

Pediatric non-alcoholic fatty liver disease: an increasing public health issue

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Abstract Non-alcoholic fatty liver disease (NAFLD) is a multifactorial condition that encompasses a wide spectrum of liver abnormalities ranging from simple liver steatosis to steatohepatitis (non-alcoholic steatohepatitis), which may be associated with fibrosis and progress to cirrhosis and end-stage liver disease. NAFLD has recently become the most common cause of chronic liver disease in children and adolescents. NAFLD prevalence, alongside obesity, continues to increase among pediatric patients. Obesity is believed to represent a major risk factor for NAFLD, which is considered to be the liver presentation of the metabolic syndrome. Although the pathogenesis of NAFLD is not fully understood, the notion that multiple factors affect disease development and progression is widely accepted. Both genetic background and environmental factors contribute to NAFLD development. A more complete understanding of the pathogenesis may aid in developing non-invasive diagnostic tools and identifying new therapeutic targets. Liver biopsy currently remains the gold standard for NAFLD diagnosis and staging. Although lifestyle and diet modifications are key in NAFLD treatment, the development of new pharmacological therapies is crucial for patients who are unresponsive to first-line therapy. **Conclusion:** Pediatric NAFLD is an increasing public health issue that remains underdiagnosed. A large-scale screening in the high-risk population, especially among the overweight pediatric patients, should be considered, including measurement of serum transaminases and liver ultrasound. It is crucial to treat this condition as soon as possible in order to avoid the progression to end-stage liver disease.

Keywords Liver fibrosis · Non-alcoholic fatty liver disease · Pediatric patients · Steatohepatitis

Introduction

Over the past few decades, non-alcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease among children and adolescents in Western countries, with cases documented in children as young as 3 years of age [15]. NAFLD refers to a wide spectrum of liver abnormalities ranging from simple liver steatosis (fat accumulation in the liver) to steatohepatitis (non-alcoholic steatohepatitis, NASH), which may be associated with fibrosis and progress to cirrhosis and end-stage liver disease.

In 1952, S. Zelman documented liver lesions compatible with NASH for the first time [73]. Ludwig et al. used the term “NASH” in 1980 [32]. Three years later, the first pediatric NASH cases were reported [38].

NAFLD prevalence is increasing, alongside obesity, essentially because of sedentary lifestyles and hypercaloric diets [4]. NAFLD is considered the hepatic manifestation of the metabolic syndrome, which is characterized by insulin resistance, visceral obesity, hypertension, dyslipidemia, and abnormalities of fasting serum glucose levels. Pediatric patients with NAFLD have been shown to exhibit higher levels of insulin, total cholesterol, triglycerides, low-density lipoprotein cholesterol, and fasting glucose, as well as higher blood pressure values than obese children without NAFLD. Moreover, children with metabolic syndrome are more likely to display NAFLD than obese children without metabolic syndrome [61]. NAFLD is also associated with an increased risk of developing cardiovascular diseases [52]. NAFLD patients have a higher prevalence of atherosclerosis [50].

NAFLD pathogenesis is not yet fully understood, but the hypothesis that multiple factors contribute to disease development and progression is now widely accepted [3].

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Histological liver analysis remains the gold standard to differentiate between simple steatosis and NASH, to perform disease staging, and to exclude other causes of chronic liver diseases [66].

No effective treatment is currently available. In children, weight loss and physical activity are considered first-line treatment. However, a poor compliance to lifestyle modifications is a daily reality. Developing new treatments to stop the disease from progressing to end-stage liver disease appears therefore crucial. Over the past several years, new pharmacological treatments have been developed and tested [5].

In this review, we will present an overview of current knowledge regarding the pathogenesis, diagnostic methods, histological features, and treatment of pediatric NAFLD.

Epidemiology

According to epidemiological data, NAFLD may affect 3–10 % of pediatric patients, with a male-to-female ratio of 2:1 [4]. Obesity is thought to be the main risk factor for pediatric NAFLD. In obese children, NAFLD prevalence may reach 70–80 % [36].

However, true NAFLD prevalence in children is unknown. Indeed, only a few studies have been conducted with children and adolescents. Moreover, in most studies on NAFLD prevalence in children, indirect measures such as blood tests and ultrasound were used as screening tools. Serum alanine aminotransferase (ALT) sensitivity and specificity are poor (64 and 81 %, respectively). Sensitivity is low, as some NAFLD children may present ALT values in the normal range [33]. Furthermore, various cutoff levels are cited in the literature. Ultrasound exhibits limited detection capabilities: this tool identifies only high levels of fat (>30 %) and cannot detect fibrosis [56]. Liver histology, the most relevant diagnosis criterion, is rarely used for screening [71].

More accurate estimates of disease prevalence in the USA were obtained from an autopsy study in San Diego. Steatosis was found in 9.6 % of individuals aged 2 to 19 years and in 38 % of obese children autopsied between 1993 and 2003 [59]. A liver biopsy study during gastric bypass surgery was performed in morbidly obese adolescents. This cohort showed a high NAFLD prevalence (83 %), with 20 % of participants meeting the histological criteria for NASH [72].

NAFLD prevalence appears to increase with age, with a mean age at diagnosis between 11 and 13 years [71]. This tendency is likely explained by adolescent hormonal changes, which result in an increase in serum insulin levels and fat accumulation in the liver [55]. Ethnicity may also affect NAFLD prevalence. Hispanic children have the highest NAFLD prevalence (36 %), whereas African American children are less affected (14 %), although both populations exhibit similar obesity rates [21]. These discrepancies may

be accounted for by genetic factors or environmental features, such as diet and exercise [16].

The prognosis of pediatric NAFLD is still unknown, as only a limited number of long-term follow-up studies have been conducted to date [3]. The first long-term study with a follow-up period of up to 20 years, which assessed overall survival of NAFLD pediatric patients, reported a shorter long-term survival than non-affected patients [71].

Pathogenesis

NAFLD was initially considered a two-hit process. At present, however, the notion that NAFLD pathogenesis is multifactorial with many factors affecting disease development and progression is widely accepted. The “multiple-hit” hypothesis is currently the established pathogenetic model [17].

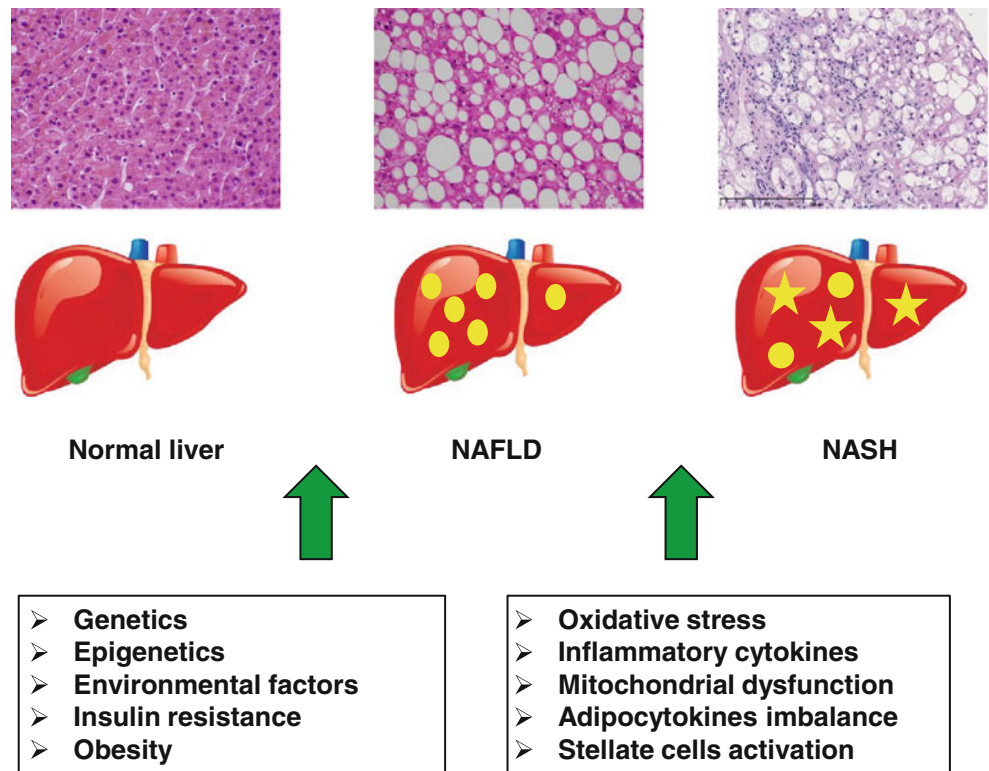
At disease onset, NAFLD is characterized by fat accumulation in the liver (steatosis) and insulin resistance, influenced by genetic susceptibility, epigenetic mechanisms, a sedentary lifestyle, and hypercaloric diets [48]. Hepatic triglyceride accumulation results from increased delivery of free fatty acids to the liver, increased lipogenesis, and impaired fatty acid metabolism in hepatocytes. Hepatic fat accumulation has been shown to exacerbate insulin resistance by interfering with phosphorylation of insulin receptor substrates [57]. Free fatty acid accumulation and insulin resistance may predispose the fatty liver to secondary hits, including oxidative stress, mitochondrial dysfunction, pro-inflammatory cytokines imbalance, and stellate cells activation, which lead to necroinflammation and fibrosis [64] (Fig. 1).

The gut’s critical role in NAFLD pathogenesis has recently been given consideration. In NAFLD, an alteration of gut microbiota and enhanced gut permeability increase liver exposure to gut-derived bacterial products, such as lipopolysaccharides. These products stimulate innate immune receptors (Toll-like receptors), which leads to activation of the signaling pathways involved in liver inflammation and fibrogenesis [22].

Hepatic stellate cells are considered the main extracellular matrix-producing cells during NASH development. However, the hepatic progenitor cell compartment of the liver has recently been shown to be expanded in children with NAFLD. Hepatic progenitor cell activation appears to play a role in liver response to oxidative stress and is correlated with fibrosis and NASH progression [43].

Adipocytokines, including adiponectin, leptin, resistin, and tumour necrosis factor-alpha (TNF-alpha), also appear to be involved in the progression of simple steatosis to NASH. Adipocytes or inflammatory cells infiltrating the adipose tissue in insulin resistance conditions are responsible for adipocytokine secretion. Leptin may activate hepatic stellate cells and suppress their apoptosis.

Fig. 1 Pathogenesis of NAFLD: the “multiple-hit” hypothesis. Genetics, epigenetics, environmental factors, insulin resistance, and obesity influence fat accumulation in the liver (steatosis). The fatty liver is then predisposed to secondary hits, including oxidative stress, mitochondrial dysfunction, pro-inflammatory cytokines imbalance, and stellate cells activation, which lead to necro-inflammation and fibrosis (*NASH* non-alcoholic steatohepatitis)



The expansion of adipose tissue, and particularly that of visceral fat, is associated with a decrease in the release of insulin-sensitizing and anti-inflammatory cytokines and an increase in the release of pro-inflammatory molecules [34]. TNF-alpha and IL-6 levels are often elevated in the liver and blood of NASH patients. These cytokines are involved in Kupffer cell recruitment and activation, as well as in hepatic stellate cell activation in myofibroblasts [48].

To summarize, NAFLD results from crosstalk between multiple organs, including adipose tissue, the pancreas, gut, and liver.

Diagnosis of NAFLD/NASH

NAFLD is often diagnosed in asymptomatic patients, with unexplained increased serum aminotransferase or gamma-glutamyl transpeptidase values detected during routine check-ups. However, some patients may suffer from abdominal pain; hepatomegaly may be present, whereas splenomegaly is rare.

For diagnosing NAFLD, it is necessary to eliminate other liver disease etiologies, such as hepatitis B and C, autoimmune hepatitis, drug-induced liver injury, Wilson’s disease, alpha 1-antitrypsin deficiency, inborn errors of fatty acid or carnitine metabolism, peroxisomal disorders, lysosomal storage disorders, and cystic fibrosis. However, positive serum autoantibodies (antinuclear and anti-SMA) are often present in NAFLD pediatric patients, in the absence of autoimmune hepatitis. Their clinical significance remains unclear [3].

Indirect markers

Enhanced ALT levels are common among pediatric patients with NAFLD [51]. Aminotransferase levels may range from normal to four to six times the upper limit of normal. Mild aminotransferase elevation is usually observed in NAFLD patients (1.5–2 times the upper limit of normal) [8]. However, circulating aminotransferases levels are frequently normal in children with NAFLD and NASH. Furthermore, normal aminotransferase levels do not exclude possible fibrosis or cirrhosis. Together with fibrosis progression and steatosis reduction, aminotransferase levels may decrease. Therefore, this test is not representative of NAFLD severity. Moreover, dietary habits and hyperalimentation may impact on serum aminotransferase levels [24].

Lipid profiles, fasting glucose, and insulin levels should be evaluated in children with NAFLD, who often present with several metabolic syndrome components [3].

Imaging techniques

Ultrasonography (US) is the most common imaging modality for fatty liver detection. US has several advantages, such as its relatively low cost and wide availability. A recent study demonstrated liver US efficacy for quantifying steatosis in children. A strong correlation between US steatosis scores and steatosis severity on liver biopsy was observed [62]. However, US sensitivity decreases when the liver contains <30 % fat or

in individuals with BMI ≥ 40 [56]. Moreover, US cannot exclude steatohepatitis or fibrosis.

Computed tomography is a more sensitive technique for detecting fat in the liver, but its use is not recommended in children because of radiation exposure. Magnetic resonance imaging is also relatively sensitive in liver fat quantification, although its costs and the need for sedation in young children limit its clinical utility. Finally, none of these imaging tools exhibits sufficient sensitivity and specificity to differentiate between simple steatosis and NASH or to perform disease staging [53].

Transient elastography is an accurate tool for liver fibrosis detection and has been validated for liver fibrosis assessment in several liver diseases. A study conducted in children and adolescents with NAFLD showed that transient elastography is an accurate and reproducible methodology for identifying children without fibrosis or with advanced fibrosis [49]. However, this tool is unable to discriminate between intermediate degrees of fibrosis and thus unsuited for providing reliable disease stage indications [47].

Liver biopsy

Liver biopsy remains the gold standard in NAFLD diagnosis. Indeed, this is the only way to distinguish between simple steatosis and NASH, to determine the severity of liver damage and inflammatory activity, and to assess the degree of fibrosis. Yet liver biopsy is an invasive method that may be associated with complication, such as bleeding. Therefore, research has been undertaken to develop non-invasive tools capable of monitoring disease evolution and therapeutic responses.

Histology remains also a useful tool to exclude other causes of chronic liver disease, as mentioned above.

Development of non-invasive tools

Certain clinical parameters, such as age, insulin resistance, BMI, waist circumference, and lipid and glucose profiles, may be useful for identifying children with potentially severe NAFLD [66]. The pediatric NAFLD fibrosis index (PNFI) was developed on the basis of three clinical parameters: age, waist circumference, and triglyceride levels. This index aims to predict liver fibrosis in children with NAFLD [41]. Although the index provides a good positive predictive value, its negative predictive value for ruling out fibrosis is not optimal.

Recently, the combination of the enhanced liver fibrosis test and PNFI has proved relatively accurate for predicting liver fibrosis in children with NAFLD [6]. The enhanced liver fibrosis test includes a panel of serum markers that are extracellular matrix components, namely the tissue inhibitor of metalloproteinase-1, hyaluronic acid, and amino-terminal propeptide of type III collagen.

Biomarkers related to hepatocyte apoptosis have been developed in order to stratify disease severity in pediatric NAFLD. Caspase-generated cytokeratin-18 fragments are

specific by-products of liver cell apoptosis. Fitzpatrick et al. showed that children with NAFLD have elevated levels of cytokeratin-18 fragments, and that those with NASH have markedly higher levels of cytokeratin-18 fragments [20].

Several other biomarkers of oxidative stress, inflammation, and fibrosis are currently under investigation. However, larger studies must be undertaken before using these markers in pediatric clinics [19].

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- NAFLD is often diagnosed in asymptomatic patients with unexplained increased ALT levels.
 - The ALT level is not correlated with NAFLD severity.
 - Ultrasonography can detect steatosis when the liver contains more than 30 % fat but cannot exclude steatohepatitis or fibrosis.
 - Liver biopsy remains the gold standard for the diagnosis of NAFLD.
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Histology

Children with NAFLD exhibit the same morphological lesions as adults, namely hepatocellular injury, inflammation, and fibrosis. However, there is a unique pattern of lesion distribution in children. This pattern is characterized by macrovesicular hepatocellular steatosis, portal inflammation, and portal fibrosis in the absence of ballooning [26].

In 2005, Schwimmer et al. described two different forms of pediatric steatohepatitis. Type 1, which is characterized by the start of steatosis in the perivenular zone, ballooning, and perisinusoidal fibrosis, is similar to the adult pattern. Type 2 is characterized by periportal or panacinar steatosis, portal inflammation, and portal fibrosis in the absence of ballooning. This pattern was found in the majority of children [58]. This classification was not widely used as, a few years later, an overlap pattern combining features of both types was found in >50 % NAFLD children [14].

Potential mechanisms that explain the different histological patterns between adults and children remain unclear. However, a recent study by Swiderska-Syn et al. hypothesized that the Hedgehog pathway, which is involved in fibro-ductular response, may account for the unique histological features of pediatric NAFLD. In fact, the portal and periportal compartments of pre-pubescent male livers were shown to exhibit high Hedgehog pathway activity [63].

Steatosis

Steatosis refers to the abnormal accumulation of fat in hepatocytes. The minimum criterion for NAFLD diagnosis is the presence of steatosis in >5 % hepatocytes [64]. In NAFLD, steatosis is mainly macrovacuolar. On occasion, microvacuolar steatosis may be found [12]. In NAFLD, steatosis may also affect the whole parenchyma.

The pattern of steatosis distribution is different in children than in adults. In adults, steatosis starts in the perivenular zone (zone 3), whereas in children, it commonly begins in the periportal zone [58].

Ballooning

Ballooning is the main morphological feature of hepatocellular damage from NASH. Ballooning is defined as a cellular enlargement of 1.5–2 times the normal hepatocyte diameter. The hepatocyte cytoplasm is clarified, rarefied, and may contain Mallory–Denk bodies, which are eosinophilic inclusions composed of cytoskeletal peptides aggregates. In adults, ballooning is usually observed in zone 3; in children, Mallory–Denk bodies and ballooned hepatocytes are rather uncommon [3].

Inflammation

Inflammatory infiltrates, a key marker of NASH, are usually composed of lymphocytes, histiocytes, and Kupffer cells, with only few granulocytes found [9]. In adults, inflammation is prevalent in lobular spaces, whereas in children, infiltrates are found mainly in the portal tracts [2].

Fibrosis

Fibrosis, a histological marker of chronic liver damage, typically starts in acinar zone 3 in adults, with a characteristic chicken wire pattern. In children, fibrosis is observed mainly in the portal–periportal tract. In advanced disease stages, bridging fibrosis and cirrhosis may develop [11].

Scoring systems

Several scoring systems have been developed, of which two most widely used are the Brunt Score for NASH [10] and the NAFLD activity score, developed by the National Institute of Diabetes and Digestive and Kidney Diseases and the NASH Clinical Research Network for NAFLD [25], respectively. Both systems provide a numerical score that allows for grading disease activity and staging fibrosis.

Since the detection of histological pattern differences between NAFLD children and adults, a new grading score (PNHS) has been developed for pediatric NAFLD. This scoring system accounts for the presence of portal inflammation, with a weighing of each histological feature [7].

Treatment

As previously mentioned, NAFLD may progress to cirrhosis and end-stage liver disease. Therefore, patients affected by this condition should be treated as soon as possible.

Diet and lifestyle modifications

The first-line treatment in all NAFLD patients concerns lifestyle modifications so as to achieve gradual weight loss. By reducing dietary intake and increasing physical activity, patients may achieve weight loss. These lifestyle modifications may positively impact on serum aminotransferase levels and various metabolic parameters, such as insulin resistance, fasting glucose, and lipids [46, 54]. Improvement in insulin resistance appears to be the parameter most strongly associated with NAFLD improvement. Insulin resistance can be evaluated using the homeostasis model assessment of insulin resistance (HOMA-IR) [27].

Nobili et al. showed that liver histology significantly improved following lifestyle modifications over a 24-month period, with improvements in steatosis, inflammation, hepatocyte ballooning, and NAFLD activity score observed [45].

It should, however, be noted that children's diets must be well-balanced, with respect of the food pyramid principle, in order to promote harmonic growth. A follow-up by a dietician is therefore crucial.

Currently, no evidence-based guidelines that recommend a particular diet or exercise are available. However, a reduction in fast-release carbohydrate consumption, especially that of fructose, is advised not only to improve insulin resistance and reduce lipogenesis, but also to counteract the pro-inflammatory and fibrogenic effects of fructose [1].

Yet, compliance to such lifestyle modifications is often poor, especially in adolescents. A multidisciplinary approach and a support by a dietician may be helpful in order to assess diet quality and measure caloric intake.

Bariatric surgery has been shown to improve liver damage in adults [70]. However, very few data are available for adolescents. Standardization of eligibility criteria for adolescents and further studies on safety and long-term efficacy of this approach are warranted [48].

Pharmacotherapy

To avoid severe organ damage, pharmacological therapies must be developed for children who do not adhere to or are unresponsive to lifestyle modifications.

Vitamin E

In pediatric studies, vitamin E efficacy was shown not to be superior to lifestyle changes alone [67, 69]. In a larger and more recent study (TONIC study), the effects of vitamin E, metformin, or placebo were assessed in NAFLD children. Although vitamin E treatment was not superior to placebo in terms of ALT level reduction, histological hepatocellular ballooning was shown to be improved under vitamin E treatment in children with biopsy-proven NASH [28].

Metformin

Metformin, an insulin-sensitizing agent, lowers hepatic glucose production and promotes glucose uptake in muscles. In 2005, Schwimmer et al. documented a hepatic steatosis reduction, evaluated using magnetic resonance spectroscopy and ALT levels, in non-diabetic children with biopsy-proven NASH who were treated with metformin 500 mg twice daily for 24 weeks [60]. A 2009 study, involving a cohort of 50 obese, multi-ethnic, and insulin-resistant adolescents, showed improvements in fatty liver prevalence and severity and in fasting insulin levels in metformin-treated patients in comparison with placebo-treated patients [39]. However, in a pediatric study comparing metformin with lifestyle interventions, Nobili et al. were not able to confirm metformin's advantages in NAFLD [44]. More recently, the TONIC study demonstrated that neither metformin nor vitamin E was superior to placebo in reducing ALT levels, whereas both approaches improved hepatocellular ballooning, with no significant improvements observed among other histological features [28].

Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA), a hepatoprotective agent, is assumed to prevent NAFLD progression by protecting hepatocytes from bile salt-mediated mitochondrial injury, activating anti-apoptotic signalling pathways, and fulfilling immunomodulatory functions.

The potential efficacy of UDCA was evaluated in a randomized controlled trial involving 31 NAFLD children. In this study, UDCA (10 mg/kg/day) was shown to be ineffective in treating liver abnormalities in obese children [65].

Probiotics

With growing evidence that gut microbiota contributes to NAFLD progression, probiotics have been considered for NAFLD treatment. Studies undertaken on NAFLD animal models suggested that probiotics may reduce liver inflammation and improve gut epithelial barrier function [13, 18]. In 2005, Loguerico et al. evaluated the effect of a probiotic (VSL#3) in patients with chronic hepatopathies, including NAFLD. In this study, probiotics were shown to reduce liver injury and improve liver function tests [31]. In 2011, a double-blind, placebo-controlled pilot study was performed in obese children with persisting hypertransaminasemia and ultrasonographic bright liver. In this study, patients receiving probiotic therapy (*Lactobacillus* GG) exhibited a significant improvement in serum ALT and anti-peptidoglycan polysaccharide antibody levels that was independent of changes in BMI z score and visceral fat [68]. Based on these study findings,

probiotics may be considered a promising tool for pediatric NAFLD treatment.

Polyunsaturated fatty acids

Polyunsaturated fatty acids include essential fatty acids, such as omega-3 and omega-6. Recent studies, performed in NAFLD animal models and in adults, evaluated the effects of oral therapy using omega-3 fatty acids. These studies demonstrated fatty acids' anti-inflammatory and insulin-sensitizing properties, suggesting their potential role in NAFLD treatment [35]. In a recent double-blind, randomized, controlled trial conducted in children with NAFLD, a 6-month treatment with omega-3-docosahexaenoic acid (DHA) was reported to improve liver steatosis and insulin sensitivity, with no significant differences observed between the 250 and 500 mg/day doses [42]. These positive results were confirmed after a 24-month treatment period. Moreover, in the DHA-treated groups, triglyceride levels were lower after a 24-month treatment period, with lower ALT levels observed after a 12-month treatment period [40].

Novel therapeutic targets

Pentoxifylline, a phosphodiesterase inhibitor, antagonizes the TNF-alpha pathway. In NASH adults, this treatment was shown to promote a reduction in serum ALT levels and an improvement in histological features [30].

Farnesoid X receptors (FXR), which are expressed in the bowel and liver, are likely involved in NAFLD pathogenesis by mediating control of lipid and glucose homeostasis and bacterial flora growth. A reduction in hepatic inflammation and fibrogenesis may be induced through various mechanisms, and FXR agonists may have a potential role in NAFLD treatment. However, further studies must be undertaken before this agent can be considered a valid NAFLD treatment [23].

Toll-like receptors (TLR) are implicated in the pathogenesis of NAFLD. TLR stimulation results in inflammatory response activation, which plays a role in the progression of NAFLD to NASH. Therefore, TLR antagonists may prove to be potential therapeutic targets for pediatric NAFLD. However, further studies are required to support this hypothesis [37].

Incretin mimetics and dipeptidyl peptidase-4 (DPP-4) inhibitors increase insulin secretion. Glucagon-like peptide-1 (GLP-1), which is an incretin secreted in response to food intake, stimulates insulin secretion and inhibits glucagon release. DPP-4 is an enzyme implicated in the degradation of circulating GLP-1. Studies conducted in animals and in human adults demonstrated the efficacy of GLP-1 receptor agonists, which were resistant to DPP-4 degradation or DPP-4 inhibitors. These pharmacological agents represent potentially new therapeutic approaches to NAFLD treatment by

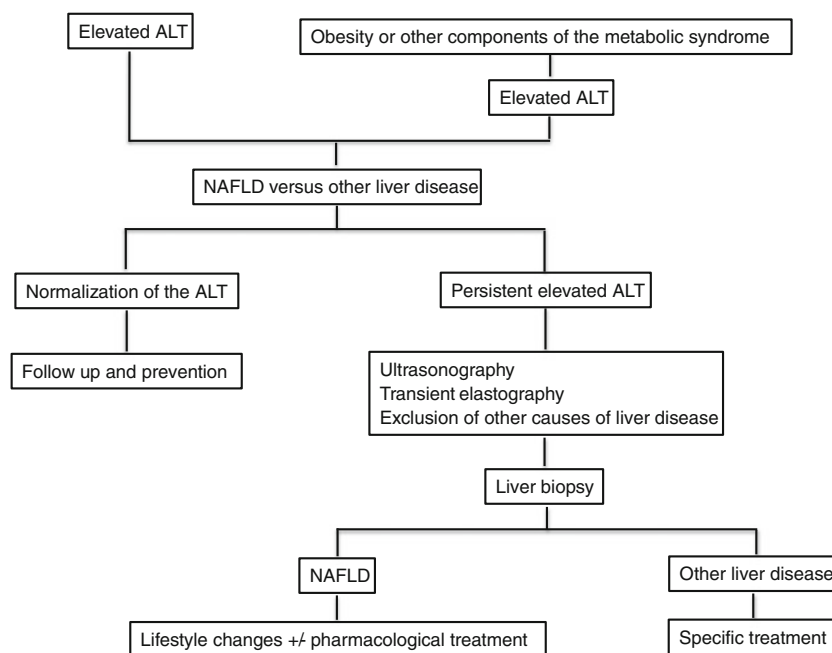


Fig. 2 Clinical algorithm for the management of pediatric NAFLD. In case of unexplained elevated ALT, of obesity, and/or of other comorbidities (insulin resistance, dyslipidemia, diabetes mellitus, hypertension), we recommend to perform a dosage of the liver transaminases. In case of normalization of the liver tests, the child has to be followed regularly by his pediatrician and a prevention should be introduced (diet and exercise). If the ALT remain elevated, an ultrasonography (and if necessary, a transient elastography) is recommended in order to detect the

presence of steatosis. Other causes of liver diseases should also be excluded. If NAFLD is suspected or if the etiology of the liver disease remains unclear, a liver biopsy is recommended in order to detect the presence of inflammation and/or fibrosis, to stage the disease, and to confirm the diagnosis. If the diagnosis of NAFLD is confirmed, lifestyle changes represent the first-line treatment. Pharmacological treatments can be considered for patients who do not adhere to or are unresponsive to lifestyle modifications

increasing fatty acid oxidation, decreasing lipogenesis, and improving hepatic glucose metabolism [29].

Nowadays, there is no real consensus on the treatments for pediatric NAFLD. The benefits of the lifestyle modifications have widely been accepted. However, some controversies persist concerning the pharmacological treatments. The best way to manage this condition is may be to adapt the treatment to each patient, considering also existing co-morbidities (such as insulin resistance or diabetes mellitus for which metformin can be useful). Vitamin E, probiotics, and polyunsaturated fatty acids emerge as potentially useful treatments, although appropriate controlled studies remain necessary before their universal recommendation.

We propose an algorithm for the management of pediatric NAFLD, in order to help pediatricians facing the problem of this condition (Fig. 2).

- Lifestyle modifications represent the first-line treatment of NAFLD. They can have a positive impact on ALT levels and can improve liver histology.
- A reduction in fast-release carbohydrates consumption (especially fructose) is advised.
- A multidisciplinary approach is crucial.
- Pharmacological treatments should be considered for patients who do not adhere or are unresponsive to lifestyle modifications.

Conclusion

While pediatric NAFLD is an increasing public health issue, this condition is still underdiagnosed, as NAFLD pediatric patients are often asymptomatic. Over the course of the disease, NAFLD may progress to NASH and end-stage liver disease. Therefore, it is crucial to diagnose and treat this condition at an early stage, and high-risk population screening should be performed. Liver biopsy remains the gold standard for NAFLD diagnosis and staging. Although some non-invasive tools have recently been developed for monitoring disease evolution and therapeutic response, there is an urgent need for new tools that are suitable for large-scale pediatric NAFLD screening.

First-line therapy focuses on diet and lifestyle modifications, and to this end, a multidisciplinary approach is recommended. However, in the case of poor compliance or in the absence of response to lifestyle changes, pharmacological therapies should be initiated in order to prevent severe organ damage. Further basic research studies are required in order to identify new therapeutic targets.

Finally, the role of the pediatrician is also to detect the overweight among their patients and to give them advices in order to prevent obesity and subsequently NAFLD.

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