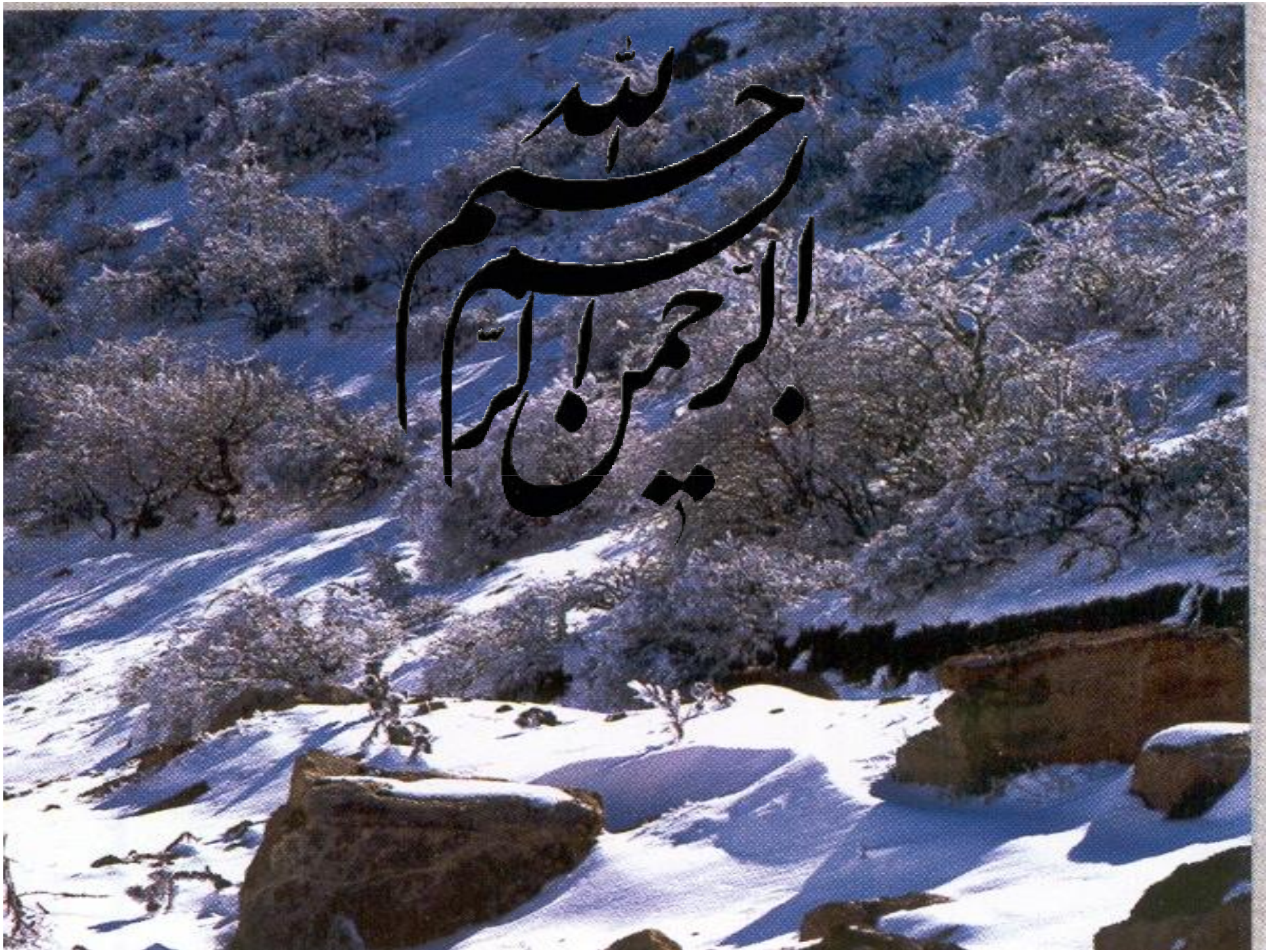

بسم الله الرحمن الرحيم

NAFLD

- Is the most common causes of liver disease in children and Adolescents
- with a prevalence of 3 to 10% general pediatric population and 70% obese children
- 3 Decades ago
- Most common causes of liver disease in the developed world

Non-alcoholic fatty liver disease prevalence among school-aged children and adolescents in Iran

- In an autopsy study performed on 896 postmortem subjects at the Forensic Medicine Center in Tehran who died of acute incidents not related to hepatic disorders, 2.1% of cases were found to have NASH upon histological evaluation.

Sotoudehmanesh R,, et al. Silent liver diseases in autopsies from forensic medicine of Tehran. Arch Iran Med. 2006 Oct;9(4):324-8.

Non-alcoholic fatty liver disease prevalence among school-aged children and adolescents in Iran

- 966 children aged 7–18 years in Iran by a cross-sectional survey in 2007.
- Fatty liver was diagnosed by ultrasound in 7.1% of children. The prevalence of elevated alanine aminotransferase (ALT) was 1.8%. NAFLD was significantly more common in the older group.

Alavian SM, et al. . Non-alcoholic fatty liver disease prevalence among school-aged children and adolescents in Iran and its association with biochemical and anthropometric measures. Liver Int. 2009 Feb;29(2):159-63.

NAFLD

- NAFLD → Histologic → Steatosis in≥5% of the hepatocytes after excluding other causes of hepatic Steatosis

↓

Type 2 NASH (Inflammation or Fibrosis)was the most common histologic pattern seen in younger children with NAFLD

↓

Cirhosis

Hepatoce illuar carcinoma 4

Pathophysiology of NAFLD

No hepatic processes

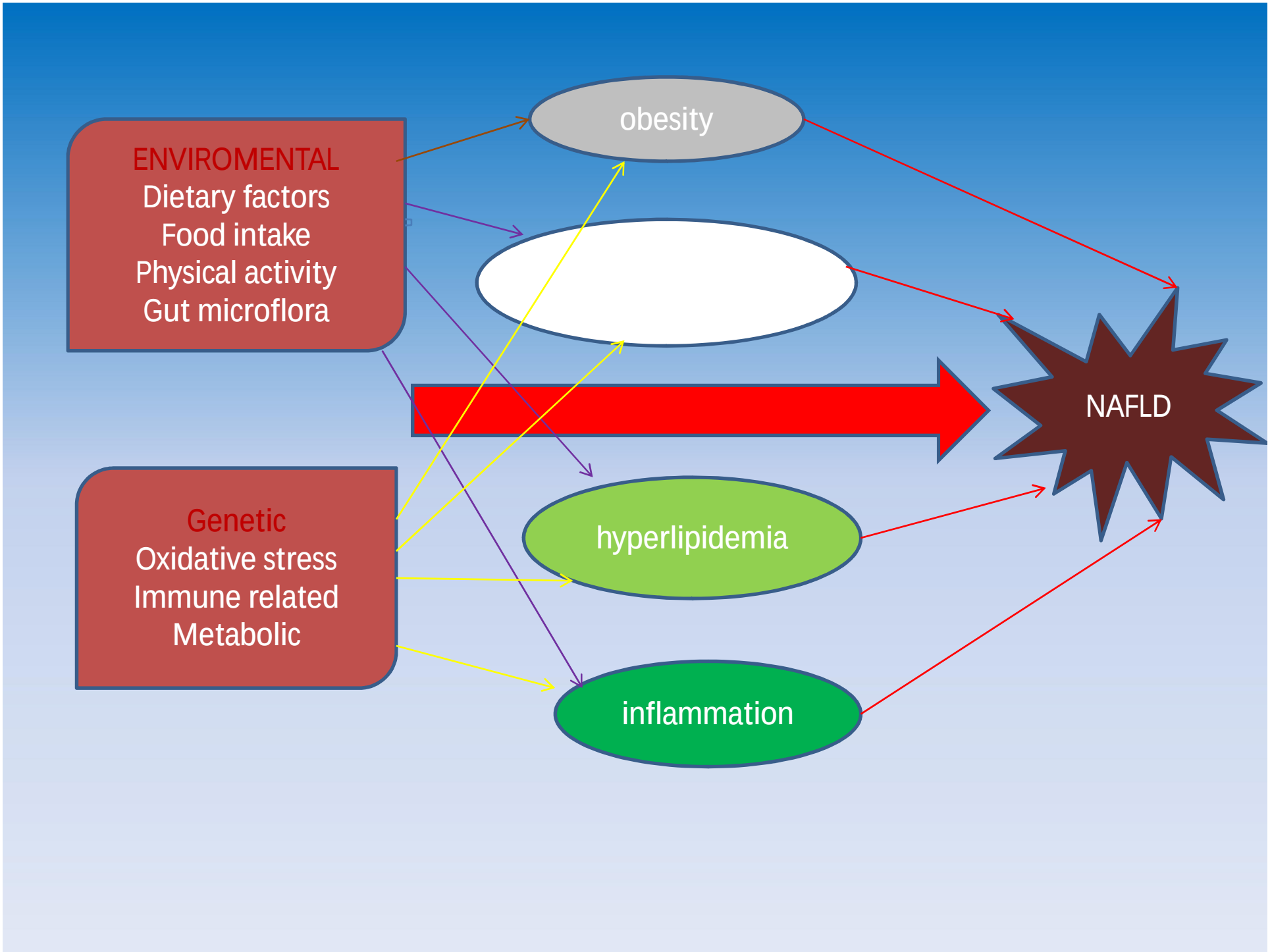
- **Lifestyle**
  (decreased physical activity and current patterns of food consumption are Involved in the epidemics of obesity and type 2 diabetes mellitus)

- **Fat mass**
  (Increased fat mass is an essential pathophysiologic factor in NASH)

- **Fat distribution**
  (increased risk for NASH is associated with central obesity and increased lipolysis of visceral tissue and an increased supply of FFAs to the liver)

- **Insulin resistance**

Hepatic processes


ENVIROMENTAL
Dietary factors
Food intake
Physical activity
Gut microflora
Genetic
Oxidative stress
Immune related
Metabolic
obesity
hyperlipidemia
inflammation
NAFLD

Causes of Hepatic Steatosis in Children

- Genetic/Metabolic
- Nutritional
- Pharmacologic
- Systemic
- infection

Genetic/Metabolic

- A1-antitrypsin deficiency
- Cyctic fibrosis
- Galactosemia
- Glycogen storage disease
- Tyrosinemia type 1
- Wilson disease

Nutritional

- Obesity
- Rapid Weight Loss
- Total parenteral nutrition

Pharmacologic

- Calcium-channel blockers
- Estrogens
- Glucocorticoids
- Toxins(alchol,pesticides,others)
- Valporate
- Vitamine A toxicity

Systemic

- Autoimmune Hepatitis
- Celiac disease
- Cystic fibrosis
- Diabetes Type 1
- Hepatitis c
- Inflammatory bowel disease
- Nephritic syndrome
- Polycystic ovarian syndrome
- Systemic lupus erythematosus
- Thyroid disorders

Signs and symptoms

Clinical Features

- Insidious disease
- Asymptomatic no symptoms of liver disease
- Secondary symptoms to complications of obesity
- RU& Abdominal Pain
- Fatigue or Malaise
- Increased Waist circumference
- Cutaneous stride
- Acanthosis-nigricans in 50%
- Hepatomegaly 40%-50% by imaging & splenomegaly
- GERD
- Obstructure sleep apnea
- Type-2 Diabetes

Risk factors and associations

1-Obesity •

2- Insulin resistance and the metabolic syndrome •

3- Age and environments •

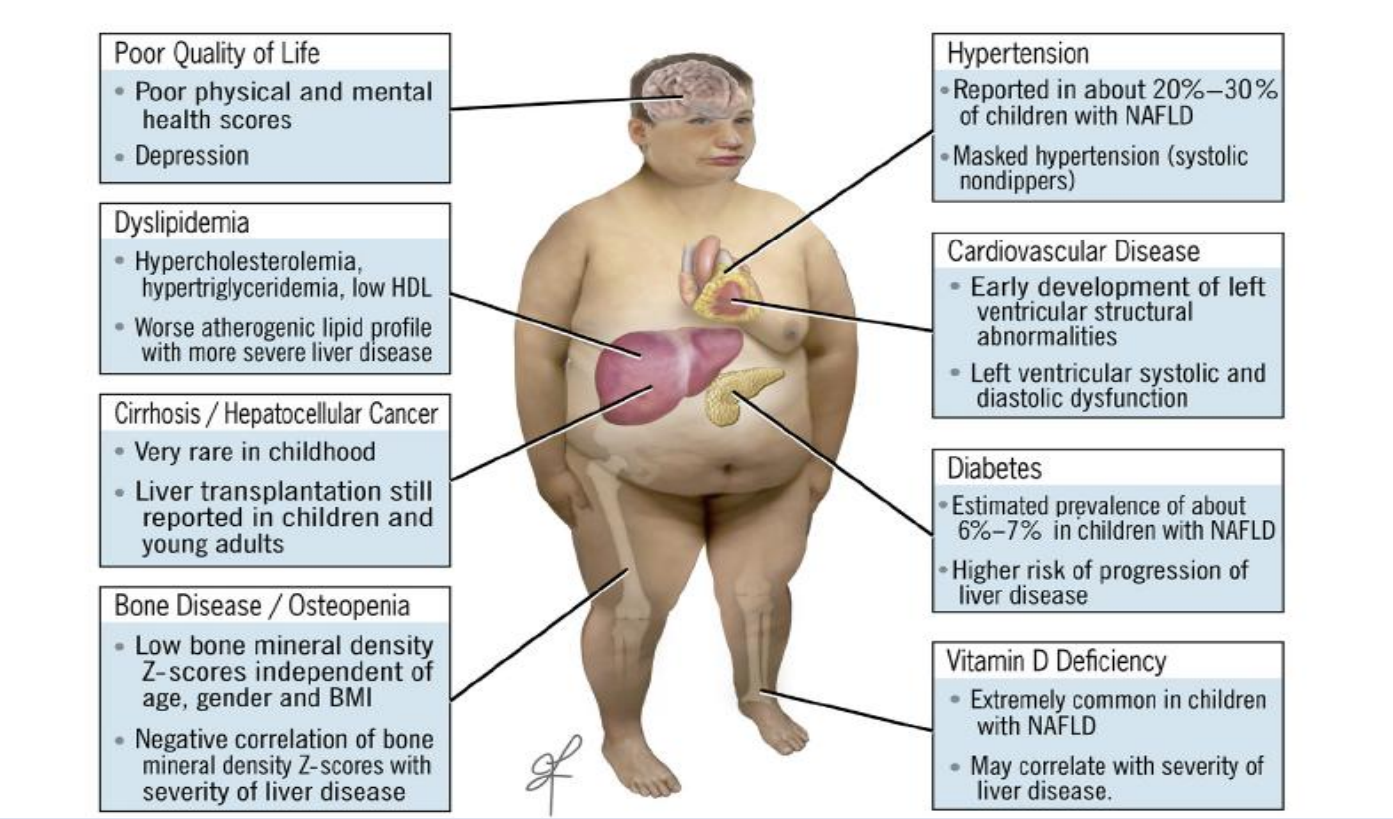
• 4-Gender and ethnicity

5-cardiovascular disease •

6- Obstructive sleep apnea •

• 7-Quality of life

Extrahepatic complications in children with NAFLD



Diagnostic Methods

- Approches in Pediatric NAFLD are not well defined

Diagnosis of NAFLD

- Suspected:

- over weight or obese

-With ALT one to six times upper limit of normal

- probable Diagnosis:

- excluding other causes of liver diseases

- definitive diagnosis :

-Liver biopsy is the gold standard for diagnosing NAFLD

Diagnostic Methods

- Approches in Pediatric NAFLD are not well defined
- Ultrasonography
- Fibscan
- Liver biopsy
- Currently, the best screening test for NAFLD in children is ALT; however, it has substantial limitations

Diagnosis

- NAFLD is a diagnosis of exclusion

  -Alcoholic Hepatitis

  -Drug induced Hepatitis (tamoxifen, amiodarone)

  -Viral Hepatitis

  -Autoimmune Hepatitis

  -Metabolic (Wilson and Hemochromatosis)

Screening(1)

1. ages 9 and 11 years for all obese children (BMI 95th percentile
2. overweight children (BMI 85th and<94th percentile) with additional risk factors (central adiposity, insulin resistance, prediabetes or diabetes, dyslipidemia, sleep apnea, or family history of NAFLD/NASH)
3. Earlier screening can be considered in younger patients with risk factors such as severe obesity, family history of NAFLD/NASH, or hypopituitarism

Screening(2)

1. Consider screening of siblings and parents of children with NAFLD if they have known risk factors for NAFLD (obesity, ethnicity, insulin resistance, prediabetes, diabetes, dyslipidemia).
2. Currently, the best screening test for NAFLD in children is ALT; however, it has substantial limitations.

Screening(3)

1. Interpretation of ALT should be based upon sex-specific upper limits of normal in children (22 U/L for girls and 26 U/L for boys) and not individual
2. Persistently (>3 months) elevated ALT more than twice the upper limit of normal should be evaluated for NAFLD or other causes of chronic hepatitis.

Screening(4)

1. ALT of >80 U/L warrants increased clinical concern and timely evaluation, as the likelihood of significant liver disease is higher.
2. routine ultrasound is not recommended as a screening test for NAFLD in children due to inadequate sensitivity and specificity.

Follow-up screening for NAFLD(1)

1. When the initial screening test is normal, consider repeating ALT every 2 to 3 years if risk factors remain unchanged.
2. Consider repeating screening sooner if clinical risk factors of NAFLD increase in number or severity. Examples include excessive weight gain or development of other medical problems that increase risk of NAFLD, such as type 2 diabetes or obstructive sleep apnea.

Follow-up screening for NAFLD(2)

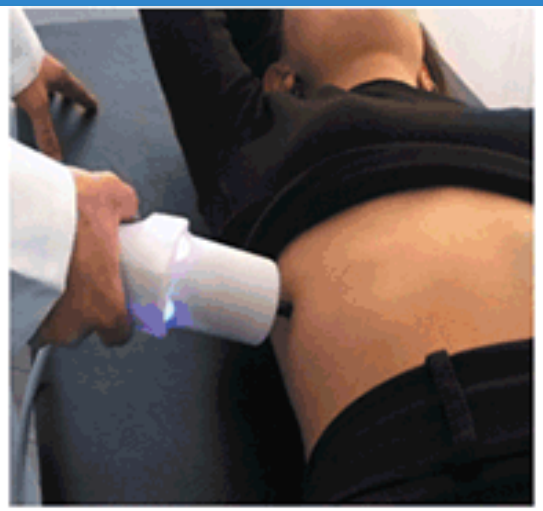
1. evaluating a child suspected to have NAFLD, it is recommended to exclude alternative etiologies for elevated ALT and/or hepatic steatosis and investigate the presence of coexisting chronic liver diseases
2. Liver biopsy should be considered for the assessment of NAFLD in children who have increased risk of NASH and/or advanced fibrosis. Potential clinical signs of increased risk of fibrosis in children with NASH may include higher ALT (>80 U/L), splenomegaly, and AST/ALT >1. Known clinical risk factors for NASH and advanced fibrosis include panhypopituitarism and type 2 diabetes.

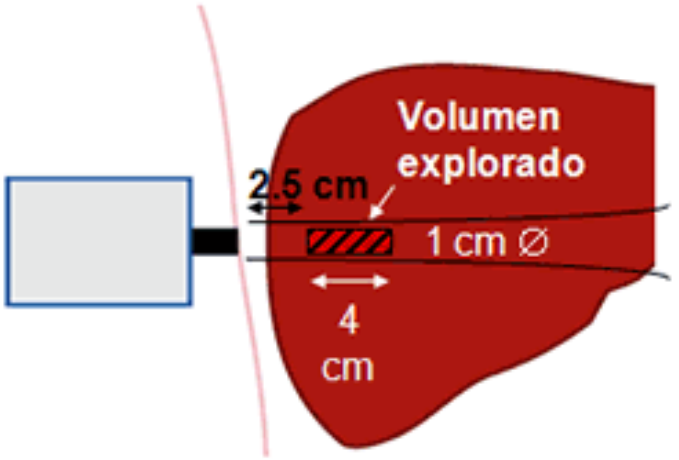
Follow-up screening for NAFLD(3)

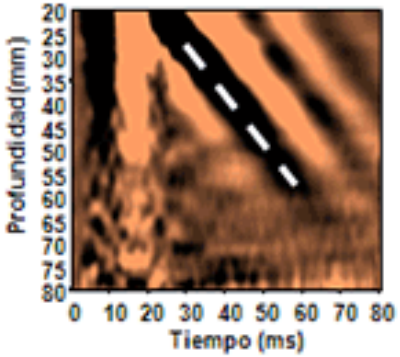
1. The use of ultrasound is not recommended for the determination or quantification of steatosis due to poor sensitivity and specificity. Ultrasound may be useful for assessing other causes of liver disease such as masses, gallbladder disease, changes associated with portal hypertension
2. The use of CT is not recommended for determination or quantification of steatosis due to radiation risk.
3. Assessment of change in fibrosis over time is reasonable as a treatment outcome in children over longer time periods (2 years) and currently requires a liver Biopsy

FIBROSCAN

- -It is a new non invasive modality which can detect Liver fibrosis
- -Many patient with fatty liver may turn out to be fibrosis in Fibroscan which
- completely change the prognosis of condition

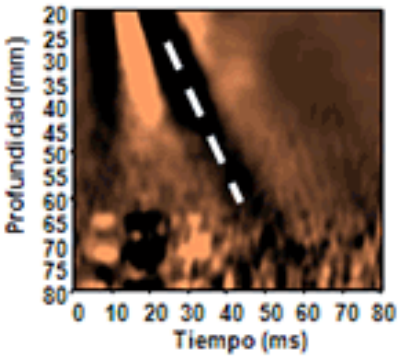






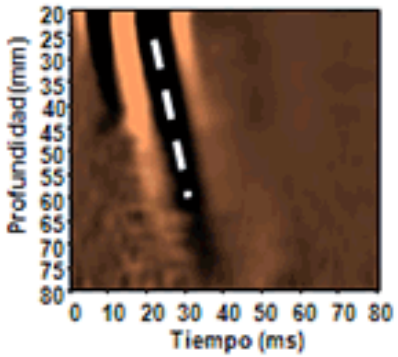
V_S = 1.1 m/s

~ 3 kPa



V_S = 1.7 m/s

~ 9 kPa



V_S = 3.6 m/s

~ 40 kPa

F0 F1 F2 F3 F4

Liver Biopsy

- NAFLD → Histologic → Steatosis in≥5% of the hepatocytes after excluding other causes of hepatic Steatosis

↓

Type 2 NASH (Inflammation or Fibrosis)was the most common histologic pattern seen in younger children with NAFLD

↓

Cirhosis

Hepatoce illuar carcinoma 4

Liver Biopsy

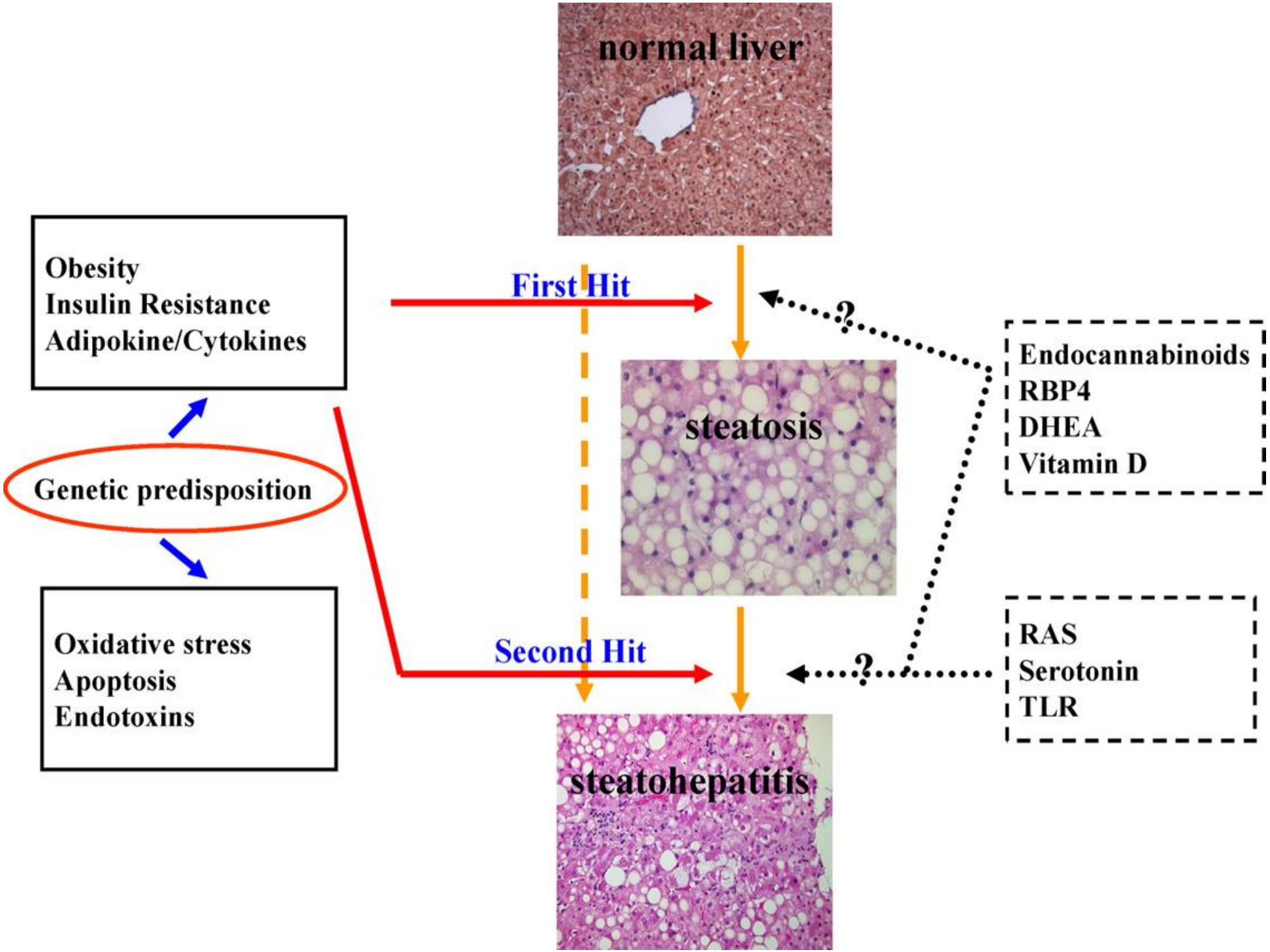
- Gold standard in the evaluation of Steatosis,NASH,NAFLD-Liver Fibrosis
- Macrovesicular Steatosis in ≥ 5 of the heptocystes
- NAFLD
- Viral Hepatitis
- Atoimmunce
- Wilson Disease
- NASH type 2(pediatric type)10-23%
- NASH Type 1(Adult type)
- Cirhosis-liver tran-Heptocellular casrcinoma

Liver Bx

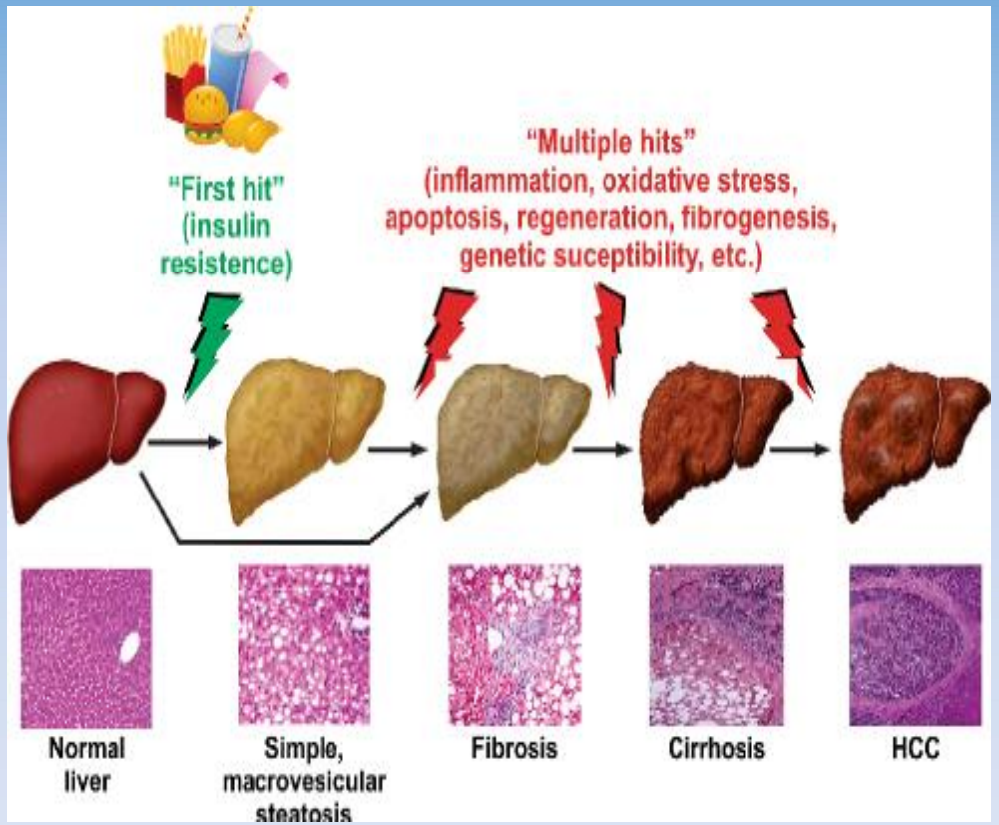
Indications for liver Bx in NAFLD:

1. ALT > 80
2. Splenomegaly
3. AST/ALT> 1
4. Panhypopituitarism
5. T2DM

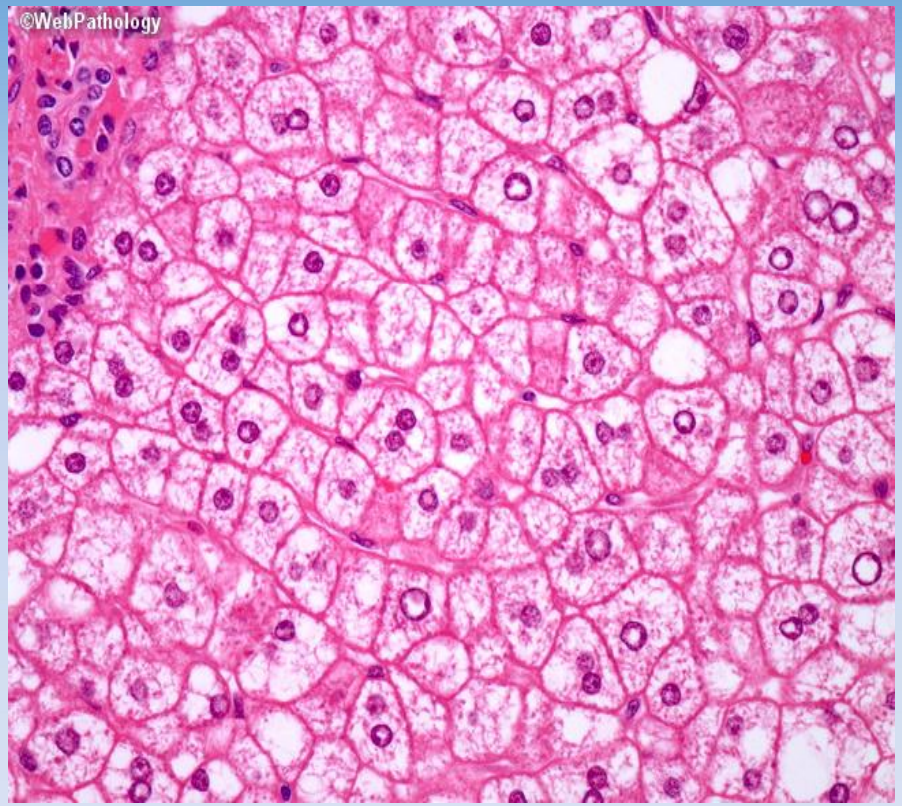
(Increased risk of NASH and/or advanced fibrosis)


normal liver
Obesity
Insulin Resistance
Adipokine/Cytokines
First Hit
?
Endocannabinoids
RBP4
DHEA
Vitamin D
steatosis
Genetic predisposition
Oxidative stress
Apoptosis
Endotoxins
Second Hit
?
RAS
Serotonin
TLR
steatohepatitis

histology

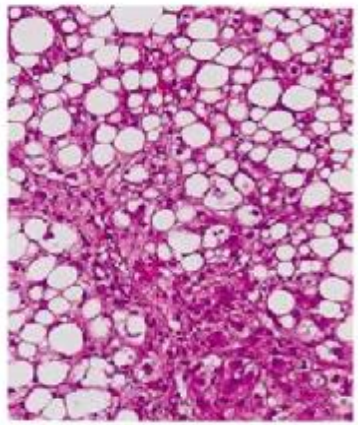

"First hit"
(insulin
resistence)
"Multiple hits"
(inflammation, oxidative stress,
apoptosis, regeneration, fibrogenesis,
genetic suceptibility, etc.)
Normal
liver
Simple,
macrovesicular
steatosis
Fibrosis
Cirrhosis
HCC

Ballooning degeneration in NASH

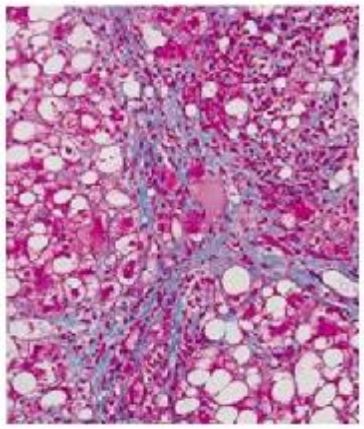


NASH

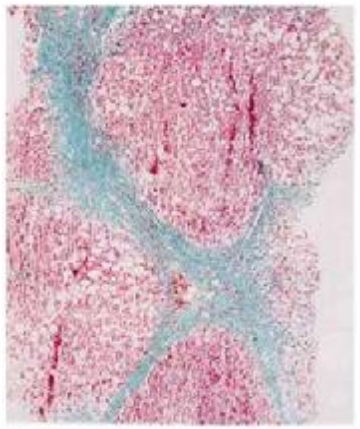
NASH HISTOLOGY



NASH: H and E stain, steatosis, swollen hepatocytes, inflammation, bridging fibrosis



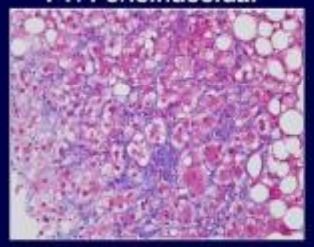
NASH: Trichrome stain: pericellular fibrosis and bridging fibrosis



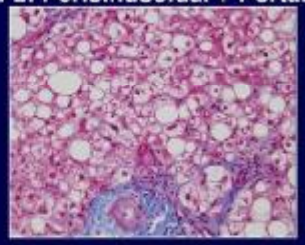
Cirrhosis: wide frbrous bands and nodularity

Fibrosis Staging in NASH

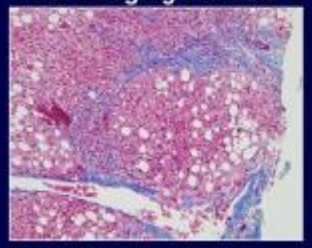
F1: Perisinusoidal



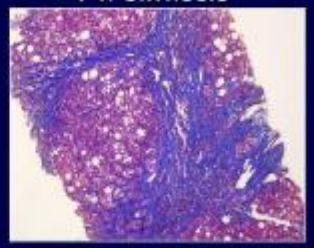
F2: Perisinusoidal + Portal



F3: Bridging Fibrosis

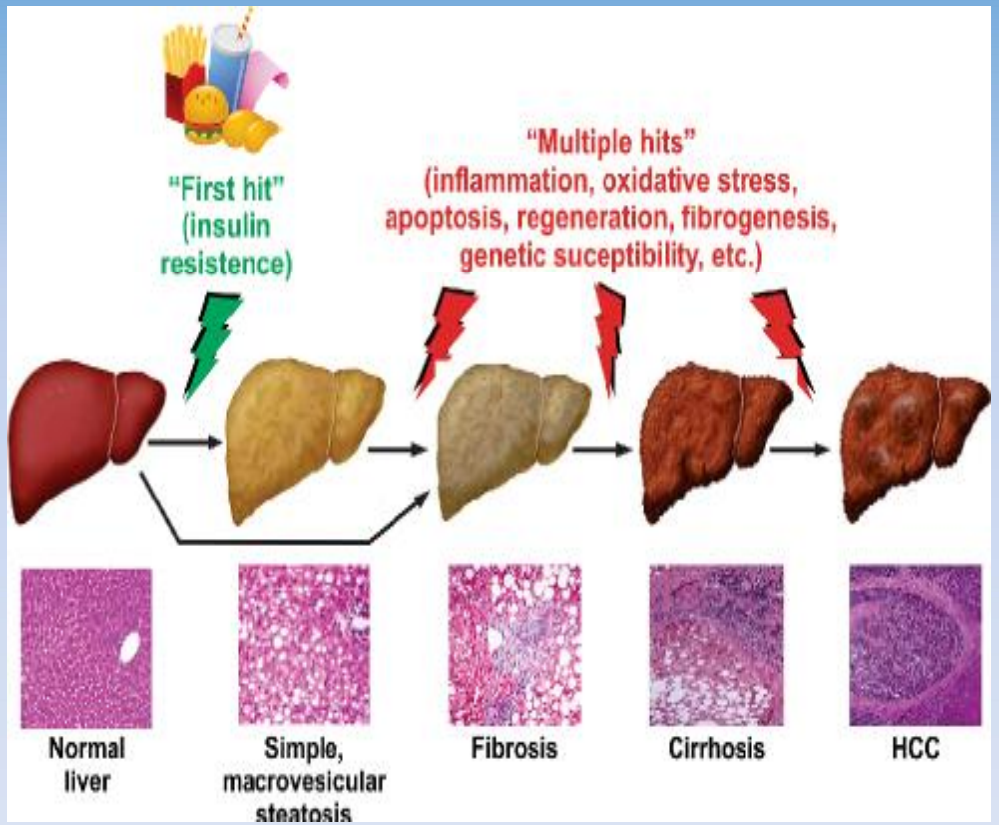


F4: Cirrhosis



Slide credit: clinicaloptions.com

histology


"First hit"
(insulin
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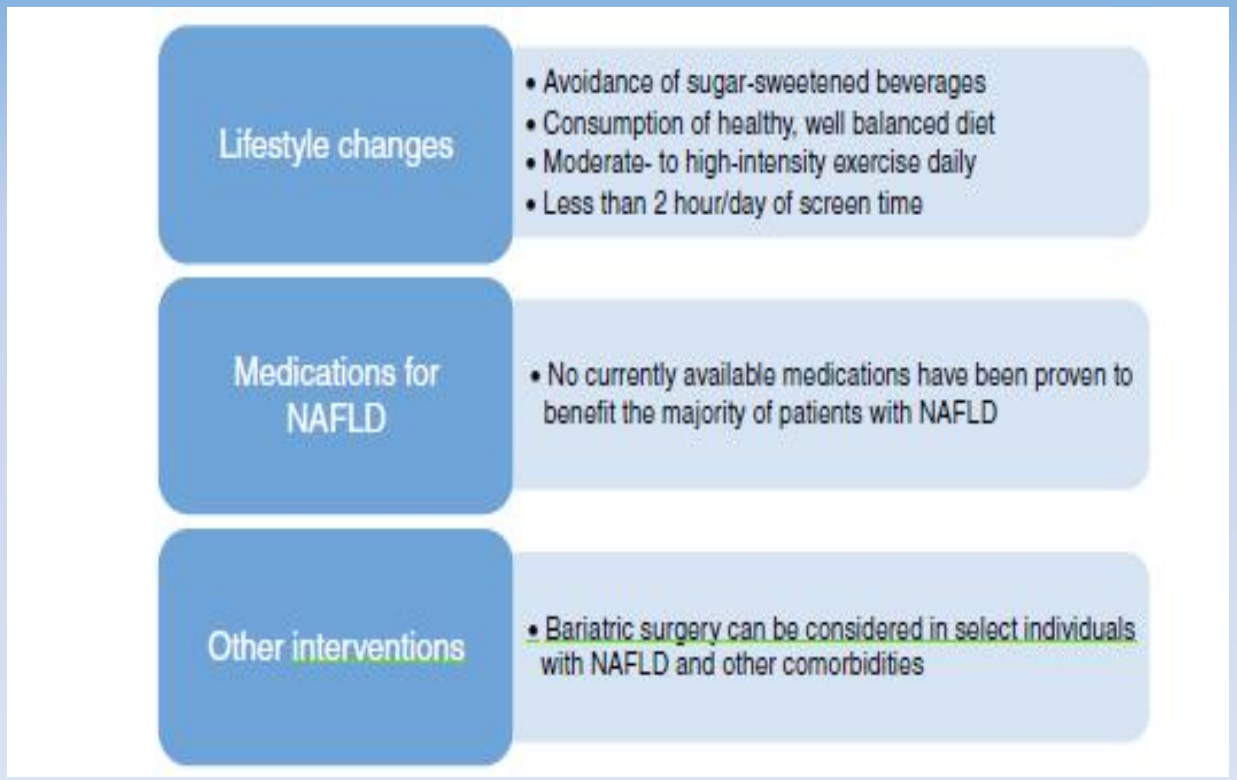
"Multiple hits"
(inflammation, oxidative stress,
apoptosis, regeneration, fibrogenesis,
genetic suceptibility, etc.)
Normal
liver
Simple,
macrovesicular
steatosis
Fibrosis
Cirrhosis
HCC

Goal of treatment

- 1-decrease in steatosis
- 2- Decrease in inflammation
- 3- Decrease in fibrosis

Treatment options in pediatric NAFLD



Lifestyle(1)

1. improve diet and increase physical activity are recommended as the first-line treatment for all children with NAFLD
2. Avoidance of sugar-sweetened beverages is recommended as a strategy to decrease adiposity
3. Increasing 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

Practical recommendations for lifestyle modification

- Exercise goal is 30–45 minutes of activities that increase heart rate at least three times weekly
- Walking is a good start for people completely sedentary, but the goal is to move onto aerobic activities as fitness improves
- Vary exercise activities over time
- Seek a trainer to guide develop and plan to maintain consistency
- Do not think of weight loss as the goal of exercise; the goal of exercise is to change the body's metabolism and improve the sense of well-being
- Limit ''screen time'' in front of televisions, computers, and video games
- Focus on healthy eating, not dieting
- Eat a protein-containing breakfast daily (eg, meat, cheese, eggs, yoghurt)
- Avoid fasting
- Eliminate sugar-sweetened beverages (sodas, sweetened tea, and so forth)
- Avoid trans-fats, including foods labeled as trans-fat free but containing hydrogenated or

partially hydrogenated vegetable oil

Lifestyle(2)

1. No currently available medications or supplements are recommended to treat NAFLD because none have been proven to benefit the majority of patients with NAFLD
2. Bariatric surgery is not recommended as a specific therapy for NAFLD given lack of outcome data in adolescents. Bariatric surgery may be considered for selected adolescents with BMI 35 kg/m2, who have noncirrhotic NAFLD and other serious comorbidities (eg, T2DM, severe sleep apnea, idiopathic intracranial hypertension) that are likely to improve with WLS

Lifestyle(3)

1. Children with NAFLD should be screened for dyslipidemia at diagnosis and periodically as indicated by current lipid guidelines for children
2. monitor blood pressure in children with NAFLD
3. screen children with NAFLD for diabetes at diagnosis and annually
4. follow children with NAFLD on a yearly basis at a minimum to monitor for progression of disease and provide treatment

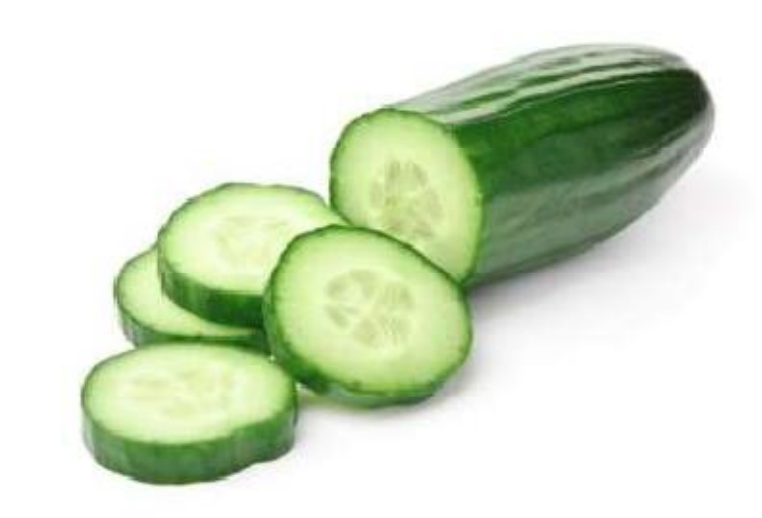
Lifestyle(4)

1. A repeat liver biopsy to assess progression of disease (particularly fibrosis) and to guide treatment is reasonable to consider 2 to 3 years after the first liver biopsy, especially in patients with new or ongoing risk factors, such as type 2 diabetes mellitus, NASH, or fibrosis at diagnosis. Strength
2. Families of children with NAFLD should be counseled about risks of secondhand smoke exposure and adolescents with NAFLD should be counseled against smoking and use of electronic nicotine delivery devices. Strength

WEIGHT REDUCTION

- -10% of body weight to be reduced in 6-8months
- -Severe hypo caloric diets are not recommended
- -Eat fewer calories and burn more calories by regular exercises

Fructose rich foods




Coca-Cola

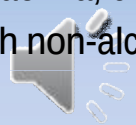
- EXERCISE
- 45min/day
- -5days/week
- -To achieve a target rate of 60-70% of maximal heart rate

- VITAMIN E
- -@ Tocopherol
- - Studies have shown that Vitamin E (400-1200 IU/day orally) if given for
- 4-12 months and led to significant improvement in Hepatic Aminotransferase
- - @ Tocopherol 300mg/day was given for 1 year to patients with liver biopsy
- proven NASH and those with a clinical diagnosis of NAFLD.
- Hepatic transaminases improved significantly compared to baseline whereas steatosis
- , fibrosis improved or remain same.
- 247 adults with nonalcoholic steatohepatitis and without diabetes
- to receive pioglitazone at a dose of 30 mg daily (80 subjects), vitamin E at a
- dose of 800 IU daily (84 subjects), or placebo (83 subjects), for 96 weeks.
- Vitamin E therapy, as compared with placebo, was associated with a significantly
- higher rate of improvement in nonalcoholic steatohepatitis (43% vs. 19%, P =

- Ursodeo
- -It is a no eoxycholic acid(endogenous bile acid)
- -Endogenous bile acids are hepatotoxic
- -Ursodeoxycholic acid are non hepatotoxins, has membrane stabilising
- activity, decreases oxidative stress on liver.
- -Studied showed no benefit over Placebo therapy when used at a dose of 13-
- 15mg/kg for 2 years .
- -Drug is found to be safe with no adverse affects
- -In few studies only improvement in liver enzymes were noticed after 6 months
- of therapy.
- - So to use or not still remains uncertain.

STATINS IN NAFLD

- -Studies are not much available
- -Studies till now has not shown any improvement in liver enzymes and histology
- as compared to placebo.
- - And they have beneficial role in preventing cardiovascular diseases.
- As statins can improve the adverse outcomes of other conditions commonly
- associated with NASH (for example, hyperlipidaemia, diabetes mellitus,
- metabolic syndrome), their use in patients with non-alcoholic
- steatohepatitis may be justified



[redacted]

- -Pentoxyfilline 400mg tds for 12months has been found to have significant
- improvement in both liver enzymes and histology in no. of studies
- Limitations : Side effects
- Side Effects
- 1) Nausea and vomitings
- 2) M.I
- 3) Pancytopenia
- 4) Anaphylactic reactions

- Pioglitazone 30mg/day for 1 year has been found to show improvement in NASH
- in all studies
- -There effect has been found to better in NASH with non diabetic when compared
- to Diabetic
- - Side effect : weight gain , edema and worsening of Heart failure.

مواظب من باشید