neurons to affect MC4R receptors decreasing appetite<br>Naltrexone – helps potentiate this response by preventing autoinhibition of POMC | **Indications:**<br>FDA approved for weight management for >18yo<br>**Dosing:** Tablets are 8mg/90 mg – increase as effective & tolerated<br>**Dose Titration:**<br>Week 1: 1 tablet daily<br>Week 2: 1 tablet BID<br>Week 3: 1 tablet AM, 2 tablets PM<br>Week 4: 2 tablets BID | Average of 5.0–9.3 % weight loss from baseline (but all adult studies) | **Additional Benefits:**<br>Both medications are indicated for addictive disorders (tobacco, alcohol, opioids), can decrease food cravings<br>**No Pediatric Studies** | **AE:** nausea, headache, constipation, dry mouth, transient BP elevation<br>**CI:** in those on MAOIs, uncontrolled hypertension, seizure disorder, anorexia or bulimia, opioid use disorder<br>**Black box warning**: suicidality, avoided in adolescents or monitored very closely if prescribed. |
| **Orlistat**<br>**Trade name:** Alli<br>**MOA:** reversible inhibitor of lipases | **Indications:**<br>FDA approved Ages ≥12 yo with BMI ≥95th percentile<br>**Dosing:** 120 mg by mouth 3 times daily with meals<br>**Available over the counter:**<br>60 mg 3 times daily with meals | At 1 year decrease in BMI by −0.55 versus Placebo of +0.31<br>Randomized, double-blind controlled trial: decrease in BMI reduction by 0.55 in treatment group vs increase by 0.31 in placebo group (P = 00.001) | Randomized, double-blind controlled trial: no significant difference in glycemic status between treatment vs placebo group<br>Modestly improve ALT levels in patients with MASLD | **AE:** Oily stools and abdominal pain, diarrhea<br>**CI:** Pregnancy, chronic malabsorption, cholestasis<br>Multivitamin supplement 2 h apart from dose |
| **Setmelanotide**<br>**Trade name:** Imcivree<br>**MOA**: MC4R agonist | **Indications:**<br>Ages ≥6 yo with monogenic or syndromic obesity due to POMC, PCSK1, or leptin receptor (LEPR) deficiency as determined by an FDA-approved test<br>**Dosing:** 1–3 mg once a day<br>**Dose Titration:**<br>6-12yo- Start at 1 mg once a day for 2 weeks then increase by 1 mg to max dose of 3 mg<br>≥12yo Start at 2 mg once a day for 2 weeks then increase to a max dose of 3 mg | In POMC/PCSK1 deficiency: mean change in body weight at 1 y of −25.6 %<br>LEPR deficiency: 45 % had weight loss of >10 % at 1 y<br>Bardet-Biedl syndrome: 16.3 % change in body weight at 12 mo. | Effective in achieving weight loss and reducing ALT<br>**Additional Benefits:**<br>POMC trial: mean fasting glucose changed from 135.8 mg/dL (SD 107.7) at baseline to 107.0 mg/dL (85.5) at ~1 y, with mean percentage decrease of −17.2 % (147) No significant change in mean fasting blood glucose in LEPR trial<br>Bardet-Biedl syndrome: was not associated with a significant percentage change from baseline in HbA1c at any time point | **AE:** Local reaction at injection sites, skin hyperpigmentation, rash, alopecia, gastrointestinal disturbance, flu-like symptoms<br>**CI:** serious hypersensitivity to setmelanotide or any of the excipients in IMCIVREE, benzoyl peroxide preservative |

respectively, compared to 17 % in the placebo group (P < 0.001 for semaglutide 0.4 mg vs. placebo) [136]. However, there was no significant improvement of noted with fibrosis [136]. The latest data Phase 3 ESSENCE trial data reinforces the potential of semaglutide as a treatment for MASH, particularly in patients with moderate to advanced fibrosis [137]. Among 800 participants with biopsy-proven MASH, semaglutide 2.4 mg administered weekly demonstrated significantly higher rates of steatohepatitis resolution without worsening fibrosis (62.9 % vs. 34.1 % with placebo) and fibrosis improvement without worsening steatohepatitis (37.0 % vs. 22.5 % with placebo) [137]. Additionally, semaglutide showed benefits in improving liver enzymes, non-invasive fibrosis markers, and cardiometabolic parameters, alongside expected weight reduction [137]. These findings highlight semaglutide's potential to target both liver disease and associated metabolic dysfunction in MASH.

GLP-1RAs have not been trialed specifically for the indication of Pediatric MASLD, but encouraging data is coming from Pediatric obesity, diabetes, and retrospective studies. In a randomized controlled trial of 201 teenage participants, ranging from 12 to <18 years old with obesity, semaglutide significantly reduced BMI by 16.1 % compared to a 0.6 % increase with placebo (P < 0.001). At week 68, 73 % of semaglutide-treated participants achieved at least 5 % weight reduction, versus 18 % in the placebo group (P < 0.001) [138]. Semaglutide also led to greater reductions in body weight and improvements in cardiometabolic risk factors like waist circumference, glycated hemoglobin, lipids, and ALT [138]. Fox et al. with the SCALE Kids trial group demonstrated that treatment with liraglutide for 56 weeks plus lifestyle interventions resulted in a greater reduction in BMI with mean percentage change from baseline of −5.8 % with liraglutide and 1.6 % with placebo, representing an estimated difference of −7.4% points (P < 0.001) in children 6–11 years of age with obesity [139]. The RCT was not designed to study the role of liraglutide in the treatment of MASLD but maybe a consideration in the future for individuals with obesity and younger age who have MASLD. A single-center retrospective study

evaluated the effectiveness of GLP-1RAs in treating pediatric MASLD in a real-world setting. The cohort included 111 patients. Median age at GLP-1RA initiation, 15 years; 51 % boys; 39 % white. Patients were prescribed Liraglutide, Semaglutide, Dulaglutide and Exenatide with Semaglutide at 41 % being the most prescribed GLP-1RA. Results showed a significant mean reduction in ALT by 23 U/L at 6 months and by 18 U/L overall ($p = 0.02$). ALT fully normalized in 58 % of patients, Greater mean reduction in ALT by 33 IU/L in T2DM cohort ($p = 0.02$). Notably, weight and body mass index (BMI), and BMI Z-score remained unchanged. This study showed the potential use of GLP-1RAs in the treatment of pediatric MASLD, specifically in patients with T2DM [140].

GLP-1RA data beyond semaglutide in MASLD continues to evolve. A systematic review of eight clinical trials involving 468 patients demonstrated that treatment with liraglutide, exenatide, or dulaglutide was linked to a reduction in transaminase levels, intrahepatic adipose tissue, and visceral fat [141]. While the beneficial effects of these GLP-1RAs on MASLD are suggested by these findings, rigorously designed clinical trials specifically investigating different GLP-1RAs for MASLD are essential to establish definitive evidence.

GLP1-RAs (Liraglutide and Semaglutide) are currently FDA approved for the management of obesity in children and adolescents 12 years and older. With evolving data from adult studies and emerging evidence in pediatrics, GLP1-RA shows promise as a treatment option for adolescents with obesity and MASLD with failed lifestyle management [136, 138]. In addition to addressing weight management, GLP1-RAs have demonstrated efficacy in improving other markers of metabolic dysfunction, including HbA1c, cholesterol, low density lipoprotein (LDL) cholesterol, and blood pressure [142,143]. This makes semaglutide an excellent option for individuals with obesity and MASLD who also have coexisting conditions such as prediabetes, type 2 diabetes, dyslipidemia, or hypertension. Furthermore, GLP1-RAs are particularly beneficial for individuals with hypothalamic obesity, food cravings, or poor satiety and satiation [144]. They have also been shown to achieve significant weight reduction and testosterone reduction in patients with PCOS [145], further highlighting their versatility in managing metabolic and obesity-related disorders. Given the current national shortage of GLP-1RAs, these medications are being prioritized for the patients who are most likely to benefit, including those with severe obesity (e.g., class 3 vs. class 1), advanced MASLD (e.g., MASH vs. simple steatosis or significant fibrosis vs. mild or no fibrosis), and more severe weight related comorbidities [146]. For patients who decline injectable formulations, GLP-1RA treatment options becomes limited. Despite very promising studies with high-dose oral formulations of semaglutide up to 50 mg daily with a high effectiveness in adult obesity similar to high-dose subcutaneous semaglutide, it is currently only available as an injectable in the pediatric age range and therefore does not represent a feasible therapeutic option for pediatric patients [147].

With the encouraging results seen with GLP-1RAs, research has now expanded to dual and triple agonists, which target additional metabolic pathways. Tirzepatide, a dual GLP-1/GIP (gastric inhibitory polypeptide) receptor agonist, offers more pronounced weight reduction effects, potentially enhancing liver health through its ability to reduce fat accumulation and improve metabolic control [148]. In a phase 2 clinical trial (SYNERGY-NASH) of 190 adult participants with MASH and moderate to severe fibrosis, tirzepatide demonstrated significant efficacy in resolving MASH without worsening of fibrosis. Compared to placebo, participants treated with tirzepatide experienced a 44 %, 56 %, and 62 % higher likelihood of achieving MASH resolution at 5 mg, 10 mg, and 15 mg doses, respectively [149]. While pediatric data for tirzepatide is limited, it could provide benefits for children suffering from MASLD. It is currently not FDA approved in children and adolescents. Survodutide, a dual GLP-1 and glucagon receptor agonist improved MASH without worsening in fibrosis in a phase 2 trial in adults [150].

Pemvidutide, a dual GLP-1/glucagon receptor (GCGR) agonist, is being studied for its potential to reduce body weight and liver fat. While GLP-1R agonists primarily promote weight reduction, GCGR agonists directly target the liver for fat reduction [151]. A recent randomized, double-blind, placebo-controlled trial to study the effects of pemvidutide on liver fat content in adult subjects with MASLD showed a 55 % reduction in liver fat and significant ALT level improvements [151].

Retatrutide, a triple glucose-dependent insulinotropic polypeptide, GLP-1, and glucagon receptors agonists, has led to substantial body weight reduction with indirect implications of improvement in MASLD parameters [148]. Adult participants in a phase 2 treated with retatrutide 8 and 12 mg for 48 weeks experienced weight reductions of 22.8 % and 24.2 %, respectively [136]. A sub-study of this randomized, double-blind, placebo-controlled trial evaluated the reduction in liver fat (LF) after 24 weeks of retatrutide treatment in participants with MASLD. Retatrutide significantly reduced LF at 24 weeks compared to placebo, with the greatest reduction observed at the highest dose. Additionally, retatrutide treatment was associated with improvements in body weight, abdominal fat, and metabolic markers related to insulin sensitivity and lipid metabolism.[150]Retatrutide is not yet FDA approved in patients with MASLD.

As tirzepatide and resmetirom are only FDA-approved for patients 18 years and older and as no clinical trials in pediatric MASLD have been conducted, those medications cannot be recommended for pediatric MASLD at this moment despite their effectiveness in adult MASLD [149, 152].

Other non-GLP-1 RA based medications that are either FDA approved or used off label for the treatment of pediatric obesity, insulin resistance or T2DM that have been investigated in the possible treatment of MASLD [Table 9]. Improvements with these medications are likely linked to their weight reduction effects, rather than targeting metabolic mechanisms in the liver.

Metformin is widely used for type 2 diabetes but also improves insulin sensitivity and can lead to modest weight reduction. While improvement in glucose metabolism would intuitively seem to have improvement in reducing liver fat, metformin does not reduce liver fat or improve fibrosis [132]. Metformin did not show any histologic benefit and therefore is not recommended for treatment of MASLD and MASH [6]. However many physicians use this off label for its weight reduction capabilities.

Topiramate is FDA approved for patients 2 years and older with epilepsy and is used off label for managing obesity and binge eating disorder, with expected BMI reduction of 4.9 % on topiramate 75 mg daily for at least 3 months. While not directly targeting MASLD or MASH vis-à-vis intrahepatic mechanisms, topiramate demonstrates indirect efficacy by reducing appetite and facilitating weight reduction [153]. A multicenter descriptive cohort study of 32 children was conducted in subjects $<18$ years with MASLD and body mass index (BMI) $>$ 95th percentile treated with topiramate for weight reduction for $\geq 3$ months [154]. ALT levels improved (76 vs 50 U/L, $p = 0.001$). Further, 43 % of patients had either ALT normalization or reduction by $>50$ % from baseline. BMI $z$ score decreased by 0.1 from baseline to 3–6 months [154]. Topiramate was well-tolerated, with mild side effects. Topiramate should be considered in younger children not responding to lifestyle interventions alone with poor satiation, food cravings, binge eating, psychotropic medication-induced obesity, migraine headaches, night eating (when dosed at night), seizure disorder, idiopathic intracranial hypertension, severe non-verbal autism, or mood lability. Caution is advised in patients with depression and suicidality [153].

Phentermine is a norepinephrine reuptake inhibitor, may also contribute to MASLD improvement through caloric reduction, though its use in children is more limited. It is FDA approved for short term use, $\leq 12$ weeks for patients $\geq 16$ years of age.

The combination of Topiramate/Phentermine extended release however is FDA approved for obesity in children 12 years and older and has shown to improve weight reduction and thereby improve some MASLD features [155]. Expected BMI reduction of 10 % at a dose of 15 mg/92 mg for 56 weeks. Phentermine/Topiramate can be selected in patients with MASLD and strong hunger with frequent snacking, poor

satiation, binge eating, or migraine headaches. Side effects are numerous include xerostomia, palpitations, dysgeusia and hypertension [156]. It is contraindicated in patients with uncontrolled hypertension, pregnancy, and arrythmias. Specific counseling regarding teratogenicity and increased birth defects should be provided. Caution is advised in patients with cardiovascular disease, anxiety, depression, and suicidality [156].

Bupropion is a norepinephrine, and dopamine reuptake inhibitor is used off label for weight reduction. Naltrexone/bupropion, FDA approved for weight management for >18yo is effective in reducing cravings and managing binge eating, indirectly improving liver fat accumulation and metabolic function through weight management in adults [157–160]. Side effects include dry mouth, insomnia, agitation [161]. Bupropion is contraindicated in uncontrolled hypertension and eating disorders [162]. However, due to the black box warning of suicidality, this medicine should be avoided in adolescents or monitored very closely if prescribed.

Lisdexamfetamine is an FDA approved for attention deficit hyperactivity disorder (ADHD) in 6 years and older, and for binge eating disorder in patients 18 years and older and is used off label in younger children with obesity and MASLD with ADHD, binge eating behavior, or impulsive mindless eating. Caution is advised in patients with cardiovascular disease and anxiety [163].

Setmelanotide is FDA approved for ages 6 years and older to treat monogenic obesity due to variants that are pathogenic, likely pathogenic or variant of unknown significance (VUS) in POMC (pro opiomelanocortin), PCSK1 (proprotein convertase subtilisin/kexin type 1), LEPR (leptin receptor) and Bardet Biedl Syndrome (BBS). Setmelanotide is effective in achieving weight reduction, reducing ALT levels, and would likely ameliorate hepatic steatosis in those conditions [164–166].

Metreleptin is a recombinant human leptin and is FDA approved for the treatment of complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy without clear age limitations. Case reports indicate that metreleptin can markedly improve hepatic steatosis and ALT levels in pediatric patients with congenital leptin deficiency and can be considered in the rare clinical scenario of pediatric obesity and hepatic steatosis due to leptin deficiency [167,168].

Orlistat is a lipase inhibitor, FDA approved Ages ≥12 y with BMI ≥95th percentile can modestly improve ALT levels in patients with MASLD. It is associated with gastrointestinal side effects including steatorrhea and rectal oily leakage and may interact with other medications thus is generally not used [169].

The growing success of AOM in promoting weight reduction offers a promising approach to treating MASLD, the hepatic manifestation of obesity and is area of critical ongoing research [128]. Fig. 3 illustrates the mechanisms of action of various AOM used in managing obesity and metabolic dysfunction across different organ systems. The approach to treating MASLD and obesity is often nuanced and should be tailored to individual patient needs and other associated weight related comorbidities. GLP-1RAs offer benefits in reducing cardiovascular risk factors, aiding in hypothalamic obesity, and improving insulin resistance. Metformin can be utilized off-label as well. For patients experiencing migraines, or those with binge-eating disorder, Topiramate or a combination of Topiramate and Phentermine may be considered [161]. The selection of a therapeutic agent in patients with MASLD and obesity depends on multiple factors including weight related comorbidities, patient and family preference, access and overage. Tailoring treatment to patient phenotype in MASLD is predicted to improve outcomes.

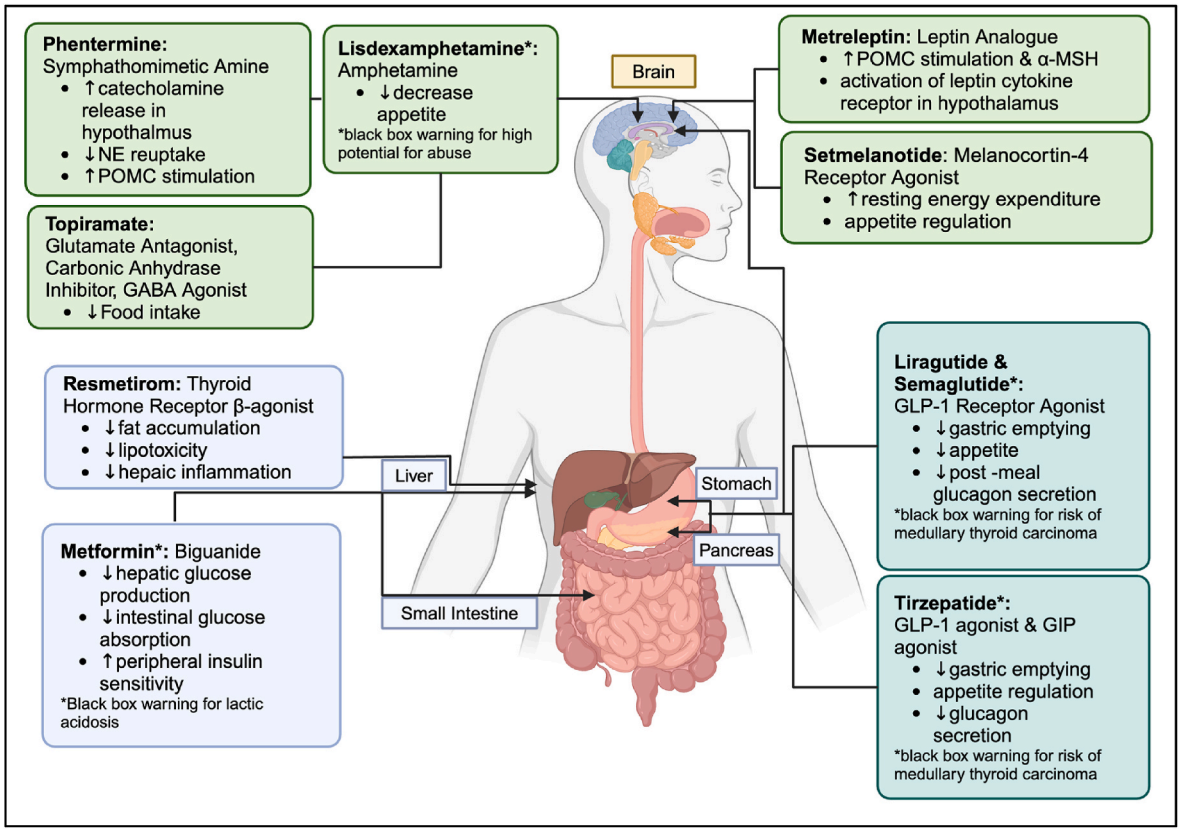


**Fig. 3.** Mechanisms of action for key pharmacological agents in the management of obesity and metabolic dysfunction. Created in BioRender. Ramirez, c. (2025) https://BioRender.com/b07w012.

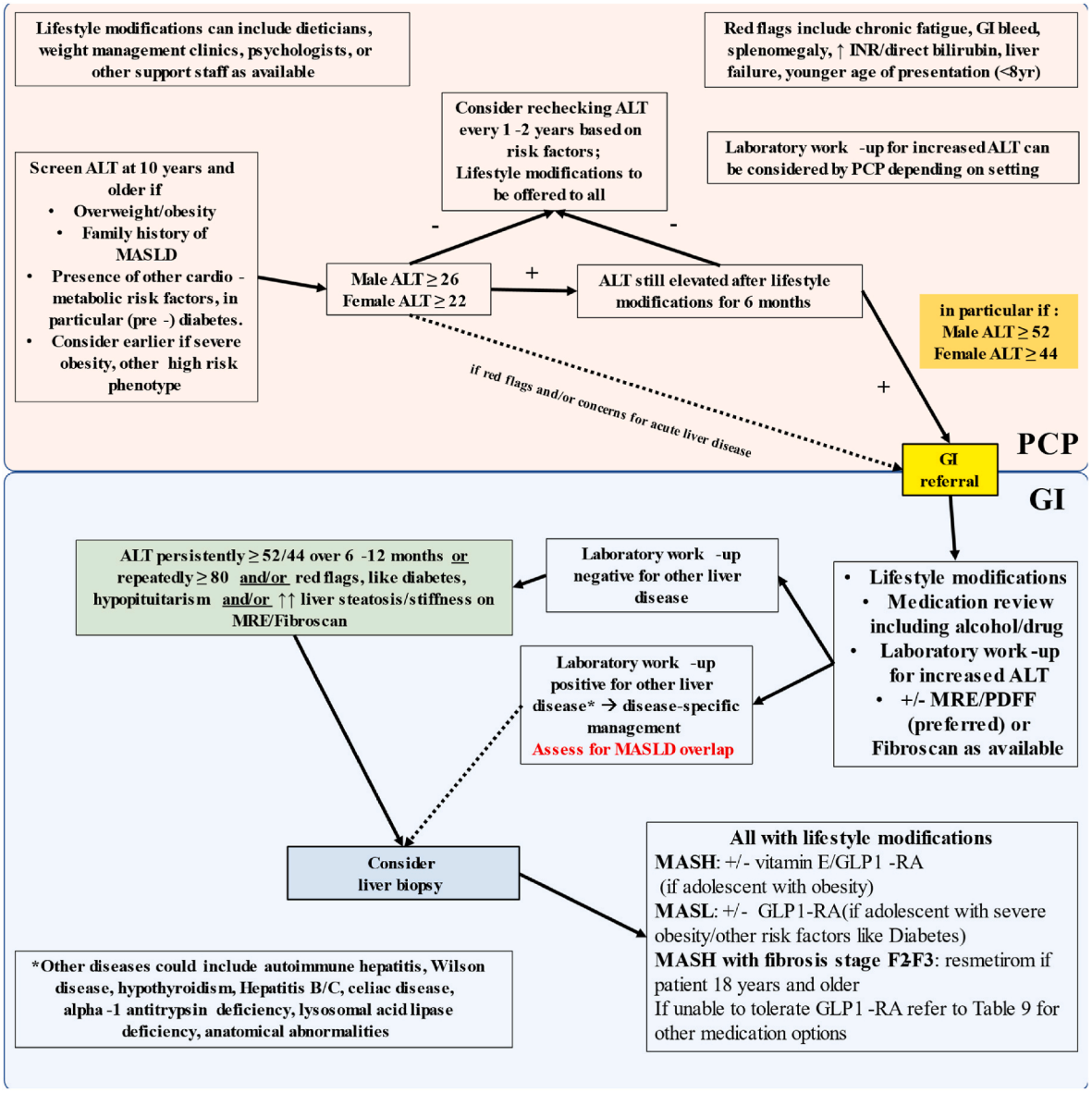


**Fig. 4.** Algorithm for the screening, evaluation, and management of pediatric MASLD

### *9.2. What are the implications of mediation discontinuation, contraindications, emerging long-term safety, and efficacy data?*

#### *9.2.1. Implications for practice (of medication discontinuation)*

Challenges associated with GLP-1RAs include their administration via injection, high cost, and frequent shortages due to high demand. Discontinuation of GLP-1RAs in patients with metabolic syndrome can have significant implications including weight regain, worsening glycemic control and increased cardiovascular risks, and can lead to potential withdrawal symptoms. GLP-1 agonist discontinuation prevalence reached 36.5 % at a year [170]. Higher odds of discontinuation were reported in patients who were Black or Hispanic, male, Medicare, or Medicaid enrollees; lived in neighborhood with social deprivation; had obesity only versus diabetes, had cardiovascular disease at baseline and new gastrointestinal adverse effects at follow-up [170].

Weight regains upon discontinuation of GLP-1RAs remain the major limitation. In the STEP 1 trial extension, 327 participants were assessed for one year after discontinuing semaglutide 2.4 mg and lifestyle intervention. During the 68-week treatment phase, semaglutide led to an average weight reduction of 17.3 %, compared to 2.0 % with placebo. Following treatment withdrawal, semaglutide participant's regained two-thirds of their prior weight reduction, with net losses of 5.6 % at week 120 compared to baseline with similar changes in cardiometabolic variables (lipid levels, glycemic control, blood pressure and inflammatory markers) [171]. Likewise, among adults with overweight or obesity who completed a 20-week run-in period with subcutaneous semaglutide, 2.4 mg once weekly, maintaining treatment with semaglutide resulted in reduction of mean body weight of 7.9 %, while switching to placebo resulted in increased body weight of 6.9 % over the following 48 weeks [172]. These implications underscore the importance of establishing a long-treatment plan to sustain weight reduction and the associated metabolic benefits.

#### *9.2.2. Contraindications*

GLP-1 RAs are contraindicated in several clinical scenarios, including primarily a history of serious hypersensitivity reaction to the drug. These medications are contraindicated in patients with personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2), due to association with thyroid C-cell tumors in animal studies [173–176]. Patients' education about these

risks and discontinuation of the drug if concerning symptoms for thyroid carcinoma (neck mass, hoarseness of the voice, difficulty swallowing or breathing) develop is mandatory. Caution is advised when prescribing liraglutide and semaglutide in patients with history of pancreatitis, severe renal impairment or ESRD, clinically significant gastroparesis, and prior gastric surgery due to potential delayed gastric emptying [138,173–175]. These contraindications and cautions are essential for ensuring patient safety and optimizing therapeutic outcomes.

Liraglutide is contraindicated in pregnancy due to fetal defects shown in animal studies. Likewise, semaglutide should be discontinued if pregnancy occurs [138]. We recommended counseling and that all female patients use contraception to prevent unintended pregnancy while on GLP1-RAs [177].

#### 9.2.3. *Emerging long-term safety and efficacy data*

Although GLP-1 RAs long-term efficacy and safety in obesity and MASLD are still unclear, emerging data based on their use in type 2 diabetes are overall reassuring. Network meta-analysis in T2DM have shown no evidence of increased risk of digestive system cancers [178]. Furthermore, meta-analysis of cardiovascular outcomes trials in T2DM showed no evidence of significantly elevated risk of acute pancreatitis or pancreatic cancer [179]. Moreover, in a 10-year US retrospective cohort study in T2DM, exenatide did not increase the risk of thyroid cancer [180]. In a real-world retrospective cohort study, White et al. reported that patients with T2DM experienced a mean weight reduction of 2.2 % over 72 weeks after starting GLP-1RAs at standard glycemic control doses, underscoring the modest but significant weight reduction achievable in a clinical setting [181]. Moreover, Mirabelli et al. reported a mean weight reduction of 5 kg and a BMI decrement of 2 $kg/m^2$ in patients with T2DM after 5 years of Liraglutide treatment, supporting the durability of weight reduction with prolonged GLP-1RA therapy [182].

### 9.3. *How should side effects be monitored and managed?*

GLP1-RAs are very effective for weight reduction. Nevertheless, there are several risks associated with their use. Common adverse events with GLP-1RAs occurring in 30–60 % of patients include gastrointestinal symptoms especially nausea, vomiting, and diarrhea or constipation. These are generally transient and resolve within 1–2 weeks of titrating the dose [183]. Patients starting GLP-1RA therapy should be advised to reduce meal sizes, avoid large, fatty meals, and avoid lying down immediately after eating. Symptomatic treatments, including ondansetron, polyethylene glycol or other laxatives, and loperamide can also be considered on a short-term basis. Hypoglycemia is a risk of GLP-1RA treatment, particularly if given in conjunction with sulfonylureas or insulin. The dose of sulfonylurea or insulin should be reduced if hypoglycemia occurs. Increased resting heart rate, by approximately 6–10 beats per minute, is a side effect of long-acting GLP-1RAs and heart rate should be monitored, particularly in patients with underlying cardiovascular disease [175]. In addition, caution is advised in patients with severe renal impairment, or end-stage renal disease (ESRD), particularly for exenatide and lixisenatide.

While initially a concern, the rate of pancreatitis does not appear to be significantly increased by GLP-1RA based on a pooled analysis of 33,457 patients enrolled in cardiovascular outcome trials [184]. However, patients should be monitored clinically for pancreatitis, should pancreatitis occur, GLP-1RA should be stopped and not restarted due to risk of recurrence [185].

### 9.4. *Nutritional considerations with GLP-1RA use*

Other risks to consider with GLP1-RAs include micronutrient deficiencies, sarcopenia, and risk of developing eating disorders. Obesity is associated with a 5–12 % lower intake of vitamins A, C, D and E, calcium, magnesium, and potassium compared with normal weight, which might be further exacerbated with decreased food intake secondary to GLP1-RA use [186]. Screening for micronutrient deficiencies and a referral to a dietician should therefore be recommended. The risk of sarcopenia or muscle loss should be considered with GLP1-RA use. Weight reduction is associated with muscle loss in general, e.g. 14 % of fat-free mass loss – as a proxy for muscle loss – can be expected with low-calorie diets and 23 % with very low-calorie diets in adults [187,188]. The marked weight reduction with GLP1-RAs is associated with 25–39 % of fat-free mass loss [189]. Therefore, adequate protein intake and resistance training in addition to aerobic exercise should be recommended. Although GLP1-RAs have been successfully employed in small pilot studies of binge eating disorder and bulimia nervosa, concerns remain about those medications potentially triggering restrictive eating disorders [190,191]. While awaiting larger clinical trials, risks of disordered eating should be routinely discussed in clinic with patients before and during GLP1-RA therapy, with those who have achieved significant weight reduction. It is vital for our patients on GLP-1 RA therapy seen and followed by nutritionist/registered dieticians, to help assess risk for macro and micronutrient deficiencies, ensure safe and healthy weight reduction while screening for patients' high risk for eating disorders. Partnering with psychologists to help address adherence, barriers and high-risk behaviors is essential.

### 9.5. *Endoscopic and anesthesia considerations with GLP-1 RA use*

Some evidence shows that GLP1-RA use may be associated with increased risk of post-endoscopy aspiration pneumonia and should therefore be held for a few days before the procedure [192]. However, newer evidence indicates that although GLP1-RA use is associated with increased retention of gastric contents and more frequent aborted procedures during upper endoscopy, adverse event and aspiration rates do not appear different [193]. Thus, a more individualized approach for patients on GLP1-RAs should be considered. As gastric emptying delay due to GLP1-RAs lessens with time, 3 months of treatment and longer should likely not pose a higher risk of aspiration pneumonia. A strict liquid diet the day prior to the endoscopy may decrease the amount of gastric food remnants and hence risk of aspiration and may be more acceptable to most patients instead of holding a GLP1-RA [194]. The American Gastroenterological Association (AGA) also endorsed an individualized approach and recommended continued GLP1-RA use preoperatively in patients without elevated risk of delayed gastric emptying and aspiration, i.e. without marked nausea and vomiting or history of exacerbating conditions such as bowel dysmotility, gastroparesis, and Parkinson's disease. The AGA specifically suggests continuation of GLP1-RA use until the day or a week prior to the procedure for daily or weekly GLP1-RAs, respectively [195].

## 10. Question 8: should bariatric surgery be considered in patients with MASLD/MASH and obesity?

Metabolic bariatric surgery (MBS) is increasingly recommended for adults with a body mass index (BMI) $\geq$40 $kg/m^2$, regardless of comorbid conditions, or a BMI $\geq$35 $kg/m^2$ in the presence of metabolic T2DM, uncontrolled hypertension, or MASLD [6,196]. Studies show that MBS not only induces significant weight reduction but also improves various metabolic parameters, including remission of T2DM, reduction in cardiovascular risk, and a decrease in cancer risk [197,198].

Currently, bariatric surgery is recommended for adults with non-cirrhotic MASLD with approved indications, showing benefits in weight reduction, remission of adverse health consequences of obesity, and liver health improvement [6]. In adults with cirrhosis, MBS requires careful assessment by a multidisciplinary team [6]. MBS is increasingly accepted for severe pediatric obesity, provided it is managed by a dedicated team. Early intervention helps prevent adult obesity and associated organ damage, warranting timely referral to a multidisciplinary pediatric MBS program [199,200].

Bariatric surgery encompasses various procedures designed to aid weight reduction and improve weight related comorbidities. Table 10 provides a comparative overview of common bariatric surgeries. Fig. 5 shows the differences between two common bariatric procedures: Roux-en-Y gastric bypass (RYGB) and gastric sleeve (sleeve gastrectomy). The Roux-en-Y gastric bypass involves creating a small stomach pouch and rerouting a portion of the small intestine, which reduces both food intake and nutrient absorption. In contrast, the gastric sleeve procedure involves removing a significant portion of the stomach, resulting in a tubular structure that limits food intake and decreases hunger by reducing ghrelin secretion. These procedures are effective in achieving weight reduction and improving metabolic conditions but differ in their mechanisms and potential risks.

### 10.1. Review of adult data

In adults, multiple studies have demonstrated that bariatric surgery results in substantial improvements in MASLD and MASH. Bariatric surgery induces weight reduction and improves insulin sensitivity, both of which are essential in managing MASLD and MASH. Research indicates bariatric surgery can effectively reduce hepatic steatosis, inflammation, fibrosis, and even cirrhosis in patients with MASLD. A meta-analysis of 30 studies on MASLD involving 3134 patients demonstrated that bariatric surgery decreased intrahepatic fat by 72 % within six months, as measured via MRI-Proton density fat fraction (MRI-PDFF) and improved histological features of MASH, including reduction in inflammation and fibrosis [197,198]. Non-invasive tests (NITs) such as FIB-4, Fibroscan-AST (FAST), and liver stiffness measurements (LSM) have been validated as surrogate markers for tracking histological response after surgery, particularly in adults [6,196–198,201]. A notable study, the BRAVES trial, demonstrated histological improvement in MASH without worsening of fibrosis in 55 % of patients undergoing Roux-en-Y gastric bypass or sleeve gastrectomy after one year, compared to only 15 % in patients who undertook lifestyle modification alone [202].

The ARMMS-T2D study pooled data from four randomized trials to assess long-term outcomes of bariatric surgery ((Roux-en-Y gastric bypass, sleeve gastrectomy, or adjustable gastric banding) versus medical/lifestyle management in T2DM [203]. Among 262 participants (mean BMI 36.4 kg/m$^2$), bariatric surgery significantly improved glycemic control, with a 1.6 % reduction in HbA1c at 7 years compared to 0.2 % in the medical group ($P < 0.001$), and higher diabetes remission rates (18.2 % vs 6.2 %, $P = 0.02$) [203]. These benefits persisted at 12 years. While anemia, fractures, and gastrointestinal complications were more common in the surgical group, no differences in cardiovascular events or mortality were observed [203]. These findings highlight bariatric surgery's efficacy in long-term T2DM management despite some increased risks.

Bariatric surgery also reduces the risk of cardiovascular events, type 2 diabetes remission, and even cancer, all of which are weight related

**Table 10**
Comparison of different Bariatric techniques to achieve weight loss.

| Surgery Type | Mechanism of Action | Benefits | Risks/ Complications | Age Recommendations | Indications | Effectiveness (Weight Loss)[a] |
|---|---|---|---|---|---|---|
| **Roux-en-Y Gastric Bypass (RYGB)** | Creates a small stomach pouch and bypasses part of the small intestine, reducing calorie intake and absorption. Impacts appetite hormones like Ghrelin, GLP-1, and PYY. | Significant long-term weight loss; T2DM remission; improves MASLD and cardiovascular risk. | Nutrient deficiencies (iron, B12, calcium); dumping syndrome; surgical risks. | Adults and adolescents (BMI ≥35 with comorbidities). | Severe obesity (BMI ≥40), T2DM, obesity-related complications (e.g., hypertension, sleep apnea). | 25–35 % of total body weight in 1–2 years [1]. |
| **Sleeve Gastrectomy (SG)** | Removes approximately 80 % of the stomach, reducing food intake and hunger hormone (ghrelin) secretion. | Effective weight loss; simpler than RYGB; lower complication rates. | Irreversible; risk of GERD; potential nutrient deficiencies. | Adults and adolescents (BMI ≥35 with comorbidities). | Severe obesity (BMI ≥40), T2DM, GERD, or other obesity-related comorbidities. | 20–30 % of total body weight in 1–2 years [2]. |
| **Adjustable Gastric Banding (AGB)** | Inflatable band is placed around the upper stomach to create a small pouch, limiting food intake. | Reversible and adjustable; shorter recovery time. | Less effective weight loss; risk of band slippage or erosion; nausea/ vomiting. | Adults; limited use in adolescents due to suboptimal outcomes. | Moderate obesity (BMI ≥40), preference for reversible procedures. | 10–15 % of total body weight in 2–3 years [3]. |
| **Biliopancreatic Diversion with Duodenal Switch (BPD-DS)** | Combines sleeve gastrectomy with extensive intestinal bypass, significantly reducing calorie and nutrient absorption. | Greatest weight loss; effective for severe obesity; T2DM resolution. | High risk of nutrient deficiencies (protein, vitamins, minerals); complex surgery. | Adults; rare use in adolescents. | Severe obesity (BMI ≥50) with metabolic complications like T2DM, dyslipidemia. | 30–40 % of total body weight in 1–2 years [4]. |
| **Endoscopic Sleeve Gastroplasty (ESG)** | Endoscopic sutures reduce stomach size without surgical incisions. | Minimally invasive; reversible; moderate weight loss; improves MASLD and T2DM. | Limited long-term data; risks of bleeding or infection. | Adolescents (experimental); adults (BMI ≥30 with comorbidities). | Obesity (BMI ≥30–40), preference for minimally invasive procedures. | 10–15 % of total body weight in 1 year [5]. |
| **Intragastric Balloon (IGB)** | Saline- or gas-filled balloon is inserted into the stomach to promote satiety and reduce food intake. | Temporary; minimally invasive; short-term weight loss. | Nausea, vomiting, balloon rupture; limited to 6-month placement. | Adolescents (experimental); adults (BMI ≥30 with comorbidities). | Obesity (BMI ≥30–40), short-term weight loss for pre-surgical preparation. | 5–10 % of total body weight in 6 months [6]. |
| **Vertical Banded Gastroplasty (VBG)** | Stomach stapling reduces capacity; rarely used today due to advancements in other procedures. | No malabsorption; avoids intestinal rerouting. | High failure rate; frequent need for revision; outdated procedure. | Rarely recommended. | Historically for severe obesity, replaced by more effective procedures. | 10–20 % of total body weight in 1–2 years (Rarely used in pediatrics; outdated procedure). |

AGB: Adjustable Gastric Banding, AT: Aspiration Therapy, BPD-DS: Biliopancreatic Diversion with Duodenal Switch, ESG: Endoscopic Sleeve Gastroplasty, GERD: Gastroesophageal Reflux Disease, IGB: Intragastric Balloon, MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease RYGB: Roux-en-Y Gastric Bypass, SG: Sleeve Gastrectomy, T2DM: Type 2 Diabetes Mellitus, VBG: Vertical Banded Gastroplasty.

[a] *Effectiveness is based on average excess weight loss (EWL) or total body weight loss (TBWL) over the indicated time period. Outcomes can vary depending on adherence to lifestyle changes, dietary modifications, and follow-up care. Individualized care and a multidisciplinary approach are essential to optimize outcomes for each patient.*

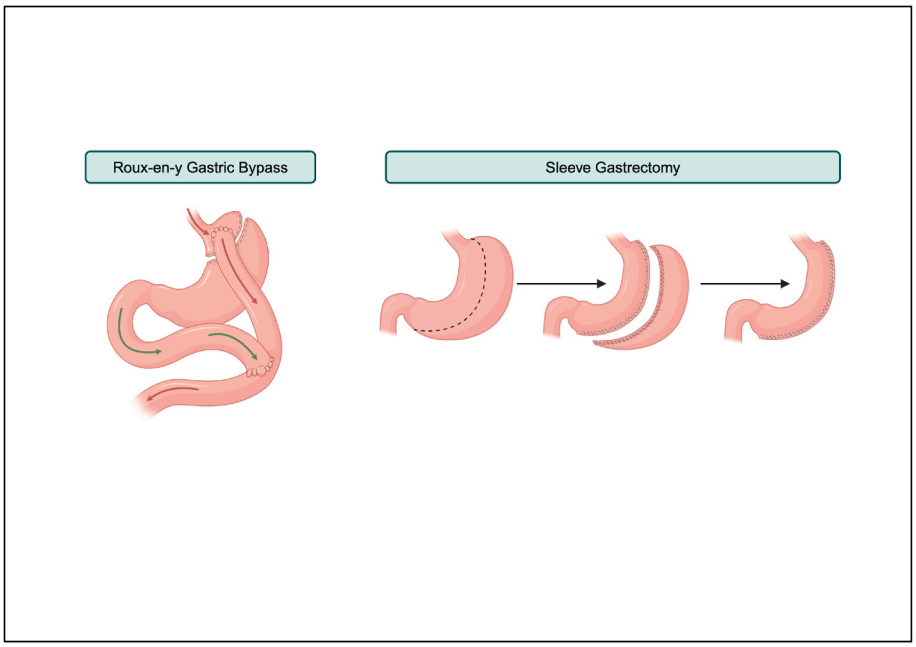


**Fig. 5.** Comparison of Roux-en-Y gastric bypass and sleeve gastrectomy procedures. Created in BioRender. Ramirez, c. (2025) https://BioRender.com/f29u469.

comorbidities in MASLD patients [6,196]. These findings position MBS as a promising intervention for MASLD and MASH, especially in early stages, by potentially halting or reversing liver damage and metabolic dysfunction [204].

### *10.2. Pediatric considerations*

In pediatrics, the American Academy of Pediatrics and the American Society for Metabolic and Bariatric Surgery (ASMBS) endorse MBS for children and adolescents with a BMI over 120 % of the 95th percentile and weight related comorbidities or a BMI over 140 % of the 95th percentile. [200]Studies like Teen-LABS have shown that MBS in adolescents leads to substantial and sustained weight reduction, often accompanied by the resolution of comorbid conditions, including improvements in MASLD and MASH. Over a three-year follow-up period, Teen-LABS demonstrated a 27 % reduction in weight and resolution rates of comorbid conditions, such as type 2 diabetes (95 %), hypertension (74 %), and dyslipidemia (66 %) [205]. Additionally, a 2022 follow-up study reported that MBS continued to be effective for 10–18 years post-surgery, with a sustained BMI reduction and improvement in liver health indicators [206].

The FABS-5+ study, with a follow-up period of 5–12 years, observed a sustained 29 % BMI reduction and improvement in cardiovascular risk factors post-RYGB [205]. Current data suggest early referral to MBS centers is beneficial, as early intervention can reduce the long-term risks associated with severe pediatric obesity [199].

### *10.3. Effectiveness of bariatric surgery in reducing liver fat and reversing fibrosis in children*

Bariatric surgery has shown promising results in reducing liver fat and reversing fibrosis in children with MASLD. Studies suggest that liver fat reduction and fibrosis improvement are achievable in pediatric patients, although specific data on the degree of fibrosis reversal are limited due to the relatively short follow-up periods in pediatric studies. The long-term FABS-5+ study, which followed adolescents post-RYGB for 5–12 years, reported sustained improvements in BMI and significant reductions in elevated blood pressure, dyslipidemia, and type 2 diabetes, all of which contribute to improved liver health [205].

In pediatric patients with genetic obesity, such as those carrying the PNPLA3 p.I148 M variant, bariatric surgery may yield greater liver fat reduction, as observed in a study showing more substantial improvements in liver fat content among PNPLA3-associated steatohepatitis patients compared to non-carriers [207]. Overall, while bariatric surgery shows promise in reducing liver fat and potentially reversing fibrosis in children, further long-term studies are needed to confirm its effectiveness, especially in advanced fibrosis cases.

### *10.4. Nutritional management in bariatric surgery: pre and post operative considerations*

Nutritional deficiencies are prevalent in bariatric surgery patients and require comprehensive evaluation and supplementation to optimize outcomes [208]. See Table 11 for suggested nutritional assessment and monitoring to prevent and address deficiencies in bariatric surgery patients.

## 11. Question 9: what is the cost-effectiveness and accessibility issues related to obesity pharmacotherapy and bariatric surgery for MASLD/MASH in children and adolescents?

The literature is sparse when it comes to studies on cost effectiveness in the treatment of children and adolescents with MASLD, with few studies specifically addressing cost effectiveness in this population for obesity management. In a study by Lim et al. on the use of AOM for the treatment of obesity in adolescents, top dose phentermine and topiramate as an adjunct to lifestyle counseling was estimated to be cost effective after 5 years [209]. Although semaglutide was associated with the most amount of quality-adjusted life years (QALYs), it was less cost effective than top dose phentermine and topiramate. In an economic evaluation of anti-obesity medications in adolescents with severe obesity using a microsimulation model, phentermine-topiramate was also found to be the most cost-effective treatment. However, there were several study limitations including only one year weight reduction effects for medications and a relatively higher representation of female and Caucasian participants in the studies analyzed. The authors highlighted that there is the need for more data on long-term weight reduction effects from more nationally representative samples to become available, to reassess the long-term cost-effectiveness of these drug therapies [210].

**Table 11**
Nutritional monitoring and supplementation in bariatric surgery.

| Phase | Assessment/Markers | Frequency | Supplementation |
|---|---|---|---|
| **Preoperative** | - Iron-related markers: Serum iron, ferritin, folate, TIBC<br>- Vitamins: Thiamine (B1), B12, A, and B6<br>- Bone health markers: Calcium, PTH, alkaline phosphatase, vitamin D, phosphorus<br>- Minerals: Magnesium and zinc | Baseline | – |
| **Postoperative Monitoring** | - Preoperative markers (except magnesium and zinc) | At 2 months | – |
| | - Full panel, including copper and selenium (for bypass/resection patients) | At 6 months and annually | – |
| | - Vitamin A (for malabsorptive procedures) | Closely monitored | – |
| **Postoperative Supplementation** | - Thiamine (B1): Preoperatively and 6 months postoperatively | Daily | Thiamine supplementation for 6 months |
| | - Vitamin B12: Sublingual or injectable forms | Daily | – |
| | - Multivitamin with Iron | Daily | To prevent common deficiencies |
| | - Calcium Citrate with Vitamin D | Daily | To support bone health |

B1: Thiamine, B12: Vitamin B12, PTH: Parathyroid Hormone, TIBC: Total Iron-Binding Capacity.

Weight reduction of at least 5 % of body weight has been associated with steatosis regression, 7 % loss with MASH resolution, and 10 % weight reduction or more associated with fibrosis regression in up to 80 % of adult patients studied [211,212]. If we assume that the weight reduction in adolescents associated with an improvement in MASLD is similar to the weight reduction associated with and improvement in MASLD in adults, then we could assume that this would translate to a 7–10 % decrease in percent of the 95th percentile of BMI. Given this, it is reasonable to conclude that treatment with top dose phentermine and topiramate, which is associated with a weight reduction of 11 %, would achieve an improvement in MASLD in adolescents. In a randomized, placebo-controlled trial of semaglutide treatment, 62 % of adolescent participants in the semaglutide group achieved a loss of body weight of at least 10 %, with 37 % of subjects achieving weight reduction of at least 20 % [138,156]. However, no studies of head-to-head trials on the treatment of MASLD with phentermine and topiramate vs semaglutide have been published, and there have been no clinical trials to date that have directly compared the anti-obesity medications in the adolescent population. Of note, in the cost effectiveness study by Lim et al. for-lifestyle counseling was found to be the most cost effective at a duration of 2 years of treatment [209]. It was not until the 5-year mark had been reached that pharmacotherapy was cost effective for any pharmacotherapeutic agent.

It is unfortunate that most of the studies done to date are not in the pediatric age group, and those studies that have been done are by pharmaceutical companies. More studies are needed focusing on unbiased assessments of head-to-head comparisons of intensive health and behavioral lifestyle therapy versus use of the AOM currently approved for obesity and including data on all co-morbidities, including MASLD.

Access to care for children and adolescents with MASLD is related to access to care for obesity in this population. Access to care for obesity remains extremely challenging for children at high risk for chronic disease, who also have the lowest amount of care delivered. In a study on Medicaid recipients, Jerrell found that black children with obesity had more diagnosed medical conditions but received less health care than non-black children [213]. Many studies have identified racial and ethnic minorities as being at highest risk for obesity and having higher rates of significant obesity complications such as diabetes and hypertension. Patients in resource constrained or low-income settings are often unable to access newer advanced therapies including anti-obesity medications such as GLP-1RA due to their high costs and insurance restrictions. These same populations face obstacles to receiving care including but not limited to challenges with transportation, lack of proximity to care, poor insurance coverage, food deserts and living in an environment not conducive to outdoor activity [214].

Improvement in weight status has been documented as an efficient strategy to improve MASLD. However, there remains a strong need for further research with diverse populations with advanced therapies specifically targeting obesity associated complications such as MASLD. It is vital to promote equitable access for high benefit populations with therapies providing durable long-term outcomes to prevent the development of irreversible hepatic changes in adulthood.

## 12. Conclusion

Pediatric MASLD is a rapidly growing public health concern, with its prevalence steadily increasing. Early identification is crucial, and while ALT remains a standard tool for screening, there is increasing interest in advanced imaging techniques such as MRI and the use of biomarkers. However, many biomarkers have yet to be validated specifically for pediatric use, underscoring the need for further studies to establish their reliability and relevance in children. Similarly, advanced imaging modalities, such as MRE, are showing promise and are expected to play an increasingly important role in the non-invasive assessment of MASLD in the pediatric population. Liver biopsy remains critical in cases of suspected advanced disease, to exclude other causes of steatosis, and when evaluating investigational treatments, which may differ significantly between adults and children. While diet, exercise, and psychological interventions form the cornerstone of therapy, these measures alone often fall short. The authors strongly advocate for the use of AOM, particularly GLP-1 receptor agonists, as adjunctive treatments for patients with obesity, T2DM, and MASH. In adults, therapies such as Resmetirom, an FDA-approved agent for non-cirrhotic MASH with moderate to advanced fibrosis, have been transformative, halting fibrosis progression and possibly will be improving survival outcomes. Extending such therapies to pediatrics through rigorous RCTs is a critical next step. Bariatric surgery remains a viable option for children with severe obesity and progressive MASLD, particularly when other interventions fail. However, systemic barriers such as limited access, surgeon comfort with pediatric cases, high costs, and inconsistent insurance coverage hinder widespread adoption of these effective treatments. Early intervention is a cost-effective strategy in theory, but additional studies are required to validate the long-term savings and metabolic benefits, which could pave the way for broader insurance support and improved access to care.

The clinical takeaways from this joint expert review:

- There is new nomenclature of steatoic liver disease that encompasses MASLD and MASH. MASLD has replaced the old terminology NAFLD and MASH has replaced the old terminology of NASH.
- The prevalence of MASLD is increasing in pediatrics and if untreated there will be more metabolic disease burden in adulthood.
- Adiposity and weight gain worsen MASLD, and improvements in this condition have been seen with weight reduction.

- Hepatic steatosis can be caused by other illnesses, alcohol, genetic diseases, nutritional deficiencies, medications, gut microbiota derangements, and endocrine disorders.
- It is important to rule out other medical conditions that cause steatosis and not assume it is related just to obesity.
- ALT remains a standard tool for screening, there is increasing interest in advanced imaging techniques such as MRI and the use of biomarkers. However, many biomarkers have yet to be validated specifically for pediatric use.
- Physical activity and nutrition is the primary treatment of MASLD and should always be continued even if other treatment modalities are employed. The plan should be tailored to the patient.
- The authors highly recommend the use of AOM to help with weight reduction, which will help improve MASLD.
- Bariatric surgery is a treatment option for patients with MASLD and obesity.
- Authors recommend early treatment to reduce the cost associated with worsening metabolic disease. Further studies are needed, however there is consensus with the authors that AOM started early may help reduce the cost of treatment of disease in the future.

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## Author disclosures

Mohit Kehar MD is a consultant for Mirum. Ibrahim Samar MD is a consultant for Mirum. Charina M. Ramirez MD is a consultant for Mirum, a consultant for Soleno Theraputics, and is on the board of directors for Global Foundation of Peroxisomal Disorders. Rohit Kohli MD is a consultant for Mirum, Ipsen, Sanofi Rare Disease Research Support, and he has grants from Epigen and Mirum. Erin Mauney MD has research funding from Tryp Therapeutics and Atai life Sciences. Suzanne Cuda MD is a speaker and consultant for Vivus Pharmaceuticals, as well as a speaker and member of the advisory panel for Rhythm Pharmaceuticals. Sara Karjoo MD is part of the speaker's bureau for Abbott, Nutricia, Mirum, and Ipsen.

## Data access statement

There was not any patient data accessed, and IRB approval was not indicated.

## Ethics review and peer review

This submission did not involve experimentation of human test subjects or volunteers. Authors who concomitantly served as journal Editors for Obesity Pillars or other journals were not involved in editorial decisions or the peer review process. Journal editorial decisions and peer review management was delegated to non-author society members or non-author journal Editors according to the policies of the OMA.

## Authors contributions

The coauthors agreed on initial questions to be answered. Each author engaged in writing original content, reviewing, and editing subsequent versions of the submission and all authors approved the final draft. MK and SK also contributed to the concept of the manuscript. JP led the revisions and made significant contributions to the manuscript. All authors certify that they take public responsibility for the contents of the manuscript. All authors approved the final draft submitted. SK approved the final manuscript submitted.

## Transparency and group composition

The authors reflect a multidisciplinary and balanced group of experts in obesity science, patient evaluation, and clinical treatment.

## Evidence

The content of this manuscript is supported by citations, which are listed in the references section.

## Conclusions and recommendations

This joint expert review is intended to be an educational tool that incorporates the current medical science and the clinical experiences of obesity specialists and those with expertise in hepatology. The intent is to better facilitate and improve the liver health and management of pediatric patients with obesity. This joint expert review should not be interpreted as "rules" and/or directives regarding the medical care of an individual patient. The decision regarding the optimal care of the patient with pre-obesity and obesity is best reliant upon a patient-centered approach, managed by the clinician tasked with directing an individual treatment plan that is in the best interest of the individual patient.

## Updating

This joint expert review may require future updates. The timing of such an update will be determined by the respective societies authoring this document.

## Disclaimer and limitations

This joint expert review was developed to assist health care professionals in providing care for patients with pre-obesity and obesity based upon the best available evidence. In areas regarding inconclusive or insufficient scientific evidence, the authors used their professional judgment. This joint expert review is intended to represent the state of obesity medicine at the time of publication. Thus, this joint expert review is not a substitute for maintaining awareness of emerging new science. Finally, decisions by clinicians and healthcare professionals to apply the principles in this joint perspective are best made by considering local resources, individual patient circumstances, patient agreement, and knowledge of federal, state, and local laws and guidance.

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