
بسم الله الرحمن الرحيم

Fatty Liver And Obesity

نوزدهمین همایش سالیانه بیماری های شایع گوارش و کبد کودکان

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دوازدهمین همایش سالیانه بیماری های شایع گوارش و کبد کودکان

خلاصه

کبد چرب و چاقی

کبد چرب شایعترین بیماری کبدی در سرتاسر گیتی است و اغلب با چاقی، دیابت، دیس لیپیدمی، هیپرتانسیون و سندرم متابولیک همراه است. به موازات افزایش شیوع چاقی در کودکان و بزرگسالان، شیوع بیماری کبد چرب غیرالکلی (NAFLD) نیزافزایش یافته است و با گذشت زمان در افراد مستعد از نظر ژنتیکی و با تاثیر عوامل محیطی التهاب در کبد استئاتوتیک تریگر می شود.

پاتوژنز بیماری کبد چرب مولتی فاکتوریال است و طیف آن از استئاتوز ساده کبد تا استئاتوهپاتیت می باشد و ممکن است به سمت فیبروز پیشرفته و حتی سیروز پیشرفت کند.

تشخیص NAFLD با تستهای آزمایشگاهی، تصویربرداری و بیوپسی کبد و با کنار گذاشتن سایر علل کبد چرب گذاشته می شود. اساس درمان NAFLDتعدیل سبک زندگی که شامل مداخلاتی برای اصلاح رژیم غذایی و افزایش فعالیت فیزیکی است می باشد.

درمان بیماری کبد چرب غیرالکلی با رژیم غذایی و بر اساس هرم تغذیه ای و با انتخاب کربوهیدراتهای پیچیده، غلات کمتر فراوری شده، غذاهای با ایندکس گلایسمی پایین، پرپروتئین و سبزیجات است و ممکن است از ویتامینها، پره و پروبیوتیکها نیز استفاده شود. در حالی که در موارد بروز استئاتوهپاتیت غیرالکلی (NASH) و فیبروز مداخلات فارماکولوژیک مانند pioglitazone در بالغین توصیه میشود. در حال حاضر هیچ دارویی برای درمان NAFLD در کودکان تایید نشده است ولی داروهای مختلفی تحت کارآزمایی های بالینی قرار دارند.

پیشرفت استئاتوهپاتیت به سمت سیروز حتی در بچه ها نیز رخ می دهد. با توجه به پیچیدگی و شیوع بالای بیماری کبد چرب، تیم های تخصصی رشته های مختلف به همراه متخصصان بهداشت عمومی باید در درمان آن مشارکت داشته باشند.


Fatty liver disease
Normal liver

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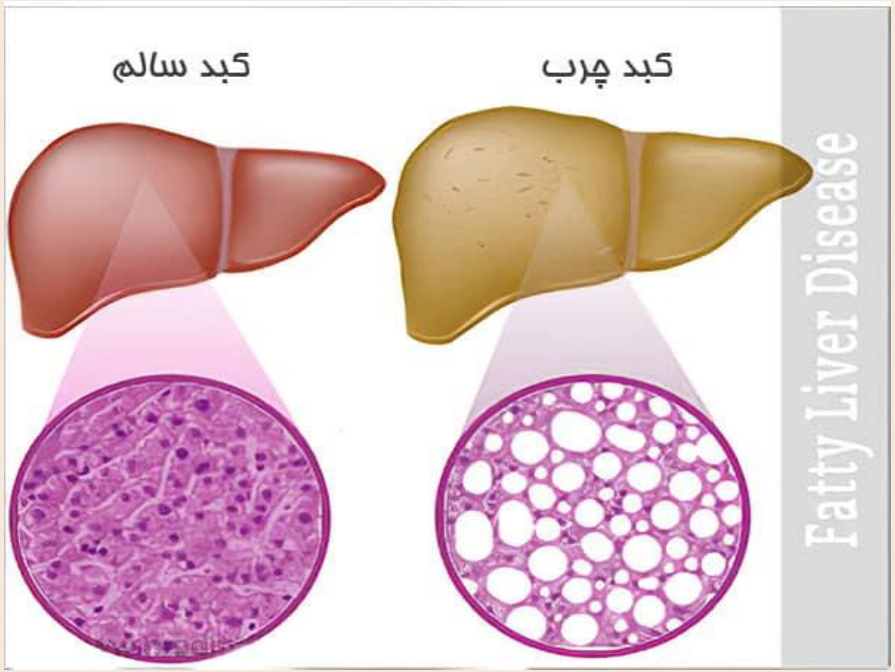
Definitions

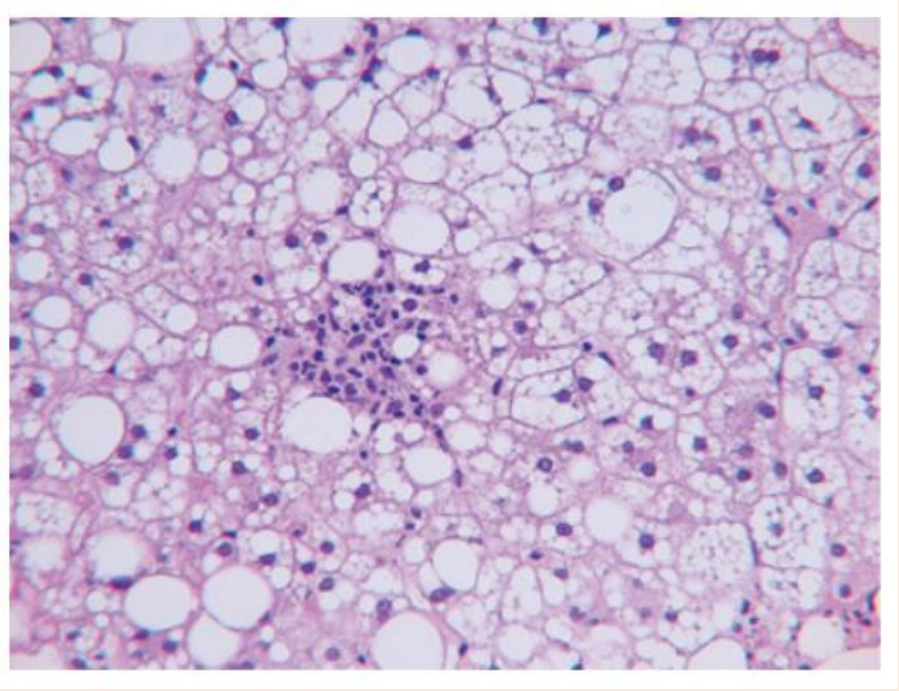
- Metabolic dysfunction-associated steatotic liver disease (**MASLD**; previously termed nonalcoholic fatty liver disease [NAFLD]) refers to liver steatosis (>5 percent hepatic steatosis) in patients with at least one metabolic risk factor (eg, overweight/obesity/visceral adiposity, dysglycemia/diabetes mellitus, dyslipidemia, hypertension).
- No other causes of steatotic liver disease.
- MASLD may progress to cirrhosis and is likely an important cause of cryptogenic cirrhosis.



Metabolic dysfunction-associated steatotic liver disease (MASLD)

Definitions

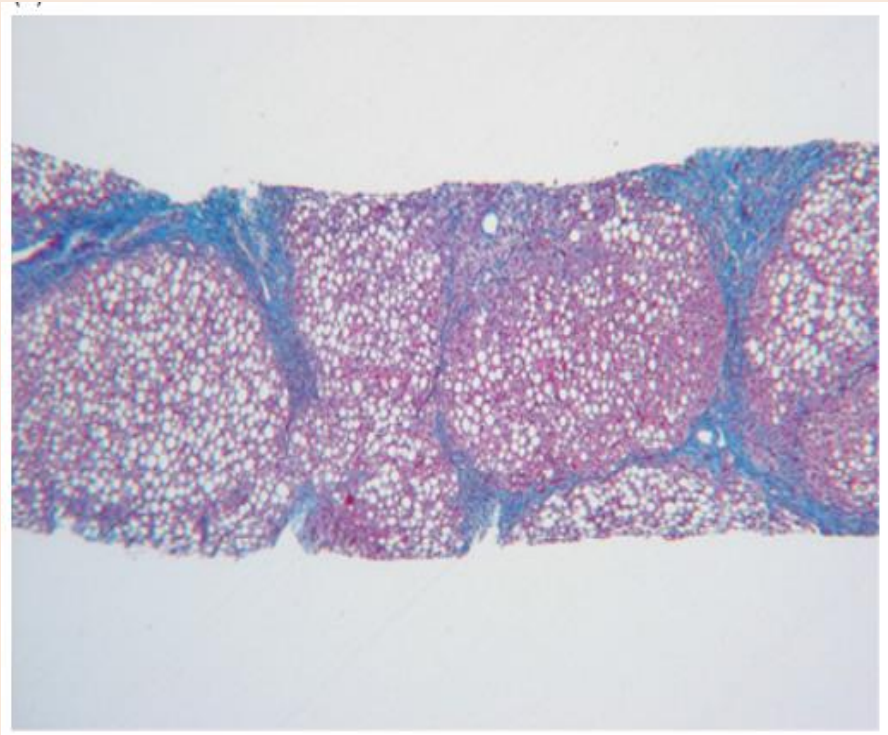
- Metabolic dysfunction-associated steatohepatitis (**MASH**; previously termed nonalcoholic steatohepatitis [NASH]).
- Patients with MASH have MASLD PLUS histologic evidence of inflammation and hepatocellular injury, such as ballooning of hepatocytes, with or without “fibrosis.
- In children, a **liver biopsy** is required to make a definitive diagnosis of MASH because there are no validated, reliable noninvasive biomarkers.



Metabolic dysfunction-associated steatohepatitis liver disease (MASH)

Definitions

- **MASH with fibrosis or cirrhosis – Patients with MASH cirrhosis have cirrhosis with current or previous histologic evidence of MASH or history of MASLD.**
- **Metabolic dysfunction- and alcohol-associated liver disease (MetALD) Patients with liver steatosis, at least one metabolic risk factor, and a history of moderate (but not heavy) alcohol use.**



MASH with fibrosis or cirrhosis

Metabolic dysfunction-associated steatotic liver disease in pediatric patients: Definitions and phenotypes

Term/phenotype [1]	Previous nomenclature [2]	Definitions
Steatotic liver disease	Fatty liver disease	■ Liver disease of any cause that results in hepatic steatosis (on imaging or biopsy).
Metabolic dysfunction-associated steatotic liver disease (MASLD)	Nonalcoholic fatty liver disease (NAFLD)	■ Refers to steatotic liver disease associated with cardiometabolic dysfunction. ■ Abnormal liver steatosis is typically defined as fat >5% of the liver by imaging or histologic estimation. ■ Requires the presence of at least 1 of 5 cardiometabolic risk factors*. ■ The diagnosis of isolated MASLD requires the absence of significant alcohol (ie, <140 g/week for females and <210 g/week for males), monogenetic diseases, or medications that cause steatosis. MASLD may coexist with these other causes.
Metabolic dysfunction-associated steatohepatitis (MASH)	Nonalcoholic steatohepatitis (NASH)	■ A definitive diagnosis of MASH can only be made by liver biopsy, but this is not always necessary for clinical management.
Definite MASH		■ Hepatic steatosis with lobular inflammation, ballooning injury to hepatocytes, with or without fibrosis.
Borderline MASH, zone 3 pattern	Type 1	■ Has some but not all components of MASH injury, in a venule (zone 3)-centered injury pattern or confluent pattern.
Borderline MASH, zone 1 pattern	Type 2	■ Has some but not all components of MASH in a portal predominant (zone 1)-centered injury pattern, often without ballooning and more commonly seen in younger prepubertal children.
MASLD with fibrosis or cirrhosis	NAFLD with fibrosis or cirrhosis	■ MASLD or MASH with periportal, portal, sinusoidal, or bridging fibrosis or cirrhosis.
MASLD and increased alcohol intake (MetALD)	None (new category)	■ Moderate alcohol use is defined as 140 to 350 g/week for females and 210 to 420 g/week for males. ■ This range of alcohol intake defines a spectrum between MASLD-predominant and alcohol-predominant disease.

Other terms such as "presumed NAFLD" (also "clinical NAFLD" or "suspected NAFLD") are terms used in the literature with varying meanings. These terms are often used when a biopsy has not been performed to confirm the diagnosis.

Note

- Because MASLD was defined in 2023, Until pediatric studies are available to determine the concordance between MASLD and NAFLD, we will maintain NAFLD.
- Concordance between NAFLD and MASLD diagnosis in children has not yet been evaluated.
- A European consortium of adults with NAFLD demonstrated a high concordance (98 percent) between MASLD and NAFLD diagnoses.

Epidemiology

- Nonalcoholic fatty liver disease (NAFLD) is a multifactorial disease that has become the most common chronic disease of the liver in children and adults worldwide.
- Over the last decades, the prevalence of NAFLD has more than doubled.

Epidemiology

- The estimated population prevalence of NAFLD was most often based on indirect evidence of a steatotic liver (imaging or elevations in serum aminotransferase levels in at-risk subjects).
- In contrast, MASLD is defined by either radiologic or biopsy evidence of steatosis in children with metabolic risk factors.
- No pediatric prevalence data using MASLD diagnostic criteria exist yet.

Epidemiology

- A modest male predominance (in studies that used biochemistry, not in studies using ultrasound.)
- Clinical practice guidelines recommend that screening begin around age 9 to 10 years.
- However, case reports describe steatosis developing earlier, and cirrhosis developing as early as eight years.

Epidemiology

- Estimates of NAFLD or MASLD prevalence may vary by method of ascertainment, as well as the population studied (ie, referral, community, ethnic group):
  - **Histology**
  - **Aminotransferase elevations**
  - **Ultrasound**

Histology

- In an autopsy study the prevalence of steatotic liver disease was 9.6 percent overall and 38 percent in children with obesity.
- Histologic steatohepatitis was seen in 23 percent of the subjects with steatotic liver, or 3 percent of the population overall.
- The prevalence of steatotic liver disease was strongly associated with race/ethnicity, independent of obesity.

Histology

- Hispanic youth had a fivefold more than Black youth, after adjustment for body mass index. White youth had intermediate levels of risk.
- Because this study used histologic measures of steatotic liver disease in an unselected population, it is the best representation of the prevalence of steatotic liver disease among children and adolescents in the United States.

Key numbers with Histology

38%

Of obese children/ adolescents are steatotic

23%

Of steatotic obese children have steatohapatitis

9.6%

Of general papulation have fatty liver

Aminotransferase elevations

- Historically, serum aminotransferase elevations were used as an indirect estimate of the prevalence of NAFLD in a population but had limited sensitivity and specificity for detection of steatosis.
- Typically, the prevalence of hepatic steatosis is underestimated using aminotransferase elevations, but this depends in part on the alanine aminotransferase (ALT) threshold employed in the study.
- In another large population-based study, 11 percent of all children had ALT above similar thresholds.

Aminotransferase elevations

- In a large population-based study in the United States (National Health and Nutrition Examination Survey 2011 to 2018), 16 percent of adolescents had elevated ALT (>22 units/L for females and >26 units/L for males) presumed to be NAFLD, rising to 39 percent of those with obesity.
- A meta-analysis estimated the prevalence of NAFLD by abnormal ALT (using various thresholds) to be 7 percent in the general population (9 studies) and 13.7 percent in children with obesity (14 studies).

Key numbers with High ALT

13.5%

Of obese children/ adolescents are steatotic

7%

Of general papulation have fatty liver

Ultrasound

- Ultrasound has poor sensitivity and specificity for the detection of hepatic steatosis.
- In a meta-analysis, the prevalence of hepatic steatosis was 7.6 percent in the general population (10 studies) and 41.3 percent in children with obesity (34 studies)

Key numbers with Ultraasound

41.3%

Of obese children/
adolescents are steatotic

7.6%

Of general papulation have
fatty liver

Pathophysiology

- **It is now clear that not all NAFLD is created equal.**
- **The interaction of genetic and epigenetic factors, enteric microbiota, diet, prepartal maternal influences and growth.**

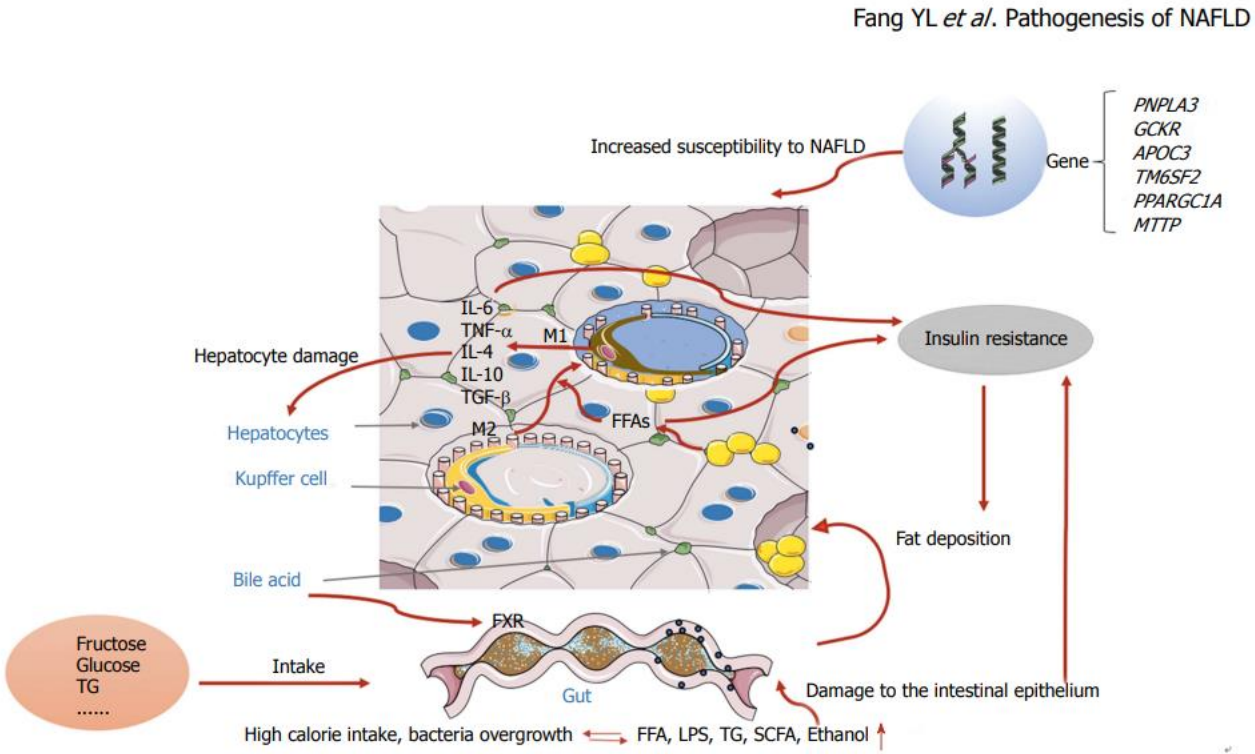


Figure 1 Schematic mechanistic diagram of the "multiple hit model". NAFLD: Nonalcoholic fatty liver disease.

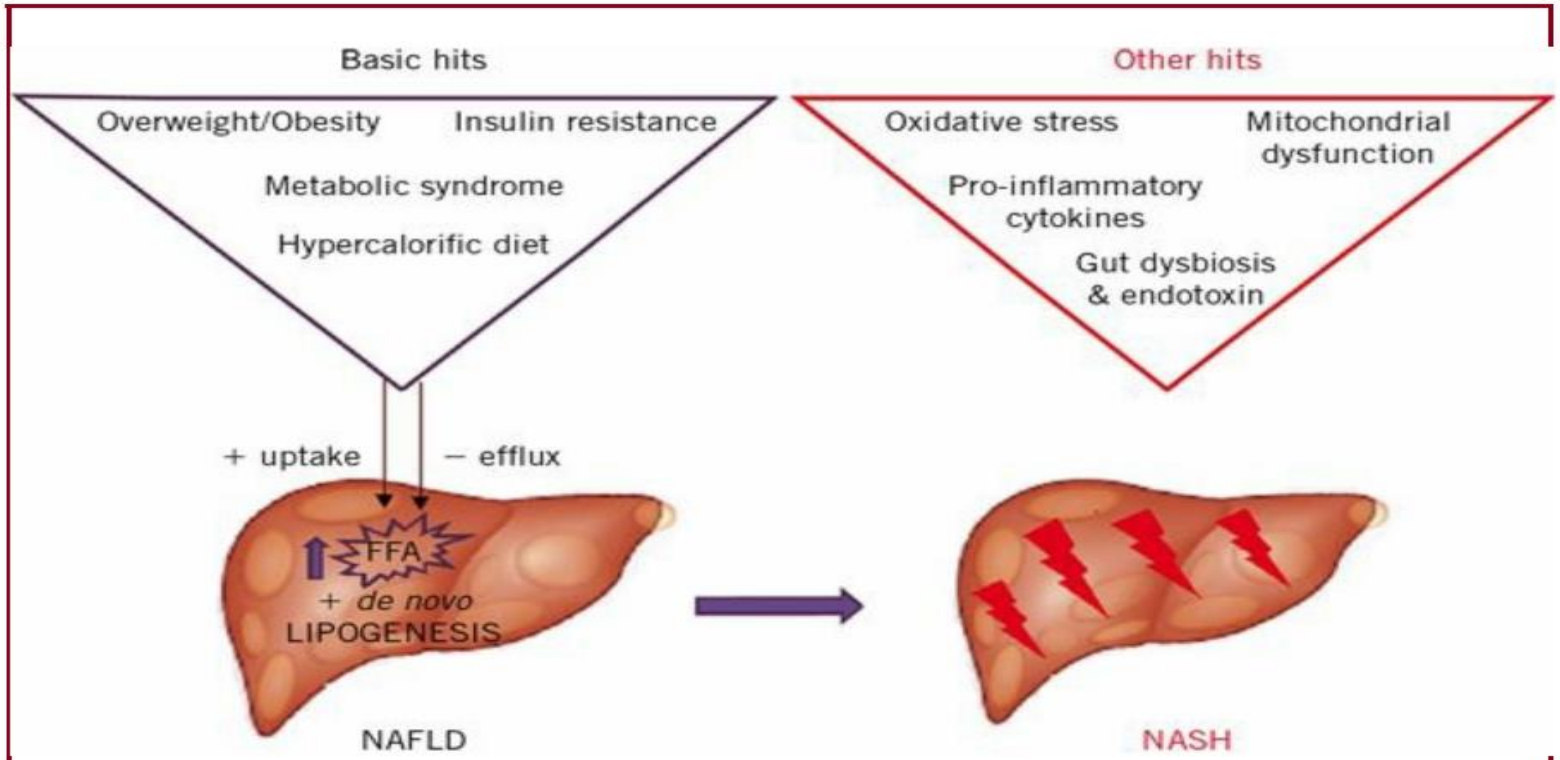


Figure 35-1 Summary for NAFLD pathophysiology.

Clinical Presentation
(History)

- Patients with suspected MASLD typically have no symptoms of liver disease.
  - Common Symptoms:
    - Fatigue.
    - Discomfort or pain in the upper right abdomen.
- Their symptoms, usually are secondary to complications of obesity.

Clinical Presentation

(complications of obesity)

- Knee/groin pain due to slipped capital femoral epiphysis
- Intermittent right upper quadrant abdominal pain secondary to gallstones
- Regurgitation due to gastroesophageal reflux disease,
- Headaches secondary to increased intracranial pressure

Physical examination in a child or adolescent with suspected metabolic dysfunction-associated steatotic liver disease

Finding	Implications
Findings associated with conditions that could lead to MASLD	
Overweight (BMI ≥85th percentile) or obesity (BMI >95th percentile)	
Goiter, decreased height velocity, short stature	Suggests hypothyroidism
Abnormal fat distribution	Suggests partial lipodystrophy
Papilledema, neurologic deficits, short stature, and/or severe obesity	Panhypopituitarism, eg, related to craniopharyngioma or its treatment
Xanthelasmata	Suggests lysosomal acid lipase deficiency
Findings associated with risk of advanced MASLD	
Increased waist circumference	Abdominal obesity
Acanthosis nigricans	Insulin resistance, diabetes
Splenomegaly	Portal hypertension
Sarcopenia (muscle wasting)	Possible advanced liver disease

BMI: body mass index; MASLD: metabolic dysfunction-associated steatotic liver disease (formerly known as nonalcoholic fatty liver disease [NAFLD]).

Graphic 116583 Version 2.0

Risk factors

- NAFLD was strongly associated with obesity in all age groups.
- By definition, MASLD is also closely associated with elements of metabolic syndrome (abdominal fat distribution, insulin resistance, diabetes, dyslipidemia, and hypertension]).
- NAFLD was also associated with polycystic ovary syndrome and obstructive sleep apnea (OSA), independent of the degree of obesity.
- Therefore, children with suspected or established MASLD should be evaluated for these comorbidities.

Risk factors

- Hepatic steatosis may occur in individuals **without** obesity, often accompanied by insulin resistance and dyslipidemia, in association with genetic disorders such as lipodystrophy syndromes.
- Other risk factors for NAFLD include
  - maternal obesity during gestation,
  - panhypopituitarism,
  - sarcopenia or lower muscle mass
  - Several single-nucleotide polymorphisms (among lean children)
  - Hispanic ethnicity (maybe due to higher concentration of a genetic risk factor (predominantly PNPLA3 variants)

Routine laboratory testing

- Complete blood count (CBC) with differential
- ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGTP), total and direct bilirubin, albumin
- Evaluation for cardiometabolic risk factors (included in criteria required for diagnosis of MASLD)
- Hemoglobin A1c and/or fasting glucose (FBS)
- Fasting lipid panel (triglycerides (TG), total cholesterol (Chol), high-density lipoprotein (HDL) and low-density lipoprotein [LDL] cholesterol)

Testing for additional comorbid conditions

Assessment for weight-related comorbidities in children and adolescents with obesity [1-5]

Condition	Clinical presentation/examination	Tests	Notes
Dyslipidemia	Asymptomatic or family history of CVD	**Screening test:** ■ Fasting lipid profile **Timing:** ■ Screen at age ≥10 years for all children with overweight or obesity [3] ■ Evaluate earlier for selected children with multiple risk factors	■ Additional risk factors include family history of CVD, other obesity comorbidities (hypertension, diabetes), or tobacco use ■ Refer to UpToDate content on dyslipidemia in children for interpretation and follow-up
Hypertension	Asymptomatic; detected on routine monitoring	**Screening test:** ■ BP measurement **Timing:** ■ Measure at all health care visits (and at least annually)	■ Use appropriately sized cuffs and age-appropriate norms ■ Multiple measurements are required to diagnose or exclude hypertension
		Follow-up tests: ■ 24-hour ABPM ■ CBC, metabolic panel, renin assay, urinalysis, kidney ultrasound	■ ABPM is used to evaluate for "masked" hypertension; rule out "white coat" hypertension ■ ABPM is suggested if the diagnosis is unclear from random office BP measurements ■ Blood tests are suggested if hypertension is confirmed to exclude other causes of hypertension

Metabolic dysfunction-associated steatotic liver disease (MASLD; formerly termed nonalcoholic fatty liver disease)	Generally asymptomatic; may have RUQ tenderness or hepatomegaly	**Screening test:** ■ Serum ALT **Timing:** ■ Initiate screening with serum ALT for all children with obesity starting at ≥10 years	■ If ALT is normal, repeat at least every 2 to 3 years * ■ Diagnosis also depends on cardiometabolic risk factors (lipids and HbA1c or fasting glucose)
		Follow-up tests: ■ Abdominal ultrasound to evaluate for anatomical abnormalities ■ Laboratory tests for cardiometabolic risk factors ¶; evaluation for viral hepatitis, autoimmune hepatitis, and endocrine disorders ■ Exclude genetic disorders in selected patients ■ Liver biopsy	■ Perform these follow-up tests if ALT is >80 units/L, persistently elevated >2 times the ULN * for 6 months, or other signs/symptoms of advanced liver disease are present ■ The purpose of follow-up tests is to determine the cause of elevated transaminases ■ Liver biopsy may be helpful in some cases, such as when diagnosis is uncertain or there is concern for severe progression ■ A definitive diagnosis of MASH can only be made by liver biopsy, but this is not always necessary for clinical management (refer to UpToDate content on MASLD)

Gallbladder disease	Recurrent RUQ abdominal pain, sometimes with fatty food intolerance, nausea, vomiting, or jaundice	■ Abdominal ultrasound ■ AST, ALT, GGTP, total bilirubin ■ Amylase, lipase	■ Complications may include acute pancreatitis or cholangitis
Type 2 diabetes mellitus or impaired glucose tolerance	Often asymptomatic; may present with urinary frequency, nocturia, polydipsia, or polyuria	**Screening test:** ■ Fasting glucose, HbA1c, or oral glucose tolerance test **Indications:** ■ Perform in children ≥10 years old with overweight or obesity **and** 1 or more risk factors for type 2 diabetes[Δ]	■ Diabetes is diagnosed if fasting glucose ≥126 mg/dL or HbA1c ≥6.5% on 2 occasions ■ Prediabetes is diagnosed if fasting glucose 100 to 125 mg/dL or HbA1c 5.7 to 6.4% on 2 occasions

Sleep apnea	Habitual snoring, mouth breathing, daytime sleepiness, or inattentive behaviors and/or adenotonsillar hypertrophy	**Screening:** ■ Routinely evaluate signs and symptoms ■ Assess tonsil size **Diagnostic test:** ■ Polysomnogram (sleep study)	■ Perform polysomnogram in patients who have obesity and symptoms suggesting obstructive sleep apnea ◊
SCFE	Unexplained limp or aching pain in hip, groin, thigh, or knee	■ Hip radiographs	■ Use frog-leg positioning for radiograph ■ Children with acute symptoms of SCFE should immediately stop all weightbearing activity (including walking) to prevent further displacement [3]

Varus (Blount disease) or valgus deformity	Varum (bow legs) or varus (knock knees) deformity on examination, with or without knee pain	■ Knee radiographs	
Polycystic ovary syndrome	Menstrual irregularity, excessive acne, hirsutism	**Initial tests:** ■ Total testosterone (or free testosterone) ■ Beta-hCG, TSH, prolactin, DHEAS, 17-hydroxyprogesterone (early morning)	■ Initial tests are to confirm whether hyperandrogenemia is present and exclude other causes of hyperandrogenemia and/or abnormal menses ■ If laboratory testing is abnormal, additional workup is indicated
Impaired kidney function	Asymptomatic	**Screening:** ■ BUN, creatinine ■ Urine for UACR **Indications:** ■ Perform in adolescents with severe obesity, hypertension, or type 2 diabetes[§]	■ Perform in adolescents with severe obesity, hypertension, or type 2 diabetes[§] ■ UACR >30 mg/g is abnormal

Precocious puberty	Appearance of secondary sexual characteristics <8 years (females) or <9 years (males)	**Initial tests:** ■ LH, FSH, testosterone or estradiol	■ Physical examination is often sufficient to evaluate ■ Laboratory testing depends on child's age and pubertal progression ■ Central nervous system imaging may be indicated in selected children with central precocious puberty
Pseudotumor cerebri	Headaches (especially morning), nausea/vomiting, blurred or decreased vision	**Initial test:** ■ Funduscopic examination and/or refer to pediatric neurologist or ophthalmologist	■ Increased intracranial pressure suggested by papilledema and confirmed by lumbar puncture

This table summarizes the evaluation for obesity-related comorbidities in children. For details on the evaluation, refer to UpToDate content on the health consequences of obesity in children and adolescents and relevant topic reviews.

ABPM: ambulatory blood pressure monitoring; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BP: blood pressure; BUN: blood urea nitrogen; CBC: complete blood count; CVD: cardiovascular disease; DHEAS: dehydroepiandrosterone sulfate; FSH: follicle-stimulating hormone; GGTP: gamma-glutamyl transpeptidase; HbA1c: glycated hemoglobin; hCG: human chorionic gonadotropin; LH: luteinizing hormone; MASH: metabolic dysfunction-associated steatohepatitis; MASLD: metabolic dysfunction-associated steatotic liver disease; RUQ: right upper quadrant; SCFE: slipped capital femoral epiphysis; TSH: thyroid-stimulating hormone; UACR: urine albumin-to-creatinine ratio; ULN: upper limit of normal.

* For interpretation of serum ALT, use the ULN of 22 units/L for females and 26 units/L for males, as determined from healthy lean children in the National Health and Nutrition Examination Survey [4]. Note that these values are substantially lower than the ULNs reported in most pediatric hospital laboratories.

¶ Screening laboratory tests for suspected MASLD include a CBC with platelets, HbA1c, and lipid panel.

Δ Risk factors for type 2 diabetes include: family history of type 2 diabetes, high-risk race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander), signs of insulin resistance (eg, acanthosis nigricans), or conditions associated with diabetes (hypertension, dyslipidemia, polycystic ovary syndrome).

◊ Symptoms suggesting obstructive sleep apnea include persistent snoring (most nights, most sleeping positions), observed gasping or apneas, nocturnal enuresis, and morning headaches.

§ Screening for impaired kidney function is recommended for patients with type 2 diabetes [5]. UpToDate authors also suggest this screening for patients with other risk factors for developing chronic kidney disease, including severe obesity and hypertension.

Differential diagnosis in a child with suspected metabolic dysfunction-associated steatotic liver disease [1]

Genetic/metabolic
Lysosomal acid lipase deficiency
Wilson disease
Fatty acid oxidation defects and other mitochondrial disorders
Partial/total lipodystrophy
Abetalipoproteinemia or hypobetalipoproteinemia
Immune-mediated
Celiac disease
Autoimmune hepatitis
Endocrine
Panhypopituitarism
Hypothyroidism
Uncontrolled diabetes
Infectious
Hepatitis C (genotype 3)
HIV-related lipodystrophy
Iatrogenic
Certain psychotropic medications
Corticosteroids
Other medications – Methotrexate, amiodarone
Rapid surgical weight loss
Parenteral nutrition

HIV: human immunodeficiency virus; MASLD: metabolic dysfunction-associated steatotic liver disease (formerly known as nonalcoholic fatty liver disease [NAFLD]).

Table. Pediatric Screening Guidelines

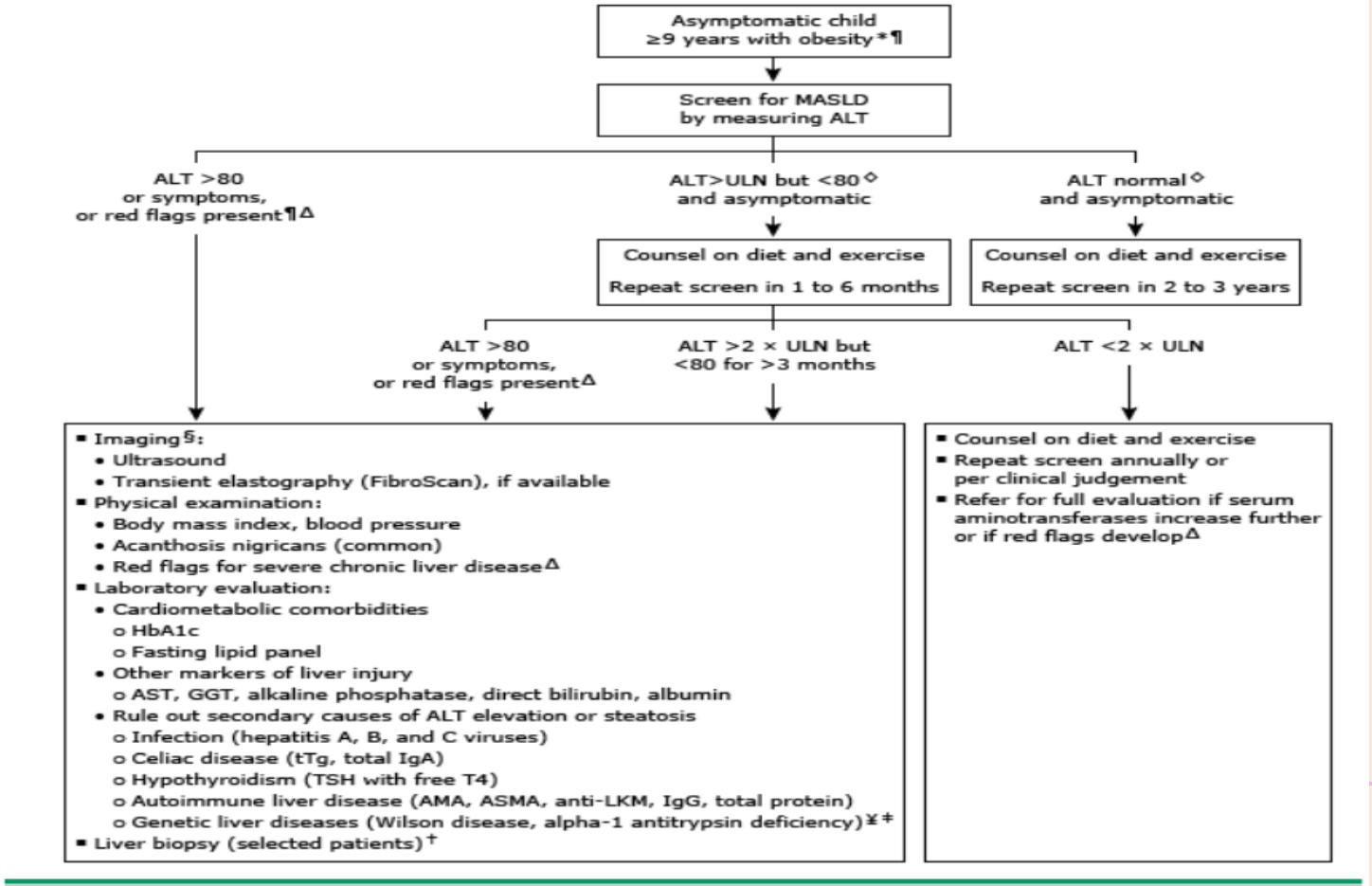
Population Specifics	Age	Tests	Action
Children with obese BMI (BMI ≥95th percentile)	9-11 years[a]	ALT Routine ultrasound not recommended as screening test for NAFLD	1. Use age- and sex-specific ULN (22 U/L for girls and 26 U/L for boys) 2. Elevated ALT (≥2 × ULN) for >3 months should be evaluated for NAFLD and other causes of chronic hepatitis 3. ALT >80 U/L should lead to expedited evaluation 4. If ALT is normal, repeat screening every 2-3 years if risk factors remain the same, and sooner if new risk factors develop
Children with overweight BMI (BMI ≥85th percentile and ≤94th percentile) with the following risk factors: • Central adiposity • Insulin resistance • Prediabetes/diabetes • Dyslipidemia • Sleep apnea • Family history of NAFLD/NASH	9-11 years		
Siblings and parents of children with NAFLD with risk factors for NAFLD	N/A		

ALT, alanine aminotransferase; BMI, body mass index; N/A, not applicable; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; ULN, upper limit of normal.

[a]Earlier screening can be considered if severe obesity, family history of NAFLD/NASH, or hypopituitarism is present.

Reproduced from Vos MB et al.[19]

Screening and evaluation for metabolic dysfunction-associated steatotic liver disease in children



ALT: alanine aminotransferase; AMA: antimitochondrial antibodies; anti-LKM: anti-liver-kidney microsomal antibodies type 1; ASMA: anti-smooth muscle antibodies; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; HbA1c: glycated hemoglobin; Ig: immunoglobulin; MASLD: metabolic dysfunction-associated steatotic liver disease; NAFLD: nonalcoholic fatty liver disease; MASH: metabolic dysfunction-associated steatohepatitis; T4: thyroxine; TSH: thyroid-stimulating hormone; tTg: tissue transglutaminase antibodies; ULN: upper limit of normal.

* Also screen children who are overweight (body mass index 85th to 95th percentile) if other risk factors are present, such as acanthosis nigricans (or other signs of insulin resistance) or a family history of MASLD or NAFLD. Younger children with overweight/obesity could also be screened if they have risk factors. NOTE: North American guidelines do not recommend obtaining imaging studies to screen all at-risk overweight and obese children for MASLD/NAFLD [1]; however, European guidelines recommend obtaining both ALT and ultrasound in at-risk children [2].

¶ This algorithm applies to asymptomatic children. If ALT is elevated in the context of a recent viral infection, repeat the test in 2 to 4 weeks and proceed with further evaluation if it remains elevated.

Δ Red flags for advanced liver disease, such as chronic fatigue, gastrointestinal bleeding, jaundice, splenomegaly, firm liver edge, enlarged left lobe, low platelets, low white blood cells, elevated direct bilirubin, or elevated international normalized ratio.

◊ For children 12 to 17 years, we define the ULN for ALT as 22 unit/L for girls and 26 unit/L for boys; for children 1 to <12 years, the ULN is 30 unit/L as they are supported by large population studies [3-5].

§ The primary purpose of ultrasound is to evaluate for structural/anatomic causes of elevated liver enzymes (eg, gallbladder disease) or complications such as portal hypertension. It has poor sensitivity for detecting or quantifying hepatic steatosis. Vibration-controlled elastography (ie, FibroScan) provides information about steatosis and liver stiffness, but its utility for the diagnosis or monitoring of MASLD in children has not been established.

ceruloplasmin and/or 24-hour urine coppe
Screening for alpha-1 antitrypsin deficiency
determination of the protease inhibitor phenotype
Protease inhibitor phenotypes associated with live
disease are ZZ or SZ.

‡ Screening for genetic liver diseases is performed fo
selected patients, depending on risk factors o
signs/symptoms.

† Liver biopsy is considered the gold standard for diagnosis of MASH but may vary by practice setting. In our practice, we suggest liver biopsy for patients who have had ALT elevations >2 × ULN for 6 or more months or for those with ALT >80 unit/L, red flags for advanced liver disease$^{\Delta}$, or features that suggest an alternate cause of the liver disease that requires biopsy for diagnosis.

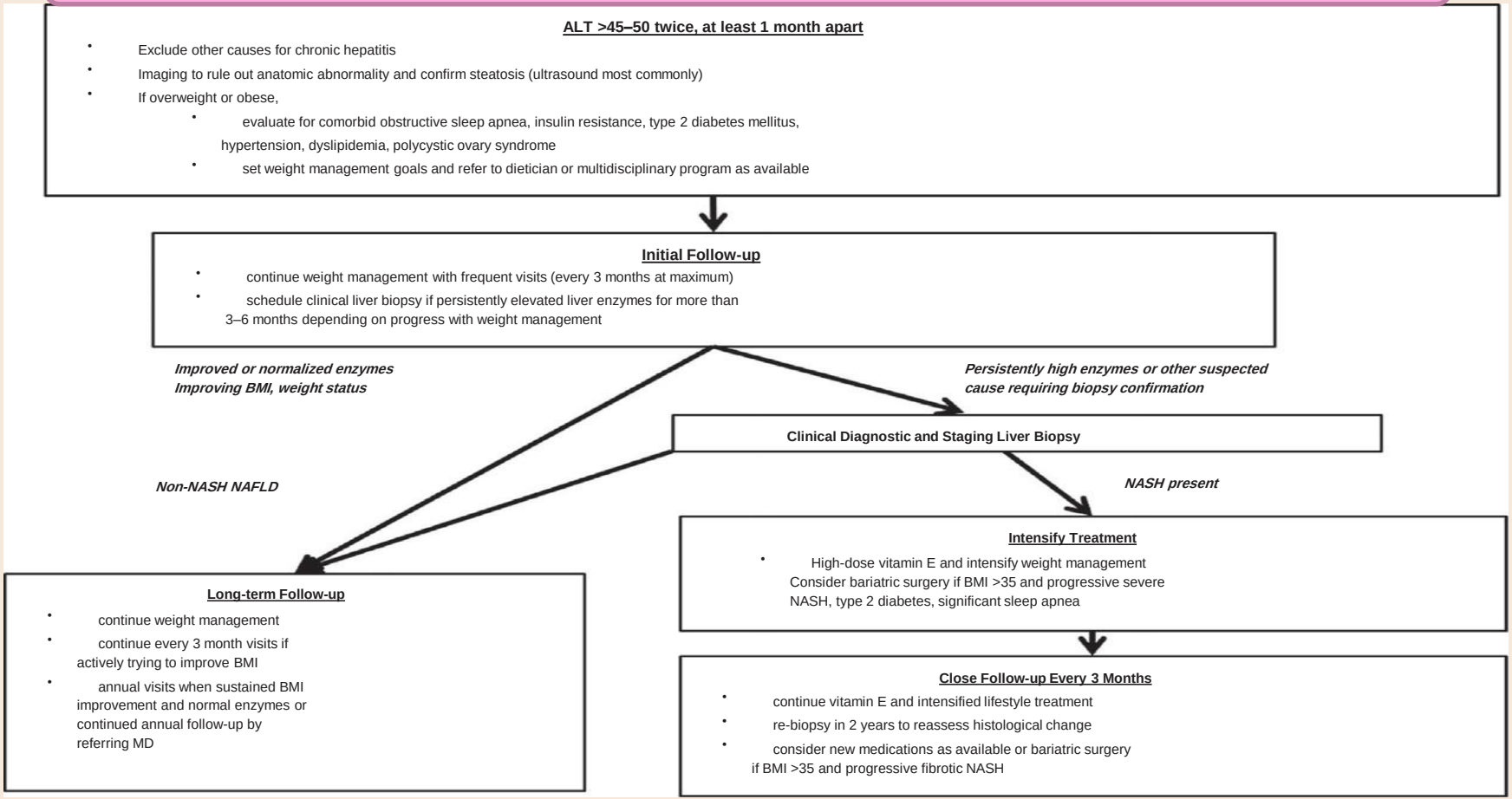
Management

- **Weight loss focused approaches**
  - **Diet and exercise**
  - **Surgery**
  - **Medications that target Wt loss and metabolic improvement**

Diet and exercise

- Lifestyle modification, with emphasis on dietary changes
- Avoidance of sugar-sweetened beverages
- Family-based and patient-centered approaches
- More intensive interventions
- Physical activity

NAFLD Management Algorithm



NAFLD Management Algorithm

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ALT >45–50 twice, at least 1 month apart Initial Follow-up

- Exclude other causes for chronic hepatitis
- Imaging to rule out anatomic abnormality and confirm steatosis (ultrasound most commonly)
- If overweight or obese,
  - evaluate for comorbid obstructive sleep apnea, insulin resistance, type 2 diabetes mellitus, hypertension, dyslipidemia, polycystic ovary syndrome
  - set weight management goals and refer to dietician or multidisciplinary program as available

NAFLD Management Algorithm

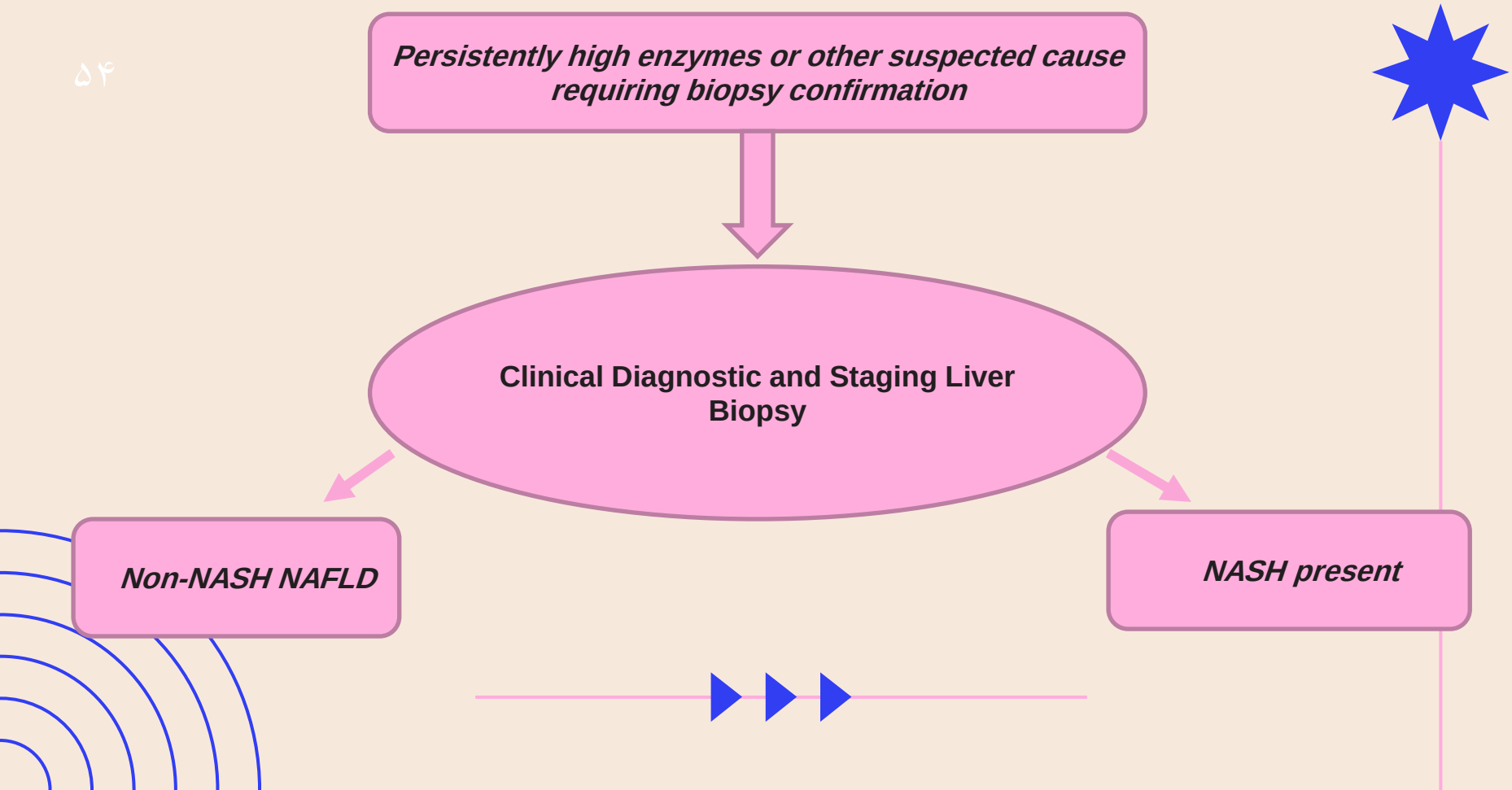
Initial Follow-up

- **Continue weight management with frequent visits (every 3 months at maximum)**
- **Schedule clinical liver biopsy if persistently elevated liver enzymes for more than 3–6 months depending on progress with weight management**

Improved or normalized enzymes, improving BMI, weight status

Non-NASH NAFLD

NAFLD Management Algorithm



Non-NASH NAFLD

Long-term Follow-up

- continue weight management
- continue every 3 month visits if actively trying to improve BMI
- annual visits when sustained BMI
- improvement and normal enzymes or continued annual follow-up by referring MD

NAFLD Management Algorithm

NASH present

➢ **Intensify Treatment**

- ➢ High-dose vitamin E and intensify weight management
- ➢ Consider bariatric surgery if BMI >35 and progressive severe NASH, type 2 diabetes, significant sleep apnea

NAFLD Management Algorithm

NASH present

- **<u>Close Follow-up Every 3 Months</u>**
- continue vitamin E and intensified lifestyle treatment
- re-biopsy in 2 years to reassess histological change
- consider new medications as available or bariatric surgery if BMI >35 and progressive fibrotic NASH

1

Surgery

- **Consider surgical intervention in adolescents, between 10 and 19 years old, with a BMI of ≥35 kg/m2 only in presence of severe comorbidity, such as T2D, OSAS, benign intracranial hypertension, or nonalcoholic steatohepatitis.**
- **They also indicate adolescents with a BMI of ≥40 kg/m2 and less severe comorbidities as potential candidates.**

2

Surgery

- Evaluation by a multidisciplinary team
- The patient and his/her family ability and motivation to adhere to recommended treatments pre- and post-operatively
- Vertical sleeve gastrectomy is the first choice technique (relatively technical simplicity, low complication profile, and high efficacy in losing weight and reducing MetS comorbidities)
- Use of intragastric balloon device
- Endoscopic-assisted placement of a percutaneous gastrostomy device (AspireAssist) approved by FDA in adults, but data in adolescents are not available yet

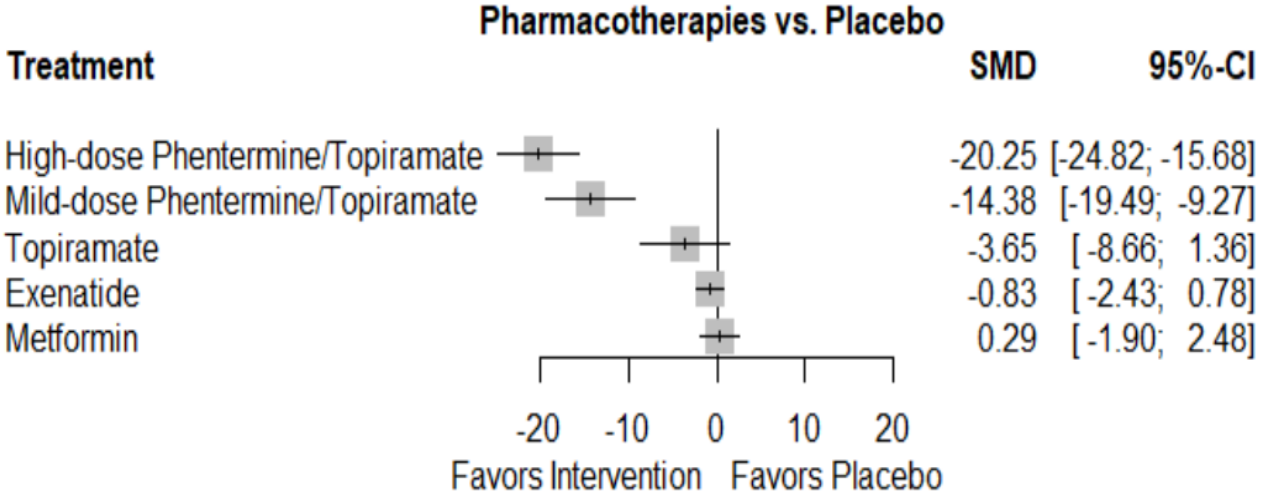
Medications that target weight loss and metabolic improvement

- **Medications that target weight loss are increasingly available and may have indirect benefits on MASLD.**
- **These include glucagon-like peptide 1 receptor (GLP-1) agonists (also approved for use in adolescents with type 2 diabetes) and phentermine-topirimate, which have not been studied as specific treatments for NAFLD or MASLD in youth but have shown benefit in studies in adults with NAFLD.**

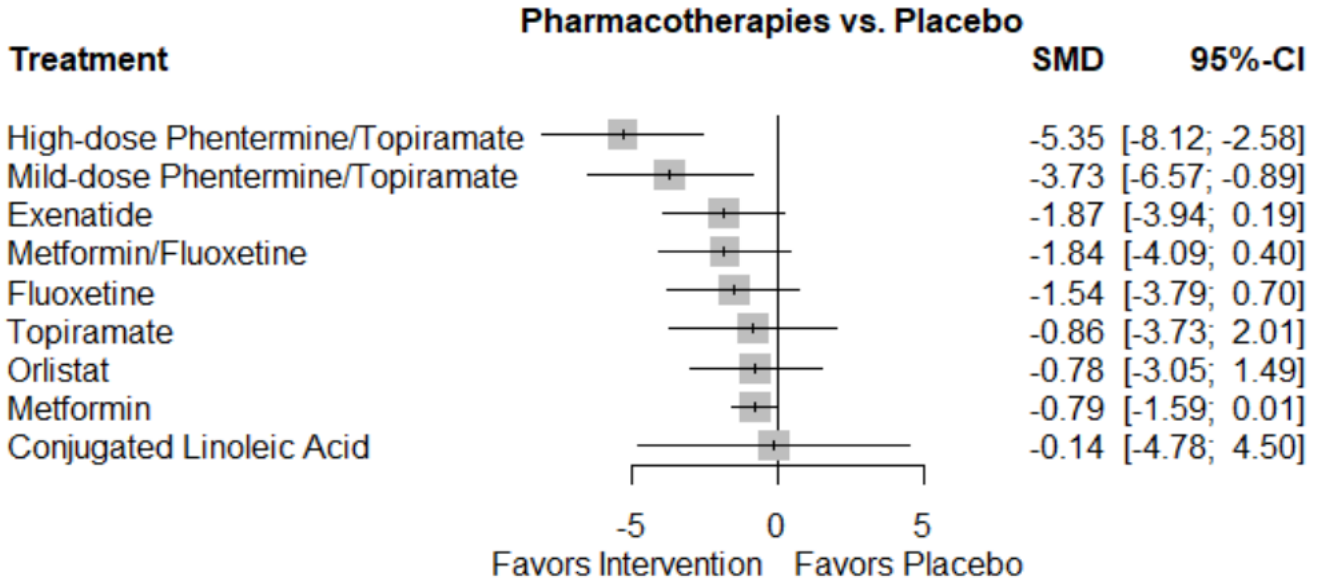
FDA approved anti-obesity medications

- Currently, five anti-obesity drugs have been approved by US FDA for long-term use.
- The weight lowering potential of these five anti-obesity drugs appears to be in following descending orders: phentermine/topiramate > liraglutide 3.0 mg > naltrexone/bupropion > lorcaserin = orlistat.

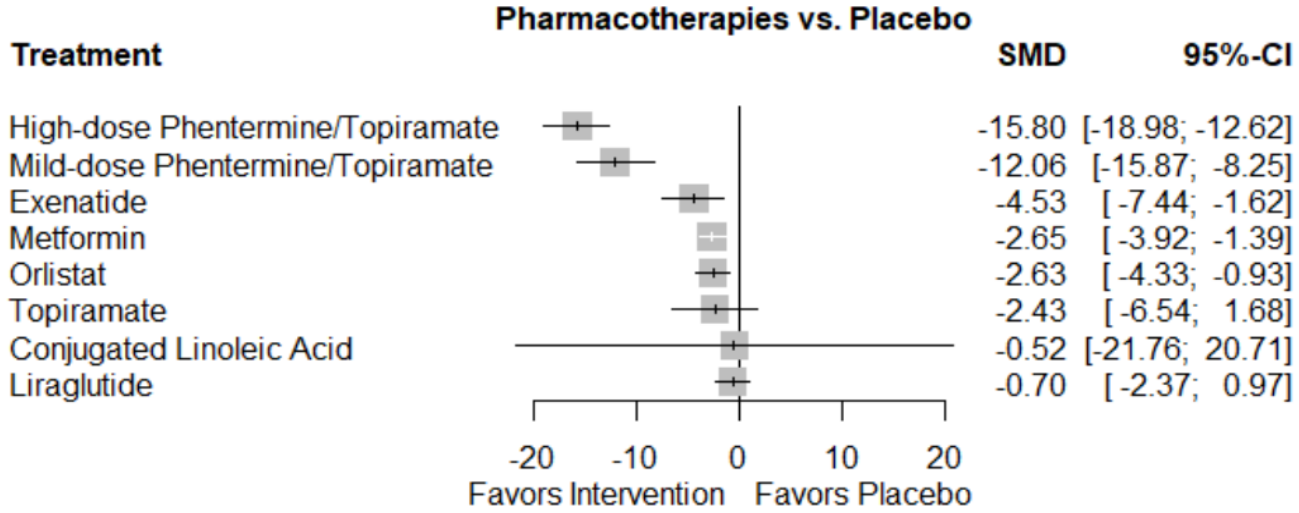
نمودار تاثیر داروها بر پرسنتایل BMI



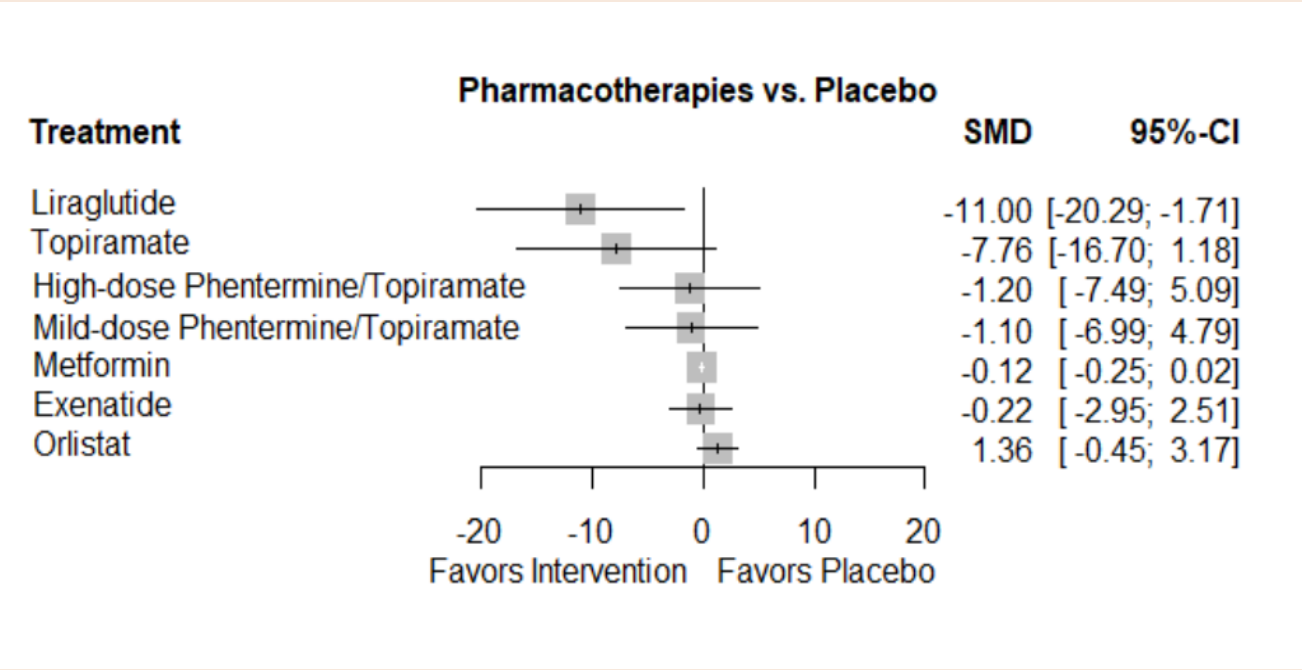
نمودار تاثیر داروها بر BMI



نمودار تاثیر داروها بر وزن



نمودار تاثیر داروها بر قند خون



Pharmacotherapy

- No medications are recommended for routine treatment of MASLD in children.
- Several pharmacologic approaches have been investigated in children with NAFLD including vitamin E, metformin, cysteamine bitartrate, and losartan.
- In clinical trials, none of these have shown a convincing advantage over lifestyle intervention alone

Table 1. A summary of selected ongoing clinical trials on NASH.

Drug	Properties	Clinical Trial Phase (possible completion date*)	Trial ID
Targeting liver steatosis			
Gemcabene	Dialkyl ether dicarboxylic acid with antihyperlipidemic activity	2 (8/2019)**	NCT03436420
Liraglutide	Glucagon-like peptide-1 analogue, injectable drug, with shown efficacy to induce weight loss and lower glucose in obese patients; approved for T2DM and obesity	3 (12/2017) 4 (9/2023)	NCT02654665 NCT03648554
NGM282 (M70)	Non-tumorigenic, engineered variant of fibroblast growth factor 21 (Receptors 1c, 4) reducing steatosis and lipotoxicity	2 (9/2020) 2 (9/2019)	NCT03912532 NCT02443116
Pemafibrate (K-877)	Selective PPAR-α modulator	2 (2/2020)	NCT03350165
Targeting oxidative stress/inflammation/apoptosis			
BI 1,467,335	Promoter of leukocyte recruitment in the liver, with monoamine oxidase activity, insulin-like effects, and initiation of oxidative stress	2 (6/2019)	NCT03166735
Cilofexor (GS-9674)	Selective non-bile acid FXR agonist, designed to avoid the side effects of obeticholic acid	2 (8/2019) 2 (10/2019)	NCT02781584 NCT03449446
Elafibranor (GFT505)	PPAR α/δ agonist, insulin sensitizer, ameliorating hepatic inflammation, steatosis and fibrosis	2 (11/2020)**	NCT03883607
Emricasan	Irreversible pan-caspase inhibitor	2 (8/2019)	NCT03205345
Losartan	Angiotensin II receptor antagonist; approved for arterial hypertension	2 (04/2020)**	NCT03467217
Metadoxine	Antioxidant, source of glutathione, capable of inhibiting adipocyte differentiation, limiting hepatic lipid accumulation and exerting antifibrotic properties	4 (1/2020)	NCT02051842
Pentoxifylline	Anti-oxidant/anti-inflammatory properties	Not applicable (6/2016)	NCT02231333
Pioglitazone	PPARγ activator, attenuating IR, steatosis, lobular inflammation, and fibrosis; approved for T2DM	4 (2/2019) 4 (9/2020) Cohort (7/2021)	NCT03796975 NCT03910361 NCT02815891
Tipelukast (MN-001)	A leukotriene receptor antagonist, which inhibits phosphodiesterase, 5-lipoxygenase and exhibits antifibrotic, anti-inflammatory activity in preclinical models	2 (5/2018)	NCT0268105
Targeting gut microbiota			
Fecal microbiota transplantation	Modulator of intestinal microbiome	1 (1/2021)	NCT03803540
IMM-124E	IgG-rich extract from cows immunized against lipopolysaccharide, which reduces the hepatic exposure to gut-derived bacterial products	2 (12/2019)**	NCT03042767
Targeting liver fibrosis			
BMS-986,036	Pegylated analogue of fibroblast growth factor 21	2 (1/2020) 2 (1/2020)	NCT03486912 NCT03486899
GR-MD-02	Galectin-3 inhibitor, resulting in improvement in liver histology with a significant reduction in NASH activity and collagen deposition	2 (9/2016)	NCT02421094
GS0976 acetyl-CoA carboxylase (Firsocostat)	Fatty acid metabolism key regulator, controlling the balance between *de novo* lipogenesis and fatty acid oxidation	2 (6/2020) 2 (10/2019)	NCT03987074 NCT03449446
Saroglitazar	PPAR-α/γ dual agonist; approved for hypertriglyceridemia in T2DM	2 (4/2020) 2 (10/2019) 2 (8/2019) 2 (9/2020)	NCT03639623 NCT03617263 NCT03061721 NCT03863574

* estimated date (month/year) of primary completion
** pediatric clinical trial

Referrences

1. Rohit Kohli, Kevin E. Bove, and Stavra A. Xanthakos . Non-Alcoholic Fatty Liver Disease in Children, in Liver disease in Children by Suchy et al. 2021; 36: 653-670
2. www.uptodate.com
3. Marzuillo P, Del Giudice EM, Santoro N. Pediatric non-alcoholic fatty liver disease: new insights and future directions. World J Hepatol. 2014; 6(4): 217–25.
4. Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Hepatology 2023; 78:1966.
5. American Association for the Study of Liver Diseases, Latin American Association for the Study of the Liver, European Association for the Study of the Liver. A call for unity: The path towards a more precise and patient-centric nomenclature for NAFLD. Hepatology 2023; 78:3.
6. Tagi VM, Samvelyan S, Chiarelli F. Treatment of Metabolic Syndrome in Children. Horm Res Paediatr 2020;93:215–225
7. Yan-Lan Fang, Hong Chen, Chun-Lin Wang, Li Liang . Pathogenesis of non-alcoholic fatty liver disease in children and adolescence: From “two hit theory” to “multiple hit model. World J Gastroenterol 2018 July 21; 24(27): 2974-2983.
8. Valentina Giorgio, Anna Alisi, Alberto Villani, Valerio Nobili. Fatty Liver Disease in Children. In Walker’s Pediatric Gastrointestinal Disease. 6th edition, 2018; 35, 4245-42-66


Thanks!
Do you have any questions?