Practice Recommendations for Metabolic Dysfunction–Associated Steatotic Liver Disease by the Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition (ISPGHAN)

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ABSTRACT

Justification: There has been an alarming increase in metabolic dysfunction-associated steatotic liver disease (MASLD) and it is now the most common chronic liver disease worldwide, in both adult and pediatric populations. The lack of regional guidelines has hampered the formulation of national policies for prevention and management of MASLD in children. Therefore, we formulated recommendations for steatotic liver disease in children.

Objectives: To review the existing literature on the burden and epidemiology of pediatric MASLD and formulate recommendations for diagnostic evaluation, prevention, and management strategies.

Process: The Indian Society of Pediatric Gastroenterology, Hepatology, and Nutrition invited national and international stakeholders to participate in a consensus meeting held on April 20, 2024, in Mumbai, Maharashtra, India. Various aspects of pediatric steatotic liver disease were deliberated upon and a consensus document and recommendations were formulated after several rounds of discussion.

Recommendations: Metabolic dysfunction associated steatotic liver disease (MASLD) should be used as the preferred term in place of non-alcoholic fatty liver disease (NAFLD). There is a high prevalence of steatotic liver disease (SLD) among Indian children and adolescents, especially those who are overweight or obese. This condition may be progressive in childhood and associated with increased morbidity and mortality in adulthood. Various lifestyle, dietary, and genetic factors may predispose individuals to MASLD, including an increased intake of calorie-dense processed foods, sweetened sugar beverages, excessive screen time, higher sedentary time and lack of moderate to vigorous

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physical activity. MASLD is usually asymptomatic or presents with mild, non-specific symptoms and therefore, a high degree of suspicion is required for early diagnosis. MASLD is usually associated with cardiometabolic factors (hypertension, insulin resistance/diabetes mellitus, and/or dyslipidemia) and secondary causes should be excluded in all cases, particularly in the presence of red flag signs. Screening for MASLD should be considered in all obese children (body mass index or BMI $\geq 95^{th}$ percentile) and in all overweight children (BMI $\geq 85^{th}$ and $<95^{th}$percentile) with additional risk factors, such as prediabetes/diabetes, dyslipidemia, positive family history of metabolic syndrome, obstructive sleep apnea, and hypopituitarism. Abdominal ultrasound in combination with alanine aminotransferase (ALT) levels should be used as a screening test for MASLD in Indian children as per the proposed algorithm. Diet (any hypocaloric diet) and exercise (aerobic, resistance, or a combination of both; moderate to high intensity; regular in frequency) remain the cornerstones of pediatric MASLD management. Pharmacotherapy and/or endoscopic/surgical techniques for obesity should be considered as adjuncts and should be considered only after a failed adequate trial of lifestyle modifications.

Keywords: *Children, Fatty liver disease, MASLD, Non-alcoholic fatty liver disease (NAFLD), Nutrition, Obesity*

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INTRODUCTION

There is an ongoing epidemic of non-alcoholic fatty liver disease (NAFLD) in Indian children and adolescents. As highlighted in a recent national news column, around 35% of Indian children currently have fatty liver disease, with similar upsurges being reported across India [1-3]. With the associated sinister implications, such as early onset diabetes, hypertension, other cardiometabolic disorders, advanced liver disease, and adult-onset cancers, it is important to draw the attention of policymakers towards this increasing menace.

A consensus meeting was planned by the Indian Society of Pediatric Gastroenterology Hepatology and Nutrition (ISPGHAN) wherein international and national experts were invited to develop recommendations for the prevention and treatment of NAFLD. Questions were identified by a subgroup of experts and allotted to individual experts to review in context of already published literature. The literature search, quality of evidence (QOE), and grade of recommendation for each question were reviewed by a subgroup of experts based on the guidelines of the American Academy of Pediatrics [4]. A meeting was held on April 20, 2024, in Mumbai, India, to discuss the consensus statements, recommendations, and guidelines. The clinical practice guidelines were finalized by discussion and a consensus was arrived.

1. New Nomenclature

The controversies in the original term 'NAFLD' were the use of stigmatizing terms like 'fatty' and 'non-alcoholic', failure to describe underlying pathophysiology i.e., metabolic dysfunction due to insulin resistance, and lack of positive and universally acceptable diagnostic criteria for diagnosis. Recently, there has been a global effort to adopt a more universal term and two new terms were adopted; metabolic (dysfunction)-associated fatty liver disease (MAFLD) in the year 2020-21 followed by metabolic dysfunction–associated steatotic liver disease (MASLD) in 2023 were proposed to replace NAFLD [5-7]. Although the superiority of one term over the other is questioned, majority of international societies (including the pediatric ones) have recently endorsed MASLD as the preferred nomenclature (**Fig. 1**) [8]. The present group endorsed MASLD as the preferred term to replace NAFLD. In this document, we replaced the term MASLD for all mentions of NAFLD, except when referring to the original studies.

Recommendation

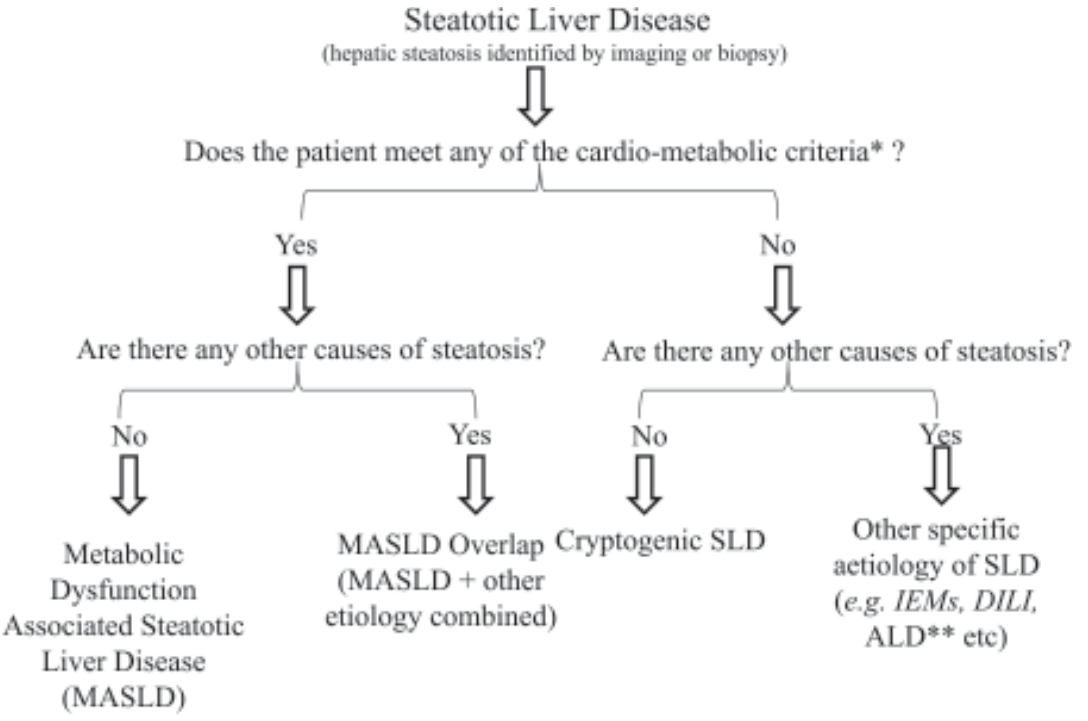
- *Metabolic dysfunction-associated steatotic liver disease (MASLD) should be used as the preferred term in place of non-alcoholic fatty liver disease (NAFLD) (QOE D, Recommendation: Moderate).*

2. Indian and Global Prevalence of Fatty Liver Disease in Children

Currently, MASLD is the most common chronic liver disease in the developed world, both in adults and children. Globally, the prevalence of NAFLD in children and adolescents has increased from 19.34 million in 1990 to 29.49 million in 2017, representing an annual increase of 1.35% independent of sex, age, and region [9]. The prevalence of pediatric MASLD in India varies from 2.5 % to 22.4% in the healthy normal weight populations [10-12]. According to a recent systematic review and meta-analysis among children (n = 2903), the estimated overall pooled prevalence of MASLD was 35.4% (95% CI 18.2, 54.7), whereas the prevalence among non-obese and obese children was 12.4 (95% CI 4.4, 23.5) and 63.4 (95% CI 59.4, 67.3), respectively [2]. This upsurge of MASLD is in parallel to the increase in childhood obesity as shown in a recent meta-analysis where the pooled data of 52 Indian studies revealed that the combined prevalence of overweight and obesity has increased from 16.3% (2001-2005) to 19.3% (after 2010) [13].

Recommendation

- *The prevalence of steatotic liver disease in Indian children and adolescents is high, even in those with*



*Pediatric Cardio-metabolic Criteria

At least 1 out of 5:

1. BMI =85th percentile for age/sex [BMI z score =+1] OR WC >95th percentile OR ethnicity adjusted equivalent
2. Fasting serum glucose =5.6 mmol/L [=100 mg/dl] OR serum glucose =11.1 mmol/L [=200 mg/dl] OR 2-hour post-load glucose levels =7.8 mmol [140 mg/dl] OR HbA1c =5.7% [39 mmol/L] OR already diagnosed/treated type 2 diabetes OR treatment for type 2 diabetes
3. Blood pressure age <13 yr, BP =95th percentile OR =130/80 mmHg (whichever is lower); age =13 yr, 130/85 mmHg OR specific antihypertensive drug treatment
4. Plasma triglycerides age <10 yr, =1.15 mmol/L [=100 mg/dl]; age =10 yr, =1.70 mmol/L [=150 mg/dl] OR lipid lowering treatment
5. Plasma HDL-cholesterol =1.0 mmol/L [=40 mg/dl] OR lipid lowering treatment

Fig. 1 Diagnostic Criteria for Metabolic dysfunction–associated steatotic liver disease (MASLD)

In the presence of hepatic steatosis, the finding of any one of the five cardio-metabolic risk criteria allows for a diagnosis of MASLD if there are no other causes of hepatic steatosis.
If additional drivers of steatosis are identified, then this is consistent with a combination etiology.
ALD Alcohol-associated/related liver disease, BMI Body mass index BP Blood pressure, DILI Drug induced liver disease, SLD Steatotic liver disease, WC Waist circumference
** *Seek history of drug intake, alcohol intake (especially in adolescents) etc*

normal body mass index (QOE B, Recommendation: Strong).

- *Overweight and obese Indian children are at a greater risk of steatotic liver disease (QOE B, Recommendation: Strong).*

3. Natural History of Pediatric MASLD

There are only a limited number of longitudinal studies on pediatric MASLD (**Web Table I**). In a single center study on eighteen biopsy-confirmed NAFLD children (mean age 13.4 years) who were re-biopsied 2 years later, 39%

patients had progression of fibrosis [14]. As per the two recent multi-center randomized pediatric clinical trials conducted by the NASH Clinical Research Network (n = 122), after a mean follow-up period of 1.8 years, NASH and/or fibrosis progressed in 36% [15]. A nationwide matched cohort study in Sweden showed a 5.88 higher overall mortality rate in patients with NAFLD due to cancer, liver disease, and cardiometabolic diseases [16]. A recent study involving the follow-up of 51 severely obese children with NAFLD demonstrated that after a mean follow-up of 10 years, one-third of young adults who had childhood obesity developed steatosis, 6% each had developed advanced fibrosis and type 2 diabetes mellitus (DM) at follow-up, and 35% developed dyslipidemia [17].

Recommendation

- *Steatotic liver disease in children may progress and is associated with increased morbidity and mortality in adulthood due to liver disease, cancer and cardio-metabolic diseases (QOE B, Recommendation: Strong).*

4. Risk Factors for Pediatric MASLD

(i) Dietary and Lifestyle factors

A tremendous increase in fast-food intake has translated into a high prevalence of obesity, insulin resistance, type-2 DM and MASLD [18-20]. There is an association between night eating behavior and MASLD, which is possibly linked to physiological maladaptation to chronic abnormal sleep and eating patterns and habits [21]. In addition, a faster rate of food ingestion and larger meal portions lead to excess food and energy intake, lower satiety, and lower water consumption [22-24]. Fructose intake in the form of sugar-sweetened beverages leads to excessive fat accumulation [25], with each additional serving of sugar-sweetened beverage per day being associated with an increased risk of MASLD [26,27]. Whole-grain and cereal fiber intake is protective against the development of cardiovascular disease, type-2 DM, obesity, and MASLD (**Web Table II**) [28-30].

A recent systematic review of six studies showed a potential association between MASLD and snacking habits and lack of physical activity [31]. The absence of sedentary time in the presence of moderate-to-vigorous physical activity is the best behavioral pattern for better hepatic health [32-35]. Excessive screen time is indirectly linked to the development of metabolic syndrome by increasing the consumption of energy-dense micro-nutrient-poor foods and affecting sleep duration and quality [36, 37]. Obstructive sleep apnea leading to poor sleep quality is associated with dyslipidemia, elevated transaminase levels, and insulin resistance [38-40] (**Web Table III**).

Higher pre-pregnancy maternal weight was associated with an increased risk of MASLD in adolescents, whereas breastfeeding had a negative association with MASLD. There is conflicting evidence regarding the association between gestational diabetes, birth weight, preterm birth, and MASLD [41]. Active or passive smoking from childhood to adulthood was also associated with MASLD [42] (**Web Table III**).

(ii) Genetic Risk Factors

Several genetic polymorphisms have been identified as risk factors for pediatric MASLD. The most significant variants are patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene variant rs738409 C > G and the E167K variant of the transmembrane 6 superfamily member 2 (TM6SF2) gene, which are associated with an increased hepatic triglyceride content and MASLD risk [43-50]. Similar findings have been observed for variations in other genes, such as membrane-bound O-acyltransferase domain-containing 7 (MBOAT7), glucokinase regulator **(**GCKR), and hydroxyl steroid 17-beta dehydrogenase 13 (HSD17B13, associated with increased steatosis but decreased inflammation) amongst others [51-53] (**Web Table IV**). Familial clustering for MASLD has been observed in both adult and pediatric studies [47, 54-57]. Schwimmer et al found that 17% siblings and 37% parents of children in USA with MASLD were suffering from MASLD [54]. In Indian children, Sood et al showed that a family history of fatty liver disease (in any parent), higher serum alanine transaminase (*ALT*) levels, and higher total cholesterol levels may independently predict the presence of fatty liver [47].

Recommendations

- *Fructose intake, in the form of sweetened sugar beverages, increases body mass index in children and adolescents (QOE A, Recommendation: Strong).*
- *Intake of calorie dense and processed foods and in larger portions leads to increased energy intake in children and adolescents (QOE B, Recommendation: Strong).*
- *Excessive screen usage, and lack of moderate to vigorous physical activity contribute to development of steatotic liver disease in children and adolescents (QOE B, Recommendation: Strong).*
- *PNPLA3 (rs738409 C > G, p.I148M) and TM6SF2 (rs5854292, E167K) gene variants are the major genetic risk factor for MASLD (QOE B, Recommendation: Strong)*

5. Clinical Presentation and Differential Diagnosis of Steatotic Liver Disease in Children

Pediatric fatty liver is a heterogeneous entity, mainly caused by two groups of diseases. The first is MASLD (steatotic liver disease associated with obesity and metabolic dysfunction) and the second is caused by various hepatic, intestinal, endocrine, and toxic factors. The third small "unexplained" group was not associated with the previous two conditions [58]. An algorithmic approach for steatotic liver disease is outlined in **Fig. 2**. There are some red flags that point towards the presence of secondary causes and warrant adequate evaluation (**Box 1**). Secondary (treatable) causes of fatty liver in children are depicted in **Table I** [59-61].

Children with MASLD are often asymptomatic and are diagnosed on screening due to obesity or other metabolic risk factors such as diabetes mellitus, hypertension, or dyslipidemia. These children may also present with mild abdominal discomfort, fatigue, weakness, or hepatomegaly. Acanthosis nigricans, menstrual irregularity, and a lack of concentration/daytime sleepiness secondary to obstructive sleep apnea may bring this condition into attention**.** The secondary causes are most often due to various liver-related inborn errors of metabolism. These can have a variable presentation, ranging from organomegaly, neonatal cholestasis, acute liver failure,

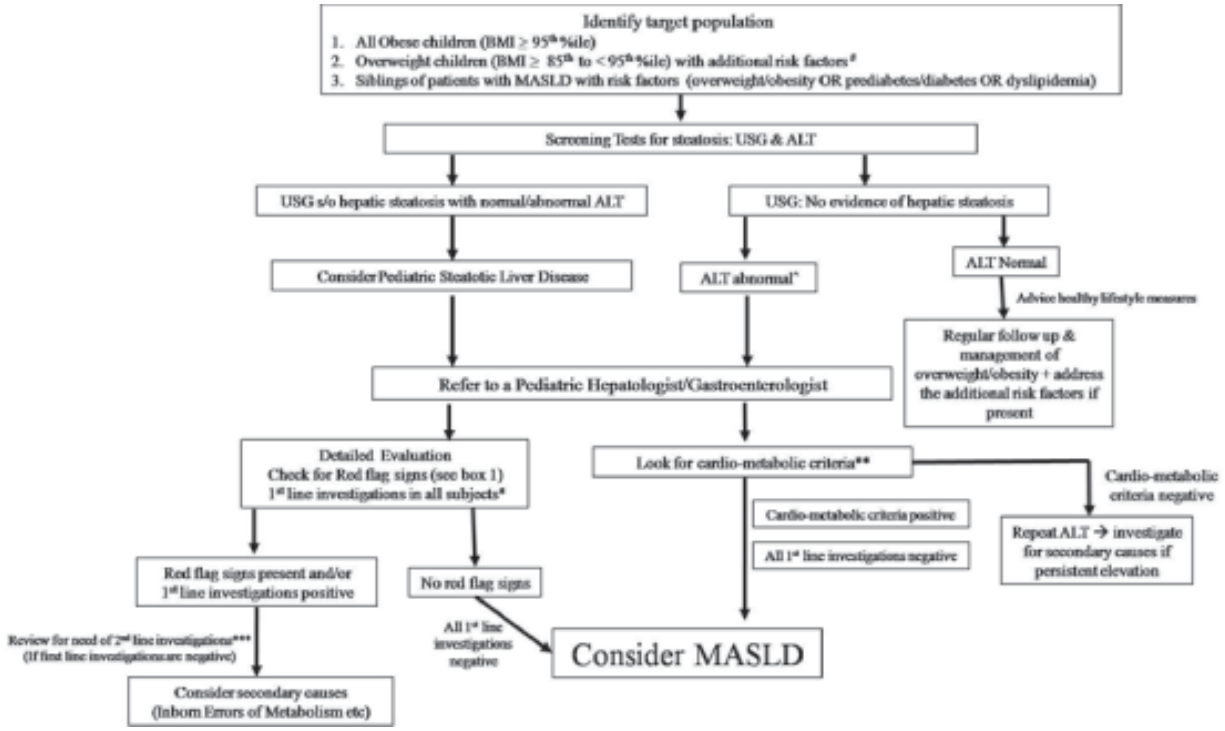


Fig. 2 Algorithmic approach to a pediatric patient with steatotic liver disease

*#**Additional risk factors:** Prediabetes/diabetes, dyslipidemia, hypertension, waist circumference greater than 70th percentile, positive family history of metabolic syndrome, obstructive sleep apnoea and hypopituitarism*

*^**Abnormal ALT:** defined as >2 times upper limit of normal (upper limit of normal for ALT is defined as per the SAFETY study cutoffs of 26 IU/L for males and 22 IU/L in females)*

***1st line investigations for steatosis:** Evaluate for autoimmune liver disease, Wilson disease, celiac disease, thyroid dysfunction, hepatitis B and C and review for history of drug induced liver injury or alcohol intake*

***Cardio-metabolic criteria:** at least one out of the following five criteria- 1) BMI = 85th percentile (or z score = 1) for age/gender OR Waist circumference > 95th percentile (OR ethnicity adjusted equivalent), 2) Fasting serum glucose = 100 mg/dl] OR serum glucose =200 mg/dl OR 2-hour post-load glucose levels = 140 mg/dl OR HbA1c =5.7% [39 mmol/L] OR already diagnosed/treated type 2 diabetes OR treatment for type 2 diabetes, 3) Blood pressure age <13 yr, BP = 95th percentile OR =130/80 mmHg (whichever is lower); age =13 yr, 130/85 mmHg OR specific antihypertensive drug treatment, 4) Plasma triglycerides age <10 yr, = 100 mg/dL]; age = 10 yr, =150 mg/dL OR lipid lowering treatment, and 5) Plasma HDL-cholesterol =40 mg/dL OR lipid lowering treatment*

****2nd line investigations for steatosis: To be undertaken only after consultation by a pediatric gastroenterologist/hepatologist- Liver biopsy, Transient elastography for controlled attenuation parameter, Magnetic resonance imaging proton density fat fraction; Investigations for specific inborn errors of metabolism, liver biopsy, exome sequencing etc*

***Abbreviations:** ALT: Alanine Transaminase, MASLD: Metabolic dysfunction associated with steatotic liver disease, USG: Ultrasonography*

Box 1. Red Flag Signs in a Child With Suspected Steatotic Liver Disease

1. Age less than 8 years
2. Not overweight or obese
3. Growth failure
4. Developmental delay
5. Syndromic features
6. Splenomegaly
7. Synthetic hepatic dysfunction or liver failure
8. Positive family history of liver disease
9. Associated multisystemic disease

and chronic liver disease.

Recommendations

- *MASLD is usually asymptomatic or presents with mild, non-specific symptoms (QOE C, Recommendation: Strong).*
- *Fatty liver associated with metabolic factors (obesity, hypertension, diabetes mellitus, and/or dyslipidemia) differs from fatty liver due to inborn errors of metabolism (IEM). However, MASLD and IEM can coexist (QOE B, Recommendation: Strong).*

6. Identifying At-Risk Population

Currently, there are no uniform international consensus guidelines for the identification of at-risk populations and screening for MASLD [61-65] (**Web Table V**). Children with obesity and associated metabolic derangement are at the highest risk of MASLD and should be screened irrespective of their age. Two studies from India have revealed an overwhelming prevalence of MASLD of approximately 45%-60% in urban obese children, making their screening an utmost priority [10,66]. Children with NAFLD have an increased prevalence of prediabetes and diabetes mellitus, with higher BMI being a consistent independent risk factor because of insulin resistance and visceral adiposity [67-69]. Waist circumference is a better indicator for visceral adiposity and 70th percentile cut-off may be better to screen for metabolic syndrome in Indian children [65]. This would pick up the children with early metabolic syndrome and help in educating parents to pre-emptively modify lifestyle which would only benefit the patient. Various cross-sectional studies have reported an

Table I Treatable Causes of Secondary Steatotic Liver Disease

- Liver diseases
  - o Galactosemia: *Dietary therapy*
  - o Hereditary Fructose Intolerance (HFI): *Dietary therapy*
  - o Cholesterol ester storage disease-Wolman: *Enzyme replacement (sebelipase alfa)*
  - o Glycogen storage disorders: *Dietary therapy*
  - o Urea Cycle disease: *Dietary therapy, medications to reduce ammonia*
  - o Cystic fibrosis: *Supportive therapy, pancreatic enzyme replacement*
  - o Tyrosinemia: *Nitisinone*
  - o Wilson disease: *Chelation (D-penicillamine, trientene), zinc*
  - o HCV genotype 3, HBV, HIV: *Antiviral drugs*
- Gastrointestinal
  - o Abetalipoproteinemia/ hypobetalipoproteinemia: *Low-fat diet, high-dose vitamin E, vitamin supplementation (A, D, E, K)*
  - o Celiac disease: *Gluten free diet*
  - o Inflammatory bowel disease: *Medications (5-aminosalicylic acid, steroids, thiopurine, biologics etc)*
  - o Short bowel syndrome: *Treat small intestinal bacterial overgrowth (SIBO) with antibiotics, supportive therapy*
- Endocrine
  - o Diabetes mellitus: *Oral hypoglycemic drugs/insulin*o Hypothyroidism: *Hormone substitution*
  - o Hypothalamic-pituitary dysfunction: *Hormone substitution*· Miscellaneous
  - o Shwachman-Diamond Syndrome (SDS): *Pancreatic enzyme replacement, HSCT (hematopoetic stem cell transplant)*
  - o Malnutrition/PEM: *Dietary therapy*
  - o Familial hyperlipidemia: *Statins for raised cholesterol, fenofibrate for raised triglycerides*
  - o Lipodystrophy: *Statins, fibrates, metformin, leptin replacement therapy*

As many of these conditions are complex entities and require expertise for management, patients should be referred to the relevant specialists including hepatologists, endocrinologists, hematologists etc. as per the diagnosis

increased prevalence of MASLD in obese adolescents with polycystic ovary syndrome (PCOS) in the presence of metabolic risk factors [70,71]. Other risk factors include obstructive sleep apnea, which leads to higher oxidative stress, and is associated with severe hepatic fibrosis in obese children with MASLD [72].

Recommendations

- *Screening for MASLD should be considered in all obese children (BMI > 95th percentile) and in all overweight children (BMI ≥ 85th and <95th) with additional risk factors– prediabetes/diabetes, dyslipidemia, waist circumference greater than 70th percentile, hypertension, positive family history of metabolic syndrome, obstructive sleep apnea, and hypopituitarism (QOE B; Recommendation: Strong).*
- *Consider screening of siblings of patients with MASLD in the presence of risk factors (overweight/obesity, prediabetes/diabetes, and/or dyslipidemia) (QOE C; Recommendation: Strong).*

7. Screening Laboratory Tests for Steatotic Liver Disease in Indian Children and Adolescents

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (*NASPGHAN*) recommends screening for ALT in all obese and overweight children with additional risk factors at 9-11 years of age [61], while the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (*ESPGHAN*) recommends ALT and ultrasound (USG) for all children and adolescents with obesity [63].

ALT and USG are easily available, feasible, and are the most commonly used tests; however, both have limitations when used as screening tests. The optimal cut-off value of ALT, as per the SAFETY (Screening ALT For Elevation in Today's Youth) study, is 26 IU/L for males and 22 IU/L for females in the age group of 12-18 years of age [73]. NASPGHAN considers twice the upper limit of the normal of this cut-off, that is, 52 IU/L for boys and 44 IU/L for girls, to be significant [61]. ALT levels are affected by infection, drug use and fasting duration as well as laboratory reference. In the absence of established Indian norms, the team of experts agreed that an ALT level greater than twice the upper limits of normal (which is defined as per the SAFETY study cut-offs) should be considered significant. USG findings which indicate steatosis are brighter liver than normal, hypoechoic renal parenchyma in contrast to liver, poor visibility of the intrahepatic vessels, liver parenchyma and diaphragm. The interpretation of USG findings is affected by various factors, including patient cooperation during the examination, fasting state, presence of abdominal obesity, and inter- and intra-observer variability. USG examination has been found to have a good sensitivity (>85%) and specificity (>87%) for moderate-to-severe steatosis (>33%) [74]. However, USG performs poorly in patients with mild steatosis (<33%).

Recommendation

- *Ultrasound abdomen along with ALT should be used as a screening test for MASLD in Indian children (QOE B, Recommendation: Strong).*

8. Radiological Assessment of Steatosis and Fibrosis in Children

Based on the liver stiffness measurement on transient elastography (TE), the overall prevalence of mild fibrosis, significant fibrosis, advanced fibrosis, and cirrhosis in pediatric patients with MASLD is up as 66.3%, 31.5%, 14.9%, and 1.2%, respectively [75]. Hence, radiological assessment of pediatric patients with steatotic liver disease should include the assessment of both steatosis and fibrosis. Further studies are required to determine the diagnostic accuracy of imaging modalities in assessing steatosis and fibrosis. As shown in **Web Table VI**, four meta-analyses have been conducted to answer this question. At least two meta-analyses have reported that the diagnostic accuracy for hepatic steatosis was best for magnetic resonance imaging–proton density fat fraction followed by TE-Controlled Attenuation Parameter (TE-CAP) [76,77]. As TE-CAP is a readily available, cheaper, and easy-to-use modality, it can be used for the assessment and monitoring of hepatic steatosis in children at a cut-off of > 236-240 db/m. Liver stiffness measurements performed using TE showed the best diagnostic performance for all grades of fibrosis [75,78]. Experienced pediatric hepatologists and gastroenterologists should interpret these tests.

Recommendations

- *Controlled Attenuated Parameter value on Transient Elastography is easy to perform in children, and can be used as the preferred non-invasive imaging technology for the diagnosis as well as monitoring of steatosis (QOE A, Recommendation: Strong).*
- *Liver stiffness measurement using transient elastography is a promising non-invasive tool for predicting liver fibrosis with good diagnostic accuracy in the management of pediatric MASLD. (QOE A, Recommendation: Strong).*

9. Role of Liver Biopsy

Liver biopsy is the gold standard for defining the presence and severity of steatotic liver diseases, including

inflammation and fibrosis. It may also help eliminate alternative and/or concurrent diagnoses and help in prognostication [61,63]. Limitations include the risk of sampling variability, inter- and intra-observer variations, invasive nature of the procedure, cost-effectiveness, lack of dedicated pediatric pathologists at many centers, and associated risks of procedure-related morbidity.

Recommendations

- *Liver biopsy in overweight/obese children with suspected MASLD is recommended:*

  In younger children < 8 years, and/ or

  If there is a high index of suspicion for advanced liver disease, and/or

  If an alternative diagnosis is considered.

- *Liver biopsy is recommended as a part of research studies or as per the individual institutional practice (QOE D, Recommendation: Strong).*

10. Diet for Weight Loss in Pediatric Fatty Liver Disease

Dietary changes and exercise are essential lifestyle interventions for the management of pediatric fatty liver disease. Adult data have shown that a hypocaloric diet (a daily decrease of 500-1,000 kcal) and weight reduction of at least (3%-5%) of body weight is required to ameliorate steatosis, but a higher weight loss (7%-10%) may be required to improve the majority of the histological characteristics of NASH.

The present evidence does not support a specific diet for MASLD treatment. The common diets investigated and available are low carbohydrate, low fat, low sugar and Mediterranean diets. Similar to the adult data, excess saturated fats, refined carbohydrates, and sugar-sweetened beverages have been associated with obesity and MASLD, and avoiding them improves hepatic steatosis. Two randomized controlled trials showed little change in hepatic steatosis after a low-fructose low-fat diet [79,80]. Other RCTs have shown that different diets (low-carbohydrate, low-glycemic load, and low-fat) can significantly reduce hepatic steatosis, fasting insulin, and ALT levels [81-84]. Poor adherence to the Mediterranean diet (MD) has been linked to more severe liver damage as well as higher levels of CRP and Insulin values, demonstrating that poor adherence had a higher propensity for inflammation [85]. In a recent study, hepatic steatosis, liver enzymes, and insulin resistance decreased with both MD and low-fat diets [86]. Another study showed that MD resulted in a greater reduction in insulin resistance than low-fat diet [87]. A recent Indian study in children with Indianized version of Mediterranean diet has shown superiority to calorie restricted diet in improving hepatic steatosis and weight loss [88]

Recommendations:

- *Any hypocaloric diet (low carbohydrate/low fat/low sugar) which focuses on weight loss may be considered (QOE A, Recommendation: Strong).*
- *Foods containing higher polyunsaturated and monounsaturated fatty acids are beneficial and may be considered within prescribed diet (QOE C, Recommendation: Weak).*
- *Processed/junk/high calorie foods, and sugar sweetened beverages should be avoided (QOE A, Recommendation: Strong).*

11. Exercise for Weight Loss

For health and wellbeing, the World Health Organization (WHO) recommends at least 150 to 300 minutes of moderate aerobic activity per week for all adults, and an average of 60 minutes of moderate aerobic physical activity per day for children and adolescents. Exercise is widely believed to improve MASLD because sedentary lifestyle, poor aerobic fitness, and low muscle mass are all risk factors for MASLD (**Web Table V**) [89]. Studies on exercise as a lone therapy for MASLD in children are limited and there are no studies on biopsy-proven MASLD. MASLD is closely related to obesity, and studies have suggested that exercise reduces the hepatic fat fraction [90]. However, this effect of exercise cannot be generalized to children with MASLD, who typically have liver fat fractions between 10 and 35% [89]. Aerobic exercise is helpful to improve circulation and to burn calories and, if done long enough, to also help burn fat stores. In resistance training, the goal is to strengthen muscles and hopefully build/maintain muscle mass. Aerobic exercise (AE) has beneficial effects on body composition, lipid profiles, blood pressure, glycemic control, and cardiorespiratory fitness [91]. Resistance exercise (RE) increases muscle mass, strength, endurance, and bone mineral density [92].

(*i*) *Aerobic Exercise (AE):* Three studies evaluated the effects of diet and physical activity interventions on MASLD [93-95]. The exercise (AE) group demonstrated a significant improvement in fatty liver indices compared to the other groups.

(*ii*) *Aerobic Exercise (AE) vs. Resistance Exercise (RE)*: Three studies investigated the effect of aerobic exercise (AE), resistance exercise (RE) versus controls in obese children and reported improvements in liver parameters in both exercise groups compared

to controls [96-98].

(*iii*) *Combined Aerobic Exercise + Resistance Exercise (AE+RE):*AE, RE, and their combination decrease abdominal subcutaneous fat. The combined AE + RE regimen resulted in decreased waist circumference and subcutaneous and visceral adipose tissues in overweight and obese adolescents. A meta-analysis [99] of 1231 children with 821 in exercise group vs. 410 in control group reported that exercise (both AE and RE) was associated with a significant reduction in subcutaneous and visceral adipose tissue, hepatic steatosis, and gamma-glutamyl transpeptidase (GGT) [100].

12. Role of Integrated Care Model Involving, Patient, Family Members, School and Community:

Studies have shown that school-based exercise programs (summer camps) in obese children are effective in reducing BMI, ALT, aspartate aminotransferase (AST), triglycerides, fasting insulin, and HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) [94]. A lifestyle intervention program based on an integrated care model that encourages patients and family members to adopt diet and exercise goals has resulted in good success rates [101]. Studies involving adult subjects with MASLD have reported the effectiveness of community-based lifestyle modification programs for normalizing liver fat levels. Based on these findings, it is ideal to advocate for all families of children with MASLD to participate in lifestyle intervention programs (exercise and dietary therapy) for weight loss. This may be a more successful strategy than child-centric solutions. In addition, it is equally important to consider school-based and community-based interventions for children for both prevention and treatment of MASLD. The preventive potential of this strategy is discussed in section 13.

Recommendations

- *Exercise (aerobic or resistance or a combination of both) is an effective measure for weight loss and reduction of intrahepatic fat content (QOE A/B, Recommendation: Strong).*
- *Moderate to high intensity exercise in 3–5 sessions for a total of 60 min/day is recommended for children and adolescents with MASLD (QOE B, Recommendation: Strong).*

13. Causes of Failure of Lifestyle Interventions

Lifestyle interventions are the first-line management of MASLD and obesity. However, it is well known that these measures are not uniformly effective and fail to achieve the desired effect in most children. Data on the causes of such failures are scarce, with most available studies being heterogeneous and with limited generalization. The most common causes and their remedial measures are listed in **Table II**.

14. Pharmacological Management of MASLD

These drugs broadly target oxidative stress, insulin resistance, dyslipidemia, and gut microbiota. However, drugs approved for children are limited (with no approved drugs specifically for MASLD), and most lack data on their long-term safety and efficacy (**Table III** and **Web Table VII**).

The most robust data are available for vitamin E, which has been shown to offer histological improvements in both adults and children with NASH [102,103]. Vitamin E also improves the transplant-free survival and lowers the rate of hepatic decompensation in adults [104]. Further studies are needed to determine the optimal duration of treatment and safety of prolonged therapy. Metformin increases insulin sensitivity and has been approved for use in diabetic children. However, they do not offer histological benefits to adults or children [105,106]. Randomized controlled trials in adults have shown that glucagon-like peptide-1 (GLP-1) analogs significantly improve NASH [107]. They have recently been approved by the Food and Drug Administration for long-term treatment of obesity in children aged ≥ 12 years. In a recent randomized controlled trial, semaglutide was shown to cause significant weight loss in adolescents with obesity as well as improvements in metabolic parameters and ALT levels [108]. Orlistat is a pancreatic lipase inhibitor approved as an anti-obesity drug for children aged > 12 years. According to a recent double-blind placebo-controlled RCT in 53 children with NAFLD, 12 weeks of orlistat therapy led to significant improvements in liver enzyme levels, steatosis score, NAFLD activity score, waist circumference, BMI *Z* score, glucose metabolism, and lipid profile [109]. Certain drugs show promising results in adults, but lack current pediatric data.

Recommendations

- *Pharmacotherapy for weight loss may be considered as an adjunct to lifestyle interventions and started only after a failed trial of life style modifications for 6 months (QOE C, Recommendation: Weak).*

15. Indications for Endoscopic and Surgical Management

Currently, surgical management and endoscopy-based treatments are alternative options, but should be considered in severe grades of obesity and only after

Table II Barriers to Success of Lifestyle Interventions and Proposed Remedial Measures

Operating level	*Causes*	*Remedial measures*
Individual/ Family level	• Poor general awareness of effects of ultra-processed and junk food. • Poor adherence to nutritional recommendations in spite of adequate knowledge. • Lack of parental support in maintaining diet. • Food delivery applications at relatively cheaper rates have led to increase consumption of outside food. • Less emphasis on sports and physical activities and more emphasis on studies. • Inability to implement the physical activity for practical reasons- weather, time, lack of facilities, etc. • Excess Screen/Mobile Time (lack of parental control, easy availability and social/peer pressures).	• Regular counselling at routine medical visits, educational programs & social media campaigns. • Using psychological techniques to improve adherence like motivational interviewing; family-based therapy; regular follow-ups with medical practitioners for continued motivation and trouble shooting. • Counselling the family about family-based therapy monitoring its effects and maintaining continued support. • Encouraging family habits like ordering food from outside only once in 30 days. • An average of 60 minutes of moderate aerobic physical activity per day for children and adolescents is recommended. • Creating tailor-made individualised programs that take the individual's daily routine, socio-economic status and other factors like accessibility into consideration. • Formulating family guidelines on screen time usage including screen-free zones, no screens at meal times, etc; monitoring screen usage, co-viewing and putting firewalls and privacy settings in place.
Health care provider	• Lacking the knowledge and skills for physical assessment and management. • Perceived resistance from parents. • Counselling advice: lack of time spent with ill-defined goals.	• Training of primary care providers in screening, evaluation and management through workshops, CMEs, training programs. • Appropriate referrals, dedicated obesity clinics with multidisciplinary personnel involvement.
School	• Lack of emphasis on healthy eating and regular physical activity. • Less emphasis on sports &physical activities and more emphasis on studies. • Lack of dedicated, regular and mandatory play-time in school. • Lack of playgrounds/ sports facilities. • Multitude of packaged snacks and junk food easily available near schools.	• Regular educational programs in schools and community for children and caregivers. • Keeping mandatory, supervised physical activity for 60 min each day. • Ensuring safe spaces and sports facilities in or near school premises. • Creating regulations along with the government regarding the kind of food items that can be sold inside school canteens and outside school premises.
Community	• Poor knowledge about healthy lifestyles. • Unreliable sources of information like online chats and social media. • Lack of collective responsibility to improve infrastructural and motivational factors.	• Regular community educational programs. • Community capacity building • Encouragement of the community to be more socially responsible.
Policy makers/ Government	• Unhealthy /junk foods are not clearly labelled/ mislabelled. • No advisories regarding the detrimental health effects are mentioned in the ads or on the covers of unhealthy foods. • Promotion of unhealthy foods through ads by role models in society (cricketers, movie stars etc). • Ultra-processed food like packaged snacks and beverages are cheaper and more easily available than healthier options like fresh fruits/vegetables. • Lack of playgrounds in school/ parks in the community. • Lack of dedicated cycling paths / footpaths near school to enable the child to walk or cycle to schools.	• Implementation of strict policies regarding labelling of packaged foods. • Creating regulations on advertising eg. playing them at off primetime hours and banning societal role models from promoting ultra-processed food; appealing to the role models to be more socially responsible. • Levy higher taxes on ultra-processed foods. • Enforcing mandatory, supervised physical activity in schools for 60 min each day. • Strengthening the infrastructure and ensuring safe open and closed spaces for physical activities for all strata of society.

Table III Drugs With Available Pediatric Data in MASLD/Obesity

Drug	*Recommendations by various societies (adult and pediatric)* [a]	*Dosage*	*Remarks*
Vitamin E	Recommended by AASLD, EASL and INASL in NASH without diabetes (adults); No recommendations in children	800 U daily PO (adults), 600-800 U daily PO (children and adolescents)	Risk of prostate cancer and hemorrhagic stroke in adults. Long term safety data not available.
Metformin	Not recommended for NASH in adults (AASLD 2023); Approved for type 2 diabetes in children above 10 years of age (ISPAD 2018); Not approved for treatment of obesity	Oral 500-1000 mg daily; maximal dose of 1000 mg BD or 850 mg TDS (adults and children)	No proven histological benefit in NASH
GLP-1 agonists	Recommended in adults with type 2 DM or obesity with concomitant NASH (AASLD 2023)		Gastrointestinal side effects like nausea, loss of appetite, constipation. Rare side-effects include gall stones and pancreatitis
Liraglutide	FDA approved for children >12 years with obesity	Adults: 1.8 mg SC daily (T2DM) 0.6-3 mg SC daily (obesity). Children: 3mg SC OD (obesity)	
Semaglutide	FDA approved for children >12 years with obesity	Adults: 0.4 mg SC daily, 0.25-2.4 mg SC weekly Adolescent: 2.4mg SC once weekly (obesity)	
Gastro-intestinal lipase inhibitor: Orlistat	Not recommended by any national/ international liver society; FDA approved for obesity in ≥12 y of age	120 mg PO TDS (adults and children)	Side effects include steatorrhea, abdominal cramps, flatulence, fat soluble vitamins deficiency

[a]*For details of the various recommendations of various international guidelines for MASLD/Obesity, please see Web Table V*
AASLD American Association for the Study of Liver Diseases, EASL European Association for the Study of the Liver, FDA Food and Drug Administration, GLP-1 Glucagon-like peptide 1, INASL Indian National Association for the Study of Liver, ISPAD International Society of Pediatric Diabetes, MASLD Metabolic dysfunction-associated steatotic liver disease, NASH Non-alcoholic steatohepatitis, OD Once daily, PO Per oral, SC subcutaneous, T@DM Type 2 diabetes mellitus, TDS Thrice daily

failure of an adequate trial of lifestyle modifications [110,111]. Severity of obesity is classified according to standard guidelines (Class 2 obesity: ≥ 120% to < 140% of 95th percentile or BMI ≥ 35 kg/m^2 to < 40kg/m^2 whichever is lower based on age and gender and, Class 3 obesity: ≥ 140% of the 95th percentile or BMI ≥ 40 kg/m^2 whichever is lower based on age and gender).

Many studies have suggested that metabolic and bariatric surgery (MBS), such as laparoscopic Roux-en-Y gastric bypass (RYGB), vertical sleeve gastrectomy (VSG), one-anastomosis gastric bypass (OAGB), and gastric band, are safe and effective and can fill the gap created by poor compliance to lifestyle modifications and the lack of universally acceptable pharmacological molecules. VSG is the most commonly used and recommended modality and has been proven to result in a significant reduction in BMI, improvement and/or complete resolution of elevated enzyme levels, steatosis, and NAFLD activity scores. It is contraindicated if there is a medically correctable cause of obesity, poorly controlled substance abuse, eating disorders, inability to adhere to recommendations, or mandatory lifestyle changes following MBS [112]. See **Web Table V** for summary of guidelines on the indications of metabolic bariatric surgery in MASLD. Endoscopic bariatric devices include intragastric balloons, sleeve gastroplasty devices, and gastric aspiration devices. Swallowable intragastric balloons have been reported to lead to a decrease in weight with minimal adverse effects [113]. Sleeve gastroplasty has also shown favorable outcomes, with sustained weight loss and complete remission of all obesity-related co morbidities without any severe adverse effects [114].

Recommendations

- *Indications for Surgery (QOE C, Recommendation: Weak)*

Children (> 12 years) who had a failure of an appropriate trial of intense lifestyle modifications and pharmacotherapy for at least 6 months and one of the following:

I. *Class 2 obesity with steatosis/steatohepatitis with significant comorbidities (type II diabetes mellitus, MASLD, obstructive sleep apnea, Blount disease, slipped capital femoral epiphyses, gastroesophageal reflux disease, idiopathic intracranial hypertension, dyslipidemia, hypertension, disease-associated depression, etc.*

II. *Class 3 obesity with steatosis/steatohepatitis with or without comorbidities*

- ***Indication for Endoscopic Therapies**: (QOE C, Recommendation: Weak)*

Same as above, when metabolic bariatric surgery is contraindicated, inaccessible, or unacceptable, or as a bridge when metabolic bariatric surgery is delayed

CONCLUSION

To conclude, it is important to correctly diagnose MASLD using uniformly used nomenclature and identify the at-risk population and severity of the disease. Ultrasound of the abdomen along with ALT should be used as a screening test, and transient elastography is required for monitoring MASLD in Indian children. Awareness about the disease should spread across various strata of the referral chain. A hypocaloric diet and exercise for weight loss are the mainstays of treatment for MASLD in children. Once identified, the disease should be followed by adequate education of the patient and family to ensure successful lifestyle modifications for the patient.

Abbreviations

AE Aerobic Exercise, ALD Alcohol-associated/related liver disease, ALT Alanine aminotransferase, BMI Body mass index, BP Blood pressure, DILI Drug induced liver disease, EBT Endoscopic bariatric therapy, *ESPGHAN* European Society for Paediatric Gastroenterology, Hepatology and Nutrition, GCKR Glucokinase regulator, HSD17B13 Hydroxysteroid 17-beta dehydrogenase 13, MAFLD Metabolic (dysfunction) associated fatty liver disease, MASLD Metabolic (dysfunction) associated steatotic liver disease, MBOAT7 Membrane-bound O-acyltransferase domain-containing 7, MBS Metabolic and bariatric surgery, MD Mediterranean diet, MetALD Metabolic dysfunction and alcohol associated steatotic liver disease, MLD Metabolic liver disease, MRI-PDFF Magnetic resonance imaging–proton density fat fraction, NAFLD Non-alcoholic fatty liver disease, NASH Non-alcoholic steatohepatitis, *NASPGHAN* North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, OAGB One-anastomosis gastric bypass, PCOS Polycystic ovary syndrome **(**PCOS), PNPLA3 Patatin-like phospholipase domain-containing protein 3, QOE Quality of evidence, RE Resistance Exercise, RYGB Roux-en-Y gastric bypass, SAFETY Screening ALT for elevation in today's youth, SLD Steatotic liver disease, TE-CAP Transient Elastography-Controlled Attenuation Parameter, TM6SF2 Transmembrane 6 superfamily member 2, USG Ultrasonography, VSG Vertical sleeve gastrectomy, WC Waist circumference

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Web Table I Studies on Natural History of NAFLD in Children

Authors, Type of Study	*Age (years)*	*Sample size*	*Duration of Follow-up*	*Intervention*	*Primary outcome measure*	*Summary of findings*
A-Kader et al [14], Retrospective	13.4 (4-18)	106 biopsy-proven; 18 had liver biopsy on follow-up	2.4 y		Biopsy	44% - no change in fibrosis, 39% - worsening of fibrosis, 17% - loss of fibrosis
Xanthakos et al [15], Follow-up of participants (placebo) of 2 DBRCT	13.3 (2.6); 8-17	122 biopsy-proven	1.8 (0.4) y	Standard of care lifestyle advice	Biopsy	20% - NASH resolved and fibrosis regressed, 52% - NASH resolved ± fibrosis regressed, 11% - NASH and fibrosis progressed, 36% - NASH ± fibrosis progressed, 5% - T2DM
Simon et al [16], Nationwide matched cohort	< 25y; 44% children	718 biopsy-proven	Median follow-up 15.8 y	None	Clinical outcome	Overall mortality risk 7.7% vs 1.1%; 5.7% higher in those with steatosis; 8.4% higher in those with NASH; Fibrotic and non-fibrotic NASH similar mortality; Increased mortality from cancer, cardiometabolic, liver causes
Draijer et al [17], Prospective	14 (2.2)	133 adolescents with severe obesity screened for NAFLD 51/133 follow-up	10 y (7-13 y)	Lifestyle intervention x 6 mo; 30% - bariatric surgery	Proton-magnetic resonance spectroscopy (1H-MRS), Enhanced Liver Fibrosis (ELF) test	47% - NAFLD at baseline; 33% - New steatosis; 13% - Worsening of steatosis; 30% - Steatosis resolved;16% - worsening in ELF; 6% - Advanced fibrosis; 6% - T2DM; 35% - dyslipidemia

LT Liver transplantation, NASH Non-alcoholic steatohepatitis, T2DM Type 2 diabetes mellitus

Web Table II Dietary Habits and Patterns Related to Overweight, Obesity and MA

Study	*Type of study*	*Participants*	*Inference*
Increase Portion size and fast foods			
Pereira et al [18]	Prospective	Young adults (18-30 y); *n* = 3031	Fast food intake associated with chan Changes in fast food frequency over l with changes in body weight and insu Restaurant visit >2 times/week associ weight and 2-fold increase in insulin
Piernas et al [19]	Result of 4 USA national surveys (1977-2006)	Children and Adolescents (2-18 y); *n* = 31,337	Intake of selected foods (sugar sweete snacks, desserts, French fries, burgers foods) increased in 2-6 years olds fro years olds from 21 to 35%, and in 13- 38% Adolescents most susceptible to incre Percentage of calories from pizzas hig groups, particularly with low househo
Bowman et al [20]	Results of two food surveys	Children and adolescents (≤ 19 y); *n* = 6212	Fast food intake 30.3% - Both gender all regions of country Controlling for socio-economic and d increased fast food consumption was gender, older age, higher household i blacks Fast food intake associated with intak (187 kcal), energy per g (0.29 kcal/g) (24g), sugars (26g), beverages (228g) fibre (1.1g), milk (65g), fruits and no
Smethers et al [22]	Cross-over randomized controlled trial	Children (3-5 y); *n* = 46	Increasing portion size by 50% increa (143±21 g/day) and energy intake (16 sustained over 5 days Children with higher weight status ha intake from larger portion meals
Night eating behaviour			
Bruzas et al [21]	Systematic review of 11 studies	Adults	Five studies showed positive associat syndrome with BMI, 5 did not and on Emotional eating and age moderated night eating and BMI.
Fast eating			
Otsuka et al [23]	Observational	Adults (*n* = 4742)	Based on self-reported categorical rat progressively increased from very slo medium, relatively fast and very fast women
Andradeet al [24]	RCT	Adult women (*n* = 30)	Slow rates of ingestion associated wit vs 579 kcal) and more water consump Satiety was lower with fast eating
Fructose intake			
Naomi et al [26]	Cross-sectional (Lifelines Cohort, NQPlus, PREDIMED-Plus, Alpha Omega Cohort)	Adults; *n* = 42024	Each additional serving of SSB per da increased risk of MASLD defined by Low/no calorie beverages also associa 1.38 for >2servings/week), while mod

Web Table III Life-style Factors Associated with Overweight, Obesity and MASLD

Study	*Type of study*	*Participants*	*Inference*
Sedentary life-style and moderate to vigorous physical activity			
Raj et al [31]	Systematic review	Adolescents; six studies	Prevalence of MASLD 8-16%. Majority of studies reported no association between lifestyle factors and MASLD Snacking habits and lack of physical activity potentially associated with MASLD
Schnermann et al [32]	Prospective observational (DONALD cohort)	Adolescents FU till early adulthood (18-30y); *n* = 240	Life style factors based on Food (≥ food groups/day), MVPA (≥ 60 min/day), Absence of sedentary behaviour (8.5-11 y: > 60 min/day, 12-16.5 y: > 120 min/day), Sleep duration (normal 8.5-12 y: 9-12 h/day, 13-16.5y: 8-10 h/day), normal BMI. There was an inverse association between Lifestyle factor score and hepatic steatotic index and fatty liver index, predominantly in men.
Julian et al [33]	Observational	Adolescents; *n* = 134	Divided into low vs high sedentary time (SED-, SED+), moderate to vigorous physical activity more or less (MVPA+, MVPA-). Liver health better with SED- vs SED+, and MVPA+ vs MVPA- after adjustment for age, gender and Tanner stages. SED-/MVPA+ had best hepatic health. SED time correlated with high ALT, low AST/ALT ratio, high liver fat content on magnetic resonance imaging independently of MVPA
Anderson et al [34]	Observational	Adolescents; *n* = 1292	Total physical activity (counts/min) and MVPA at 12-14 y associated with less risk of NAFLD at mean 18y 15 min increase in MVPA associated with reduced liver fat (OR = 0.47)
Medrano et al [35]	Observational	Obese / overweight children	High cardiorespiratory fitness on Alpha-fitness tests associated with lower %hepatic fat on magnetic resonance imaging, lower gamma glutamyl transpeptidase, and higher AST/ALT ratio. Fit children had lower gamma glutamyl transpeptidase, homeostasis model assessment for insulin resistance, triglycerides/high density lipoprotein ratio and higher AST/ALT ratio.
Screen time			
Sina et al [36]	Observational	Children and adolescents; *n* = 10359	Digital media exposure increased with age (2.2h/day at 2 y → 4.2h/day at 16 y) Increased media usage associated with Metabolic syndrome z-scores. Higher digital media had 30% higher risk of Metabolic syndrome (OR = 1.30). Boys had steeper digital media trajectories.
Perez-Farinos et al [37]	Observational ALADINO	Children and Adolescents; *n* = 9093	Higher screen time associated with consumption of energy-dense, micronutrient-poor foods, and less intake of fruits and vegetables. Sleeping sufficient hours associated with higher intake of fruits and vegetables.
Obstructive sleep apnea and Sleep quality			
Lei et al [38]	Observational	OSA (*n* = 241) vs Primary snoring (*n = 155)*	OSA patients had higher total cholesterol, triglycerides, low density lipoprotein and low density lipoprotein/high density lipoprotein ratio On Multivariate: Serum triglyceridescorrelated negatively with lowest oxygen saturation. BMI Z score positively influenced triglycerides
de Cuevillaset al [39]	Observational	Children overweight or obese (2-18y); *n* = 854	There was an inverse correlation between hepatic steatotic index (HIS) and sleep time, and positive association between HIS and SSB intake and screen time. 39% of the relationship of body fat distribution on hepatic steatotic index explainable by sleep time
Widjaja et al [40]	Observational	Obese adolescents with MetS	<8 y of sleep → Higher fasting insulin levels andhomeostasis model assessment for insulin resistance Sleep duration negatively correlated with homeostasis model assessment for insulin resistance
Maternal and perinatal factors			
Querter et al [41]	Systematic review	Children and adolescents; 33 studies (27853 participants)	Pre-pregnancy weight associated with increased risk of MASLD in adolescents (OR 2.29-2.97) Maternal BMI correlated with infant intrahepatic lipid content (more in obese mothers with diabetes) Breastfeeding reduced risk of MASLD Data was conflicting on association of gestational diabetes, birth weight or preterm birth and MASLD
Smoking			
Wu et al [42]	Prospective observational (31-year cohort)	Adults; *n* = 1315	MASLD in 16.3%. Relative risk of MASLD 1.41 (for childhood smoking) and 1.35 (for adulthood smoking) after adjusting for age, sex, childhood socio-economic status, adulthood physical activity and alcohol consumption in comparison to those without passive smoking in either childhood or adulthood. Persistent exposure throughout childhood to adulthood had highest risk (RR 1.99)

ALT Alanine aminotransferase, AST Asparate aminotransferase, BMI Body mass index, MASLD Metabolic dysfunction-associated steatotic liver disease, MetS Metabolic syndrome, MVPA Moderate-to-vigorous physical activity, OR Odds ratio, RR Relative risk, SED Sedentary

Web Table IV Genetic Risk Factors and Their Roles in The Pathogenesis of Fatty Liver Disease

Genetic variants	*Prevalence*	*Risk impact*	*Role in pathogenesis*	*Study*
PNPLA3 rs738409 C>G	149 children Age 6-13 years	Strongly associated with severity of steatosis ($P < 0.0001$), fibrosis ($P = 0.01$)	Increases hepatic fat content and fibrosis	Valenti et al [43]
TM6SF2 E167K	8% of obese children	Association with steatosis ($P < 0.0001$), higher ALT levels ($P < 0.001$)	Increases hepatic triglyceride content	Grandone et al [50]
MBOAT7 rs641738	31% of obese children	7% higher ALT level	Affects phosphatidylinositol acyl-chain remodelling	Viitasalo et al [51]
GCKR	frequency was 0.446 in Caucasians, 0.129 in African Americans and 0.355 in the Hispanics	Associated with 9 to 32% hepatic fat fraction	Lack of inhibition of glucokinase activity by fructose-6 -kinase and unrestrained lipogenesis	Santoro et al [52]
HSD17B13 rs72613567:TA	26% in the study cohort	30% decreased risk of LFT derangement in NASH	Associated with increased steatosis but decreased inflammation	Abul-Husn et al [53]

ALT Alanine aminotransferase, GCKR Glucokinase regulator, HSD17B13 17 Beta hydroxy steroid dehydrogenase 13, IFNL-4 Interferon Lambda 4, LFT Liver function tests, MBOAT7 rs641738 Membrane-bound O-acyltransferase domain-containing 7, MERTK Mer Tyrosine kinase, PNPLA3 Patatin-like phospholipase domain-containing protein 3, TM6SF2 E167K Transmembrane 6 superfamily member 2,

Web Table V Recommendations of Various International Guidelines for MASLD/Obesity

Society	*Population to be screened*	*Screening tests*	*Exercise*	*Indications of metabolic bariatric surgery*
ESPGHAN [63]	➢ No clear-cut screening recommendations ➢ At Risk population defined – Obese (>95th percentile) and overweight (sex- and age specific body mass index [BMI] >85th percentile), Hispanic origin, children from families with insulin resistance, obesity, type II DM and NAFLD, children with obstructive sleep apnea	ALT levels + USG abdomen	-	-
EASL-EASD-EASO [62]	➢ No clear-cut screening recommendations for pediatric age group ➢ Patients with insulin resistance or metabolic risk factors (obesity or metabolic syndrome) should be screened for NAFLD	USG Abdomen	Moderate-intensity AE in 3–5 sessions for a total of 150–200 min/week is generally preferred. RE is also effective and promotes musculoskeletal fitness, with effects on metabolic risk factors Diet and physical activity improve steatosis and hepatic inflammation in pediatric NAFLD, but no beneficial effects on fibrosis have ever been demonstrated.	In patients unresponsive to lifestyle changes and pharmacotherapy, bariatric surgery is an option for reducing weight and metabolic complications, with stable results in the long-term
NASPGHAN [61]	➢ Screening should be considered beginning between ages 9–11 years for all obese children (BMI ≥95th percentile) and for overweight children (BMI ≥85th and < 94th percentile) with additional risk factors (central adiposity, insulin resistance, pre-diabetes or diabetes, dyslipidemia, sleep apnea or family history of NAFLD/NASH). ➢ Earlier screening can be considered in younger patients with risk factors such as severe obesity, family history of NAFLD/NASH or hypopituitarism. ➢ Consider screening of siblings and parents of children with NAFLD if they have known risk factors for NAFLD (obesity, Hispanic ethnicity, insulin resistance, pre-diabetes, diabetes, dyslipidemia).	ALT levels	Moderate to high intensity physical activity and limiting screen time activities to < 2 hours per day is recommended for all children including those with NAFLD.	Bariatric surgery is not recommended as a specific therapy for NAFLD. It may be considered for selected adolescents with BMI ≥ 35 kg/m2, who have non-cirrhotic NAFLD and other serious comorbidities (e.g., T2DM, severe sleep apnea, idiopathic intracranial hypertension) that are likely to improve with weight loss surgery
AASLD [64]	➢ Higher risk of hepatic fibrosis in: o T2DM, o Medically complicated obesity o NAFLD in context of moderate alcohol use o First-degree relative of a patient with cirrhosis due to NAFLD/NASH ➢ Higher rates of NAFLD reported in patients with hypothyroidism, hypogonadism, growth hormone (GH) deficiency, and polycystic ovarian syndrome (PCOS).	Prefer TE-CAP and/or MRI PDFF for steatosis (USG not recommended)	Although the optimal duration and intensity of exercise need to be individualized, patients should be encouraged to exercise as much as possible	BMI ≥ 40 kg/m2 irrespective of metabolic comorbid disease or BMI ≥ 35 kg/m2 with comorbidities (T2DM or pre-DM, uncontrolled hypertension, osteoarthritis of hip or knee, urinary incontinence),
IAP Obesity guidelines [65]	Not applicable	Not applicable	Age-appropriate, moderate to vigorous physical activity for at least 60 minutes per day, should be recommended for the prevention of obesity in older children and adolescents (5-17 years) ➢ Infants, toddlers and preschoolers should be encouraged to remain active throughout the day through age-appropriate activities and play	Children (> 12 years old) who had a failure of an appropriate trial of intense lifestyle modifications and pharmacotherapy for at least 6 months and one of the following: 1. Class 2 (BMI> 35kg/m^2) obesity with significant comorbidities 2. Class 3 (BMI >40 kg/m^2) obesity with or without comorbidities

\SLD American Association for the Study of Liver Diseases, ALT Alanine aminotransferase, BMI Body mass index, ESPGHAN European Society for Pediat
ıstroenterology Hepatology and Nutrition, EASL European Association for the Study of the Liver, EASD European Association for the Study of Diabet
\SO European Association for the Study of Obesity, IAP Indian Academy of Pediatrics, MRI-PDFF Magnetic resonance imaging–proton density fat fracti
\FLD Non-alcoholic fatty liver disease, NASH Non-alcoholic steatohepatitis, NASPGHAN North American Society for Pediatric Gastroenterolo
epatology and Nutrition, T2DM Type II diabetes mellitus, TE-CAP Transient Elastography-Controlled Attenuation Parameter, USG Ultrasonography

Web Table VI Meta-analyses for Diagnostic Accuracy of Imaging Modalities for Hepatic Steatosis and Fibrosis.

Author	*Radiological modality*	*Number of Studies*	*Sample Size*	*Parameter MRI-PDFF Vs TE*	*Interpretation*
Gu et al [76]	Magnetic resonance imaging- Proton Density Fat Fraction (MRI-PDFF) and Transient Elastography-Controlled Attenuation Parameter (TE-CAP)	24	2979	MRI-PDFF: HSROCs: 0.97 for ≥S1, 0.91 for ≥S2 and 0.90 for ≥S3 TE-CAP: HSROCs: 0.85 for ≥S1, 0.83 for ≥S2 and 0.79 for ≥S3	MRI-PDFF and TE-CAP: both highly accurate for quantifying and staging hepatic steatosis
Jia et al [77]	Magnetic resonance imaging- Proton Density Fat Fraction (MRI-PDFF) and Transient Elastography-Controlled Attenuation Parameter (TE-CAP)	8	874	MRI-PDFF: S1–3 steatosis, with sensitivity of 0.95, specificity of 0.92, and HSROC of 0.96. TE-CAP: S1-3 steatosis sensitivity 0.86 specificity of 0.88, and HSROC of 0.94	MRI-PDFF and TE-CAP are both accurate but former is superior to latter.
Yu et al [78]	Magnetic resonance Elastography-hepatic fat fraction (mMRE-HFF) transient elastography (TE)	11	-	mMHRE-HFF: Highest sensitivity for steatosis (87%), TE: Irrespective of the grade of fibrosis: highest sensitivity (97-100%),	TE: Best diagnostic accuracy for significant fibrosis
Dong et al [75]	Liver stiffness measurement as a quantitative method for liver fibrosis in children	7	436	The sensitivity, specificity and AUROC values of LSM were 80, 92 and 0.94 for the prediction of mild fibrosis; 91, 97 and 0.98 for the prediction of significant fibrosis; and 89, 93 and 0.96 for the prediction of advanced fibrosis.	Liver stiffness measurement exhibited good diagnostic performance in predicting liver fibrosis

AUROC Area under the receiver operating characteristic curve, CAP Controlled Attenuation Parameter, HSROC Hierarchical summary receiver operating characteristic curves, LSM Liver stiffness measurement, MRE-HFF Magnetic resonance elastography-hepatic fat fraction, MRI-PDFF Magnetic resonance imaging-proton density fat fraction (MRI-PDFF), TE Transient elastography

Web Table VII Drugs with Limited or no Pediatric Data in MASLD/Obesity

Drug name and class	*Adult data*	*Pediatric data*	*Recommendation*	*Remarks*
PPAR agonists Pioglitazone Dual PPAR α and -δ agonist- Elafibranor	Significant improvement in histopathology, liver enzymes, HOMA-IR and lipid profile Significant resolution of NASH	None Some reduction in transaminases (observational data)	Recommended by AASLD (2023) in NASH with type 2 diabetes and by INASL (2023) in with/without diabetes in adults -	Side effects include weight gain, osteoporosis in postmenopausal women, debated risk of bladder cancer, heart failure
SGLT-2 inhibitors Empagliflozin	Improved body composition, insulin resistance, hepatic enzymes and steatosis	None	-	Approved for type 2 diabetes in children
Polyunsaturated fatty acids including Docosahexaenoic acid and Eicosapentaenoic acid	Conflicting data on changes in transaminases and liver histology; some improvement in liver fat on imaging and lipid profile	Conflicting results in terms of ALT and fat No data on histological improvement	-	Limited sample size in pediatric studies, short follow-up
Probiotics *Lactobacillus rhamnosus GG, VSL#3, Bifidobacterium lactis*	Improvement in liver steatosis on USG, transaminases, lipid profile, HOMA-IR No significant effect on BMI, waist circumference, fasting blood sugar	Some improvement in ALT and steatosis	-	Limited data on histology Limited sample size, short duration, different strains of probiotics used
FXR agonists Obeticholic acid	Improved histology in NASH and significantly improved fibrosis	None	-	Promising results in adult trials, around 20% have pruritus
TSH receptor agonist Resmetirom	Significantly more NASH resolution and significant fibrosis improvement in phase 3 trials	None	-	Promising data in adult NASH Recently approved in 2024 by U.S. Food and Drug Administration for treating adult patients with noncirrhotic metabolic dys-function–associated steatohepatitis, or MASH) and moderate-to-advanced hepatic fibrosis
CCR2-CCR5 antagonists Cencriviroc	Improvement in fibrosis in phase 2 trial	None	-	-

AASLD American Association for the Study of Liver Diseases, ALT Alanine aminotransferase, BMI Body mass index, CCR2-CCR5 Chemokine receptor 2-chemokine receptor 5, FDA Food and drug administration, HOMA-IR Homeostasis model assessment for insulin resistance, INASL Indian National Association for the Study of Liver, MASH Metabolic dysfunction associated steatohepatitis, NASH Non-alcoholic steato hepatitis, PPAR Peroxisome proliferator-activated receptor, SGLT-2 sodium-glucose transport protein 2, TSH Thyroid stimulating hormone, USG Ultrasonography