Nonalcoholic fatty liver disease (NAFLD) is highly common and potentially serious in children and adolescents. The term NAFLD refers to a spectrum of diseases ranging from accumulation of fat in the liver (simple steatosis or nonalcoholic fatty liver "NAFL") to the potentially progressive form of nonalcoholic steatohepatitis (NASH) characterized by hepatocyte ballooning, inflammation, and often associated with fibrosis. While large prospective longitudinal studies in pediatric NAFLD are still lacking, growing evidence suggests that children with NAFL are at increased risk for cardiometabolic complications, while those with NASH and advance fibrosis are also at risk for significant liver-related morbidity including cirrhosis and its complications. Pediatric NAFLD shares features of adult NAFLD but also shows many different characteristics in terms of prevalence, histology, diagnosis and management. Translational studies suggest that NAFLD is a highly heritable disease in which genetic variations and environment closely interact to determine the disease phenotype and the progression to the more advanced forms of the disease. Changes in lifestyle, targeting gradual weight reduction, and physical exercise continue to be the mainstay of treatment for NAFLD in children. Recent advances in development of noninvasive diagnostic modalities and the potential for identifying effective pharmacological interventions may result in significant progress in the management of NAFLD in the pediatric population.

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Keywords: Nonalcoholic fatty liver disease, Nonalcoholic steatohepatitis, Liver fibrosis, Noninvasive diagnosis, Children.
1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as steatosis affecting more than 5% of the hepatocyte in the absence of significant alcohol consumption or other liver diseases. The histologic spectrum ranges from simple fatty deposition in the hepatocyte (simple steatosis or nonalcoholic fatty liver “NAFL”) to the potentially progressive form of nonalcoholic steatohepatitis (NASH) which is characterized by inflammation and hepatocyte injury leading to progression to fibrosis, cirrhosis, and potentially end-stage liver disease and hepatocellular carcinoma (HCC) [1].

From a historical perspective, scientists recognized an association between obesity and fatty liver more than 100 years ago. In 1884, Pepper was the first to describe the presence of fatty liver in a diabetic patient. Thereafter, several publications discussed the similarities between liver histology of patients with alcoholic liver disease and those with severe obesity and diabetes [2]. However, it was not until 1980, when Ludwig first used the term of NASH to describe the progressive form of liver disease in obese, diabetic female patients in the absence of alcohol intake [3]. At that time it was thought to be an adult disease. Three years later, the first three cases of NAFLD were described in children [4]. Obesity, insulin resistance, metabolic syndrome, and dyslipidemia are well known risk factors associated with NAFLD. Given the rapid rise of obesity rates and diabetes, NAFLD is the most common cause of chronic liver disease and it is of major public concern secondary to the increase in prevalence. The aim of this review article is to provide an understanding about current knowledge related to pediatric NAFLD and to highlight differences between the adult and pediatric disease.

2. Literature Search

An extensive structured search using the PubMed database was performed to identify studies providing information about pediatric and adult NAFLD, NASH, epidemiology, natural history, genetics, diagnosis, and management. Studies published in English were included up to August 2015, focusing on studies published within the last 10 years. We also manually searched the references of retrieved articles to identify additional relevant studies. Further updates were performed whenever needed during the revision process.

3. Epidemiology and Risk Factors

Epidemiologic studies in adults have estimated that the prevalence of NAFLD in the Western countries ranges from 20% to 30% [5] with approximately 10-20% of these patients having NASH. The presence of type 2 diabetes is associated with an increased prevalence of NAFLD (ranging from 45% to 75%), and these patients are at a higher risk for NASH and developing liver-related complications [6].

Estimating the true prevalence of NAFLD in children is very challenging. An autopsy based study concluded that after adjusting for age, gender, race, and ethnicity, the prevalence of NAFLD in the American pediatric population was 9.6%, increasing with age and obesity (17.3% in adolescents and 38% in obese children) [7]. Another study tried to estimate the changes in prevalence of suspected NAFLD, defined as overweight or obesity in addition to elevated serum alanine aminotransferase (ALT), in adolescents aged 12-19 years using different periods of the National Health and Nutrition Examination Survey (NHANES) database. Unfortunately, the prevalence of NAFLD more than doubled among US adolescents over the previous 3 decades rising from 3.9% in 1988–1994 to 10.7% in 2007–2010 [8]. This increase in NAFLD is projected to add more cost to the already high cost of taking care of obese children. Indeed, childhood obesity costs $19,000 more per child when compared to those with normal weight according to an analysis done by researchers at Duke University [9].

It is known that the prevalence of NAFLD in children is affected by many factors, and it is determined by a complex interaction of genetic and environment influences [10]. In general, however, the risk of liver disease increases with the weight of the patient. Indeed, as in adults, NAFLD in children is strongly associated with obesity, as well as with several of the cardiometabolic complications of obesity [11]. Moreover, growing evidence suggests that the presence of NAFLD directly influences the metabolic profiles, as well as early markers of cardiovascular risk factors in overweight or obese children [12,13]. Other traditional risk factors linked to pediatric NAFLD include pubertal stage, gender, and ethnicity with NAFLD being more common in the pubertal age group, have male predominance, and a higher incidence in children of Hispanic origin [7]. Indeed, the highest rates of NAFLD and signs of liver damage on histology (higher grades of ballooning and Mallory bodies) are found in Mexican Americans, as well as Asian Indians and Americans, probably due to higher rates of insulin resistance and increased visceral adiposity at equivalent body mass index (BMI). African-American patients have lower rates of NAFLD, NASH, and less severe fibrosis, suggesting a protective genetic or metabolic effect in this group. These differences may also be influenced by several environmental factors, including the type of diet, exercise choice, socio-economic status, and living location.

The association between NAFLD and polycystic ovarian syndrome (PCOS) has been described [14,15] and is of clinical significance given the young age at which both PCOS and NAFLD may occur. Other non-traditional risk factors that have been growingly linked to pediatric NAFLD include obstructive sleep apnea and hypoxemia, psoriasis, and panhypopituitarism [14,16–18].

4. Natural History

The natural history of adult NAFLD is well established with NASH being considered the aggressive form of the disease. However, this concept has been recently challenged with a large longitudinal study that demonstrated that only fibrosis stage, and no other histological features, was the strongest predictor of long-term overall mortality and liver disease complications [19]. NAFLD-related cirrhosis is currently the second leading etiology of liver disease among adults awaiting liver transplantation in the United States [20,21].
and is associated with a significant risk of developing hepatocellular carcinoma [22]. Importantly, more recent studies have demonstrated clearly that HCC may also develop in non-cirrhotic NAFLD [23].

Data on the prognosis and clinical complications of NAFLD in children remain scarce due to lack of prospective studies evaluating children over time. A number of cross-sectional studies have shown that the entire spectrum of NAFLD may occur during childhood from hepatic steatosis to NASH to cirrhosis [24]. Even more alarming is the fact that HCC has been described in children with NAFLD although this is considered rare [25]. A landmark study examined the long-term prognosis of children with NAFLD and compared their survival with the expected survival of the general population [26]. Sixty-six children with NAFLD with a mean age of 14 years were followed-up for up to 20 years with a total of 409.6 person-years of follow-up. The metabolic syndrome was present in 19 (29%) children at the time of NAFLD diagnosis with 55 (83%) presenting with at least one feature of the metabolic syndrome including obesity, hypertension, dyslipidemia, and/or hyperglycemia. Four children with baseline normal fasting glucose developed type 2 diabetes 4–11 years after NAFLD diagnosis. A total of 13 liver biopsies were obtained from five patients over a mean of about 5 years showing progression of fibrosis stage in four children. During follow-up, two children died and two underwent liver transplantation for decompensated cirrhosis. NAFLD recurred in the allograft in the two cases transplanted, with one case progressing to cirrhosis and requiring retransplantation. The observed survival free of liver transplantation was significantly shorter in the NAFLD cohort as compared to the expected survival in the general US population of the same age and sex with a standardized mortality ratio of 13.6 (95% CI 3.8, 34.8). This study demonstrated for the first time that children with NAFLD may develop end stage liver disease with the consequent need for liver transplantation during adolescence or early adulthood.

Extra-hepatic complications may occur as part the natural course of NAFLD. Studies have shown that compared to the general adult population, patients with NAFLD have a higher risk of systemic health complications including the development of type 2 diabetes, cardiovascular disease, and cancer [27,28]. Similar data have emerged recently in the pediatric population demonstrating that children with NAFLD have increased cardiovascular risk factors including the presence of atherogenic dyslipidemia, an increase in pro-inflammatory markers, and changes in the structure and function of their arteries and cardiac muscle [29].

5. Pathogenesis of NAFLD: Multiple Parallel Hits

The pathogenesis of NAFLD has still to be fully elucidated. A two hit hypothesis was initially described involving the accumulation of triglycerides within the hepatocyte, also known as the first hit, followed by a second hit that leads to hepatocellular injury and inflammation [30]. Insulin resistance causes increased influx of free fatty acids (FFAs) to the liver, causing fatty infiltration and the increased levels are enough to induce liver damage via lipid peroxidation, formation of reactive oxygen species (ROS), and mitochondrial dysfunction. [31,32] However, other factors might be involved in the pathogenesis of NAFLD. Giving its complexity, a multiple parallel hit hypothesis has been proposed emphasizing the importance of the gut-fat-liver axis and its activation [33] (Fig. 1). An increase in gut derived endotoxins due to gut permeability has been proposed to play a crucial role in the development and progression of NAFLD [34]. Obesity is an inflammatory state, and adipokine imbalance caused by adipose tissue inflammation has also been considered an important mechanism of injury [35]. Furthermore, our group and others have established lipotoxicity-induced hepatocyte apoptosis as a driving force behind fibrosis progression and the development of NASH [36]. (See Fig. 2.)

Growing evidence supports the concept that pediatric and adult NAFLDs are highly heritable diseases in which genetic variations and environment closely interact to determine the disease phenotype and the progression to the more advanced forms of the disease [37,38]. Human genome-wide association studies (GWAS) in adults have provided important insights into the genomic variation in NAFLD and have identified specific loci contributing to fat accumulation in the liver and NASH development [39] that have been subsequently shown to also be important determinants of pediatric NAFLD in studies using gene candidate approaches [40]. A major limitation of most of the GWAS, as well as other genetic studies in NAFLD, has been the lack of assessment of the crosstalk between genetic variations with key environmental factors that influence the development of NAFLD and progression to NASH. In this regard, two recent pediatric studies have provided evidence for the interplay between host genetics and environment in human NAFLD [41,42]. In the first one, Santoro et al. studied a large cohort of children and adolescents followed at an obesity clinic. They demonstrated that the consumption of a diet with a high n-6 to n-3 polyunsaturated fatty acids (PUFA) ratio resulted in higher hepatic fat fractions as assessed by liver MRI [42]. However, this effect was seen only in children with a genetic polymorphism in the patatin-like phospholipase domain-containing 3 (PNPLA3) gene, which has been identified as the strongest modifier of NAFLD and NASH pathogenesis in most of the GWAS performed to date. In a more recent study, we analyzed the crosstalk between diet and genes with regard to liver cell death and liver injury [41]. We demonstrated that the association between hepatic fat accumulation and liver cell death may be in part dependent on ethnicity. Indeed, in this study of more than 220 obese children we found that for the same degree of hepatic fat content, obese African American youths showed lower levels of liver cell death – as measured by circulating cytokeratin 18 fragments – than their Caucasian and Hispanic controls independent of the degree of insulin resistance. These translational studies have started to integrate genetic data in the context of key environmental influences that contribute to the disease development and progression. Future studies taking a system biology approach integrating data from novel gene technologies (such as whole-genome or whole-exome sequencing, transcriptome sequencing), with environmental factors, metagenomics, and epigenomics are warranted and will result in a significant advancement in our understanding of complex metabolic disorders such as fatty liver disease.
6. Histologic Features of Pediatric NAFLD: Similarities and Differences from Adult NAFLD

As in adults, liver biopsy remains the ‘gold standard’ for establishing the diagnosis of NAFLD in children and grading and staging the severity; in other words, distinguishing steatosis from steatohepatitis, and assessing the degree of fibrosis. The predictive value of liver enzymes for NASH and fibrosis is poor and as it was previously demonstrated in adults, in children the entire spectrum of NAFLD including NASH and fibrosis can be found in those with normal liver enzymes [43]. Moreover, a liver biopsy is also helpful in ruling out alternative etiologies resulting in hepatic steatosis, in particular chronic hepatitis C infection, Wilson disease, autoimmune hepatitis, and other metabolic liver disorders.

Fig. 1 – The multiple parallel hits theory for NAFLD development and progression to NASH and liver cirrhosis. Insulin resistance in the setting of childhood obesity and the appropriate genetic background results in increased delivery in free fatty acids to liver and de novo lipogenesis leading to the development of nonalcoholic fatty liver (NAFL). Multiple secondary hits including hepatocyte apoptosis, oxidative stress, and increased gut permeability contributes to disease progression to nonalcoholic steatohepatitis (NASH) and liver fibrosis.

Fig. 2 – Histologic features of pediatric NAFLD. A is from a child with the classic, adult type 1 NASH with lobular inflammation and hepatocyte ballooning. B is an example of the pediatric type 2 NASH with mainly portal-based injury and inflammation.
A central limitation for the use of liver biopsy in the clinic is its invasiveness and the potential for significant complications such as bleeding and pain. The histological diagnosis of NASH in pediatric cases may also be a challenge as the features found in liver biopsy often differ from those commonly seen in adults [44]. The typical adult pattern (termed NASH type 1) is characterized by the presence of steatosis (mainly macrovesicular) with ballooning degeneration and/or perisinusoidal fibrosis (zone 3 lobular involvement), with the portal tracts being relatively spared. The pediatric type NASH (NASH type 2) is described as the presence of steatosis along with portal inflammation and/or fibrosis in the absence of ballooning degeneration and perisinusoidal fibrosis [44]. However, a large proportion of patients may have overlapping features of both type 1 and type 2 NASH [45,46]. While the presence of chronic portal inflammation appears to be more common in pre-pubertal boys and has been linked to more severe fibrosis [45,47], it remains to be determined whether patients with the pediatric pattern differ in the natural history, etiopathogenesis, prognosis, or response to treatment compared to patients with adult type or with overlapping features.

7. Noninvasive Diagnosis of NAFLD, NASH and Fibrosis

7.1. Diagnosis of NAFLD

Given the high prevalence of NAFLD and the serious limitations of liver biopsy in children, it is paramount to have a simple noninvasive method to screen for this disease. An expert committee for the prevention, assessment, and treatment of overweight and obese children and adolescents recommended that every child over the age of 10 years with a BMI ≥95th percentile or those with BMI between 85th percentile and 94th percentile with risk factors (family history of diabetes, cardiovascular disease, and signs of insulin resistance) should have ALT and aspartate aminotransferase (AST) measured biannually [48]. Of note, the commonly proposed cut-off values for elevated ALT (>50 U/L in boys, >44 U/L in girls) are set too high to reliably screen for NAFLD and considerations should be given to lowering these values to 25 U/L in boys and 22 U/L in girls [49].

Lever ultrasonography remains the most widely used imaging method to screen for NAFLD (fatty infiltration leads to increased brightness of the liver compared to the kidney and vascular blurring). In fact, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends using the combination of abdominal ultrasound and liver function tests to screen for NAFLD in overweight and obese children older than 10 years of age [54]. However, the sensitivity of ultrasonography to diagnose NAFLD is poor when the fat content in the liver is <20% [50]. This has led to the development of more accurate imaging modalities for steatosis such as magnetic resonance spectroscopy (MRS) which is able to detect the presence of hepatic fat >5% and controlled attenuation parameter (CAP) [51,52] although widespread use is still limited due to cost and availability. New quantitative ultrasound techniques (QUS) have also been proposed as a modality to quantify liver fat but more studies are needed [53].

In a small pilot study, we have recently investigated the utility of breath volatile organic compounds (VOCs) to diagnose NAFLD in children with interesting results [54] that if validated by others may lead to the development of a simple hand-held device (similar to an alcohol breathalyzer) to screen for NAFLD by physicians in their clinics.

7.2. Differentiating NASH from Simple Steatosis

Identifying potential non-invasive markers that differentiate simple steatosis from NASH would be of great interest to the clinician. Multiple biomarkers and predictive scores have been studied in adult patients in an attempt to diagnose NASH noninvasively [55,56]. Of the NASH biomarkers studied to date, cytokeratin-18 (CK18) has been the most widely validated in both adults and children, although some recent adult data have casted doubts about its sensitivity [57,58]. CK18 is a breakdown product that is released into the bloodstream upon apoptotic hepatocyte death due to lipotoxicity-induced liver damage. Because such apoptotic activity is associated with NASH but not to hepatic steatosis, elevated CK18 levels in the blood are associated with the presence of NASH on biopsy [59,60]. In a large cohort of children with NAFLD, CK18 levels were significantly higher in patients with NASH compared to those with steatosis and correlated with the histologic severity of their disease [61].

More recently, our group demonstrated that serum levels of soluble Fas (sFas) and soluble Fas ligands (sFasl), both markers of the extrinsic pathway of apoptosis, were significantly higher in children with NASH when compared to those with no NASH further validating the role of hepatocyte apoptosis biomarkers as potential noninvasive tests for NASH [62]. However, it is important to note that the available data on NASH biomarkers in children are limited and require further validation before integration into clinical practice.

Other predictive models which combine routinely assessed clinical variables with laboratory tests and biomarkers have been proposed to make the diagnosis of NASH in adults. These include the NASHTest (undisclosed formula), NASH diagnostics (CK-18, adiponectin, and resistin), the Nice Model (CK-18, ALT, presence of MetS), HAIR (hypertension, increased ALT, and IR), the oxNASH (13-hydroxy-octadecadienoic acid/linoleic acid ratio, age, BMI, and AST), and the NASH score (PNPLA3 genotype, AST, and fasting insulin). Unfortunately, most of these scores need further external validation [52].

7.3. Predicting the Presence of Liver Fibrosis

The presence of significant fibrosis may be the most important factor in determining the prognosis of NAFLD and its risk of progression to end-stage liver disease. Several noninvasive fibrosis scoring systems composed of routinely measured clinical and laboratory variables have been developed in adult patients with NAFLD to identify those with advanced fibrosis including the AST/ALT ratio, NAFLD fibrosis score (NFS), the AST/platelet ratio index (APRI), and the FIB4 score [55]. However, recent data from our group and others...
have suggested that these adult scores may not be accurate in predicting advanced fibrosis in children [63,64]. Using a large cohort of 242 children with biopsy-proven NAFLD, we have recently developed a new predictive model for advanced fibrosis called the pediatric NAFLD fibrosis score (PNFS) which incorporates readily available clinical variables including gamma glutamyl transferase, alkaline phosphatase and platelets into a mathematical model. This score needs further external validation before it can be recommended for routine use [65]. Measuring liver stiffness to assess for fibrosis by imaging the propagation characteristics of shear waves in the liver has gained wide acceptance among adult hepatologists. This can be done by different technologies that include transient elastography (TE), MR elastography (MRE), and acoustic radiation force impulse imaging (ARFI). Studies are ongoing in children with NAFLD but require further validation before these imaging modalities can be accepted as reliable alternatives for liver biopsy [66-68]. Table 1 provides a summary of imaging modalities that have been evaluated for diagnosing the presence of significant fibrosis in children with NAFLD.

8. Management

8.1. Role of Nutrition and Weight Loss Surgery

Change in lifestyle, targeting gradual weight reduction, and physical exercise continues to be the mainstay of treatment for NAFLD in children [32]. Weight reduction has been widely studied in adults and has been shown to improve not only the biochemical parameter but also the liver histology. Based on studies in adults, weight loss of 7–10% was associated with significant improvement in liver histology. The relative efficacy of weight loss and degree of weight loss needed to induce histologic improvement in pediatric NAFLD remain unknown. In the context of evidence-based recommendations for NAFLD patients, dietary advice is based on the pathological mechanisms of disease progression, favoring nutrients that have beneficial effects on metabolic syndrome parameters, as well as on inflammation. Consumption of carbohydrates should be limited (especially high fructose diet) and low glycemic index foods prioritized. Trans-fats should be limited in favor of monounsaturated fatty acids while a balanced ratio of omega-6 to omega-3 polyunsaturated fatty acids should be achieved. Recent pediatric studies evaluating lifestyle dietary changes and weight loss have suggested that intervention resulting in persistent weight loss is associated with improvement of serum AST and ALT, ultrasound liver brightness, as well as liver histology [69]. A multidisciplinary approach, including a consultation with a registered dietitian, a psychologist, and an exercise physiologist may result in better success with lifestyle interventions [69]. For compliance purposes it is beneficial to encourage participation of other family members in dietary and lifestyle changes.

Finally, bariatric surgery is now suggested for adolescents with a BMI ≥35 kg/m² with a major comorbidity (type 2 diabetes, moderate to severe obstructive sleep apnea, pseudotumor cerebri, and severe NASH) or BMI ≥40 kg/m² with milder comorbidities (hypertension, insulin resistance, substantially impaired quality of life or activities of daily living) [70]. A recent prospective, multicenter observational study in adolescents with severe obesity observed a favorable short-term complication profile, supporting the early postoperative safety of weight loss surgery in select adolescents [71]. Future longitudinal study of this cohort will permit accurate assessment of long-term outcomes of adolescents undergoing bariatric surgery. Although adult studies suggest a significant improvement in histology after bariatric surgery in patients with NAFLD [72], no such studies are yet available in pediatric patients with fatty liver.

8.2. Pharmacologic Treatment

Long-term maintenance of weight loss by lifestyle interventions is largely unsuccessful. For this reason, pharmacological interventions have been a major focus of recent clinical trials in both adults and children. The Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with NASH (PIVENS) trial evaluated the efficacy of pioglitazone, an insulin sensitizer, to vitamin E, an antioxidant, in improving the histologic features in adult patients with NASH [73]. Only vitamin E achieved the primary outcome of prespecified improvement in certain histologic features. Patients

<table>
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<th>Imaging test</th>
<th>Description</th>
<th>Performance</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>TE</td>
<td>Uses ultrasonography technology to measure shear wave propagation through the liver</td>
<td>AUC: 0.99 (90% CI: 0.92–0.99)</td>
<td>- Can be performed by clinicians in clinic with real-time results&lt;br&gt; - Good accuracy for excluding advanced fibrosis and cirrhosis</td>
<td>- Increased failure rate with obesity&lt;br&gt; - False-positive results with liver inflammation and congestion&lt;br&gt; - Requires an expensive device</td>
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<tr>
<td>MRE</td>
<td>Uses MR technology to measure shear wave propagation through the liver</td>
<td>AUC: 0.92 (95% CI: 0.79–1.00)</td>
<td>- Examines the entire liver&lt;br&gt; - Accurate in obese patients</td>
<td>- Needs further validation in children&lt;br&gt; - Expensive and time consuming</td>
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AUC: area under the ROC curve; TE: transient elastography; MRE: MR elastography.
in both arms showed a reduction in the aminotransferase levels and also improvement in steatosis and lobular inflammation, but no improvement in fibrosis scores.

The Treatment of NAFLD in Children (TONIC) trial was a multicenter randomized placebo-controlled trial that used a similar approach to PIVENS by evaluating the efficacy of vitamin E and an insulin sensitizer, in this case metformin, in pediatric NAFLD [74]. The primary outcome was the sustainability of reduction in ALT levels and unfortunately was achieved by neither metformin nor vitamin E. However, patients on vitamin E had greater resolution of NASH when compared to the other groups (p = 0.006) with significant improvement in their histologic activity score (p = 0.02). Our approach has been to consider using vitamin E only in patients with biopsy-proven NASH after discussing potential side effects including increased risk of overall mortality and prostate cancer that have been suggested by adult data [75,76].

Omega-3 fatty acids, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), have been shown to improve hepatic fatty acid metabolism by inhibiting lipogenesis and by stimulating fatty acid oxidation. Adult and pediatric studies have looked into the use of omega-3 fatty acids in the treatment of NAFLD. A pediatric study by Nobili et al. reported the results of a six-month randomized controlled trial that tested the efficacy of DHA (250 mg/day and 500 mg/day of DHA [78]. EPA-E had no significant effect on the histologic features of NASH [79].

Data in adult patients with biopsy proven NASH showed improvement in steatosis, hepatocellular ballooning, lobular inflammation, and fibrosis [80].

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<th>Table 2 – Similarities and differences between pediatric and adult NAFLD.</th>
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<td><strong>Children and adolescents</strong></td>
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<td><strong>Epidemiology</strong></td>
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<td>- Prevalence in children is around 10%.</td>
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<td>- The prevalence increases with increasing age, among those who</td>
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<td>are overweight or obese, and in Hispanics [7].</td>
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<td><strong>Natural history</strong></td>
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<td>- Progression of NAFLD to advanced fibrosis and cirrhosis during childhood is well documented.</td>
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<td>- However, data on the prognosis and clinical complications of NAFLD remain scarce due to lack of prospective studies evaluating children over time.</td>
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<td><strong>Diagnosis</strong></td>
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<td>- Liver biopsy remains the gold standard.</td>
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<td>- Noninvasive diagnosis of steatosis and advanced fibrosis is</td>
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<td>more established and being utilized in clinical practice.</td>
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<td><strong>Obeticholic acid</strong></td>
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versus placebo) on liver fat content as detected by ultrasonography in a group of 60 children [77]. There was an improvement in liver steatosis in both DHA groups compared to placebo but there was no improvement in ALT levels. In their long-term follow up study that assessed the same cohort of patients at 12, 18, and 24 months [78], ALT levels decreased significantly in both DHA groups from month 12 onwards. However, more recent trials in adults have failed to prove the efficacy of omega-3 fatty acids in improving any of the major histologic features of NAFLD [79].

Bile acids have recently emerged as potent modulators of metabolism by binding to nuclear receptors, including the farnesoid X receptor or FXR to promote insulin sensitivity and decrease hepatic gluconeogenesis. Obeticholic acid is a synthetic variant of the natural bile acid chenodeoxycholic acid with potent activity on FXR. The Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment (FLINT) trial evaluated the efficacy of obeticholic acid in adult patients with biopsy-proven NASH and showed promising results [80] with improvement in all the main histologic features of NASH compared with placebo including (steatosis, hepatocellular ballooning, lobular inflammation, and fibrosis). The main side effects were pruritus and an elevation in low-density lipoprotein (LDL). A recent meta-analysis comparing the effectiveness of different pharmacological interventions for adult NAFLD based on NASH resolution and improvement in fibrosis stage [81]. This analysis may serve as additional resource for the interested reader.

Cysteamine, an amino thiol derived from coenzyme A degradation, plays an antioxidant role by enhancing glutathione synthesis and improving cellular redox homeostasis. Furthermore, cysteamine has anti-inflammatory and insulin-sensitizing effects by the up-regulation of the adiponectin levels [82]. An ongoing randomized clinical trial is evaluating the potential effects of cysteamine bitartrate delayed-release capsules on the histologic severity of NAFLD in children aged 8–17 years (ClinicalTrials.gov Identifier: NCT01529268).

9. Conclusions

Pediatric NAFLD is now the most common cause of liver disease in children. Its incidence is predicted to continue to rise with the increase in pediatric overweight and obesity. The full spectrum of the disease can occur in children from isolated hepatic steatosis, the most common form that seems to be a relatively benign condition to NASH that may progress to advanced fibrosis and cirrhosis. At present, only a liver biopsy can differentiate hepatic steatosis from NASH and reliable noninvasive diagnostic techniques are urgently needed. Lifestyle modifications, particularly weight loss, have been shown to be beneficial and clinical trials assessing different agents to treat NAFLD are underway in both adults and children (Table 2). Research efforts are of extreme importance as there is still much to be learned concerning the pathogenesis of NAFLD, its natural history and the difference between adult and pediatric disease. Learning more about the pathogenesis and natural history of adult NAFLD will facilitate the understanding of pediatric NAFLD with the ultimate goal of future prevention of the disease and its progression.

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Conflict of Interest

No conflict of interest for any of the authors.

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