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Journal

Gastroenterology, 150(8)

ISSN

0016-5085

Authors

Nobili, Valerio
Alisi, Anna
Newton, Kimberly P
et al.

Publication Date

2016-06-01

DOI

10.1053/j.gastro.2016.03.009

Peer reviewed

HHS Public Access

Author manuscript

Gastroenterology. Author manuscript; available in PMC 2017 June 01.

Published in final edited form as:

Gastroenterology. 2016 June ; 150(8): 1798–1810. doi:10.1053/j.gastro.2016.03.009.

Comparison of the Phenotype and Approach to Pediatric Versus Adult Patients with Nonalcoholic Fatty Liver Disease

V Nobili[1,2], **A Alisi**[1,2], **Kimberly P. Newton, M.D.**[3,4], and **Jeffrey B. Schwimmer, M.D.**[3,4,5]

[1,2]Hepato-metabolic Disease Unit and Liver Research Unit, Bambino Gesù Children's Hospital and IRCCS, Rome, Italy

[3]Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of California, San Diego School of Medicine, La Jolla, California

[4]Department of Gastroenterology, Rady Children's Hospital San Diego, San Diego, California

[5]Liver Imaging Group, Department of Radiology, University of California, San Diego School of Medicine, San Diego, California

Abstract

Nonalcoholic fatty liver disease (NAFLD) is one of the main chronic non-communicable diseases in westernized societies; its worldwide prevalence has doubled during the last 20 years. NAFLD has serious health implications not only for adults, but also for children. However, pediatric NAFLD is not only an important global problem in itself, but it is likely to be associated with increases in comorbidities such as metabolic syndrome and cardiovascular diseases. There are several differences between NAFLD in children and adults and it is not clear whether the disease observed in children is the initial phase of a process that progresses with age. The increasing prevalence of pediatric NAFLD has serious implications for the future adult population requiring appropriate action. Studies of NAFLD progression, pathogenesis, and management should evaluate disease phenotypes in children and follow these over patient lifetimes. We review the similarities and differences of NAFLD between children and adults.

Keywords

Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; children; adults

Correspondence: Jeffrey B. Schwimmer, M.D., Director, Fatty Liver Clinic, Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of California, San Diego, 3020 Children's Way, MC 5030 San Diego, CA 92123, ; Email: jschwimmer@ucsd.edu, phone: 858-966-8907, fax: 858-560-6798

Author Contributions: All authors equally contributed to the manuscript

Conflicts of interest: The authors disclose no conflicts.

Introduction

Concurrently with the sharp increase of obesity, nonalcoholic fatty liver disease (NAFLD) has become one of the main chronic non-communicable diseases among children and adults in westernized societies.[1–3] The minimum criterion for the diagnosis of NAFLD is ≥ 5 % of hepatocytes with macrovesicular steatosis, with no excessive alcohol intake and no evidence of viral, autoimmune, metabolic, or drug-induced liver disease. However, NAFLD encompasses a spectrum ranging from hepatocellular fat accumulation (isolated steatosis) to an advanced form of liver injury known as nonalcoholic steatohepatitis (NASH), which refers to distinct histological features including hepatocellular steatosis and injury, necro-inflammation and eventually fibrosis.[4] Since the first evidence of pediatric NAFLD in 1983 by Moran et al[5], we have developed an understanding of the features in children and its potential long-term effects on health status. Adult and pediatric NAFLD share some common features but also have several important differences. NAFLD is a multisystem disease, with dysregulation of several biological pathways affecting diverse extra-hepatic organs including adipose tissue and intestines.[2] Although a few studies have demonstrated that NAFLD may progress more rapidly in children than in adults, there is evidence to suggest that low-grade chronic tissue inflammation leads more frequently to fibrosis and end-stage liver disease after children become young adults.[6] There is also some divergence between children and adults with NAFLD in terms of differential diagnostic and therapeutic management. In this article, we reviewed key differences and similarities in the pediatric and adult forms of NAFLD.

Epidemiology

Epidemiological studies reveal that globally the prevalence of NAFLD in adults ranges between 20 and 30% in Western nations, and between 5 to 18% in Asia,[7,8] whereas, the global prevalence of NASH has been estimated to be between 2 and 3%.[9] Interestingly, it has been reported that countries with higher economic status exhibit a higher prevalence of NAFLD among adults.[10]

The prevalence of NAFLD both in children and adults varies widely across the world in terms of ethnicity and population studied. Moreover, it is important to consider that the methodology used for assessing prevalence may profoundly affect the estimate. Most epidemiological studies have used surrogate measures such as serum alanine aminotransferases (ALT) or liver sonography to estimate the prevalence of NAFLD, although liver biopsy remains the diagnostic standard. Based on a threshold of serum ALT > 30 U/L, a prevalence of NAFLD of 8% was estimated for adolescents (aged 12–19 years) within the USA from the National Health and Nutrition Examination Survey (NHANES).[11] Using multiple cross-sectional measures over time from NHANES, the number of American adolescents with NAFLD has nearly doubled over the last twenty years.[12] In adults, the rate of ALT > 43 U/L was similar to the rate of ALT > 30 U/L reported for adolescents.[13,14] In contrast a population-based study on 1,543 Korean adolescents (aged 10–19 years) reported a prevalence of ALT > 40 U/L of only 3.2%.[15] It is unknown how close the estimates of prevalence would be if they reported the same thresholds for ALT.

In the 1990's, based on ultrasound, a study reported a 2.6% prevalence of NAFLD among 810 Japanese children aged between 2- and 12-years-old.[16] This is in contrast with the prevalence of NAFLD estimated by ultrasound in a cohort of 35,519 Japanese adults, which increased from 13% in the 1990's to 30% 12 years later.[17] More recently, it was reported that the prevalence of NAFLD in healthy European adolescents was estimated to be 2.5% based upon evaluation with ultrasound.[18] Multicenter population studies in Europe estimated a higher prevalence of NAFLD based upon ultrasound evaluation in adults than that observed in children (Spain: 33.4% men and 20.3% women; Italy: 33% in men and 20% in women).[19,20] It is important to acknowledge that there are limitations of both ALT and ultrasound which can both underdiagnose NAFLD because of inadequate sensitivity for detecting NAFLD and over diagnose NAFLD because abnormal findings are not specific for NAFLD.

General population prevalence rates in adults recently reported in a systematic review are shown in Figure 1, representing by different colors the macro-geographical regions of Europe, Asia, Middle East, North America and South America.[21] In children, estimates for the prevalence of NAFLD range from 5.0% to 25.1% in different populations including North Americans, South Americans, Europeans, Asians and Middle East and Oceania individuals.[22] In aggregate, based on the overall comparison of data from general population studies, it emerges that prevalence of NAFLD in children is lower than observed in adults.

Interestingly, the prevalence of NAFLD varies according to age in both pediatric and adult populations. The Study of Child and Adolescent Liver Epidemiology (SCALE), reviewed the records and liver histological features of 742 children aged 2 to 19 years, who died from unnatural causes between 1993 and 2003, reporting a 38% prevalence of NAFLD in obese individuals.[23] From this study also emerged an estimated prevalence for NAFLD of 17% in teenagers compared to 0.7% in children 2–4 year olds, highlighting that the prevalence of pediatric disease increases with age. In adults, prevalence of NAFLD increases with age until peaking during middle age, and decreases among the elderly.[24] The changes in the prevalence of NAFLD associated with age in both children and adults is likely to be modified by numerous additional risk factors. Unfortunately, much less is known about NAFLD in young adults from age 20 to 39.

In addition to age, there are differences in prevalence by sex; the prevalence of NAFLD is higher in males than females in both adults and children overall, but differences by sex are more pronounced in the pediatric population. In the pediatric age range, males are approximately 40% more likely to have NAFLD than females.[25] In adults, clinical populations of NAFLD have more women than men. However, in population-based studies, men are slightly more likely to have NAFLD than women; in NHANES the reported prevalence was 5.7% in men *vs* a 4.6% in women.[14,26] Reasons for this difference may include sex differences in seeking health care, and the greater use of alcohol among men. Furthermore, studies have consistently reported that Hispanics subjects have the highest and non-Hispanic blacks have the lowest prevalence of NAFLD independent of age and sex.[14,25,26]

Histology

NAFLD in both children and adults is defined as 5% or greater macrovesicular steatosis in hepatocytes after exclusion of other causes of steatosis, however, the distribution pattern of this steatosis along with NASH-associated liver injury is frequently different (Table 1).[27] NASH in adults is characterized by hepatic steatosis, lobular inflammation consisting of a mixed inflammatory cell infiltrate (infiltration by mononuclear cells or polymorphonuclear cells, or both) and hepatocyte injury (ballooning), with or without fibrosis. Other histological sub-lesions include Mallory-Denk Bodies; iron deposition within hepatocytes and/or the cells of the reticulo-endothelial system; ductular reaction; megamitochondria observed in hepatocytes; glycogenated hepatocyte and vacuolated nuclei.[28]

In 2005, a study evaluated the histological appearance of 100 children with NAFLD, and categorized two prevalent phenotypes of pediatric NASH: an adult-type (type 1 NASH), in which the steatosis, of mild to moderate grade and zonal distribution in zone 3, was associated with lobular inflammation, ballooning and perisinusoidal fibrosis; and, a pediatric-type (type 2 NASH), in which steatosis of moderate or high grade was associated with portal inflammation and portal fibrosis in the absence of ballooning degeneration.[29] In particular, type 1 and type 2 NASH were reported to be present in 17% and 51% of children, respectively. In the remaining cases (32%), it was found an overlap pattern with a variable combination of features of the type 1 and type 2 NASH, that was confirmed in subsequent clinic-pathological series.[29–31] Notably, children with portal-based NASH have more severe fibrosis.

In an attempt to standardize and grade the histological criteria for the diagnosis of NAFLD and NASH, different methods have been elaborated. Currently, the most widely used comprehensive histological scoring system for grading histological features in NASH is the NASH Clinical Research Network (CRN) scoring system which includes staging/grading of steatosis, ballooning, inflammation and fibrosis.[32] The NAFLD Activity Score (NAS) is derived from the NASH CRN scoring system, and is meant for use in clinical trials, and not for directing patient care. The score is based on features most likely to be amenable to change with pharmacologic therapy, and is a composite of steatosis, inflammation and ballooning. One key aspect pertaining to the use of the NAS in pediatric populations is that the NAS takes into account lobular but not portal inflammation. Although chronic portal inflammation may be present in adults where it has been proposed as a marker of disease severity or of NASH improvement[33], in children, chronic inflammation in the portal tract is more frequent and may also be the only site of inflammation.[34] Furthermore, the NAS includes ballooning which is a major distinguishing feature of NASH that confers an increased risk of disease progression in adults, however, the significance of ballooning in children is less clear, as children can develop meaningful fibrosis in the absence of ballooning.[29,35]

Similar to other forms of chronic hepatitis, the response to the insult of NASH is fibrosis. Generally, in adult NASH, the initial deposition of collagen and other extracellular matrix fibers occurs along the sinusoids of zone 3 and around the hepatocytes, distinctive of pericellular *chicken wire* fibrosis. Fibrosis in children reflects the prevalent zone 1 damage

and dominant portal-periportal pattern of fibrosis, even if pericellular and perisinusoidal fibrosis may be also found.[36]

In summary, the heterogeneity of the patterns of the histological lesions found in pediatric NAFLD/NASH may be an early pathology that starts in zone 1 and that after various steps resembles the adult pattern, or, alternatively, NAFLD/NASH in children may be a different pathology from that observed in adults. It is also possible that both scenarios are true; this topic needs focused investigation.

Pathogenesis

It is unclear if differences between and adults and children are due to different mechanisms in the pathogenesis of NAFLD, or they represent two sides of the same coin along a spectrum of advancing age. The knowledge gap is due in part to a paucity of studies about pathogenetic mechanisms in models that may resemble pediatric NAFLD. Therefore, in the next paragraphs we provide an overview of NAFLD pathogenesis as experimental studies and clinical studies have shown to date, discussing what is known about children (Table 1).

Molecular factors

The mechanisms driving NAFLD onset and outcome involve several molecular factors and pathways, which require a continuous and dynamic crosstalk between the liver and at least two other organs: the gut and adipose tissue.[37–39] A few clinical studies have suggested that the role of the gut microbiome and adipose tissue in inducing respectively endotoxemia and chronic systemic inflammation, and consequent liver tissue necro-inflammation, could be crucial for pediatric NAFLD as well as for the adult form of disease.[40–42] Over the past 5 years there has been a growing understanding of the role of gut microbiome in NAFLD pathogenesis. Notably, some difference have been shown in the gut microbiota composition that differ in children with NASH compared with healthy and obese subjects.[41] In adults, there is an association between the severity of NAFLD and the condition of gut dysbiosis with a shift in metabolic function of intestinal microbes.[43,44]

Over the last several years, a growing body of evidence has demonstrated that among different factors, adipocyte-derived soluble cell signaling proteins, known as adipocytokines, may play a key role in NAFLD pathogenesis and define disease progression in adults.[45,46] Some released adipocytokines, including tumour necrosis factor α (TNF-α), interleukin 6 (IL-6), leptin, adiponectin, retinol-binding protein-4 (RBP4) and resistin play a major role in both liver inflammation and insulin resistance. Accordingly, clinical studies have reported an association between pediatric NAFLD and the altered expression of some adipocytokines, including leptin, resistin and adiponectin, suggesting these molecules as potential biomarkers of disease severity.[47–50] Interestingly, recently systemic and hepatic levels of IL1-β were found strongly correlated to inflammation and fibrosis in children with NAFLD.[51] During NAFLD pathogenesis, adipocytokines may establish a network of communication with the liver, which may respond with the production of specific circulating molecules referred as hepatokines. Hepatokines may affect lipid and glucose metabolism, exerting several roles also in NAFLD.[52] Among the hepatokines, two, including fetuin-A, fibroblast growth factor 21 (FGF21) and insulin-like growth factors (IGFs) I and II, could be

important as potential non-invasive biomarkers and have been suggested as a promising therapeutic targets for NAFLD in children, as already reported in adults.[53–55] Interestingly, several lines of evidence indicated that both in adult and pediatric patients with NAFLD, the activation of hepatic stem/progenitor cells is associated with inflammation and NASH development.[56,57]

Genetics

The differences in disease distribution by race and ethnicity observed in adults and children with NAFLD indicate that genetic susceptibility may play a role in the development and progression of NASH. Several of the genetic variants reported in adults have been studied also in children with NAFLD (Table 1). These SNPs include: the SNP of a gene coding for PNPLA3 that has been found to be associated with the severity of disease; the SNP of the Glucokinase Regulatory Protein (*GCKR*) gene that was associated with higher fat content in the liver among all ethnic groups; the SNP of a gene coding for the Kruppel-like factor 6 (KLF6) that was associated with fibrosis; the SNP of a gene coding for manganese-dependent superoxide dismutase (SOD2), that was associated with liver fibrosis.[58–62] The SNP on *LPIN1* gene (coding for Lipin-1) that displayed an inverse association with disease severity was only investigated in children.[63] The relevance of several other genetic variants, such as Apolipoprotein C3 gene (*APOC3*), have not been confirmed or validated in either children or adults.[64] Conversely, very recently, two novel gene variants, including the transmembrane 6 superfamily member 2 gene (*TM6SF2*) and membrane bound O-acyltransferase domain-containing 7 gene (*MBOAT7*), were found associated with NAFLD in both children and adults.[65,66]

Outcomes

The natural history of NAFLD is not yet fully elucidated in children or adults, but it seems that the prognosis varies based on disease spectrum. Adults with isolated steatosis generally have an uncomplicated course, whereas adults with NASH have a greater long-term mortality with respect to general population.[67] The natural history of progression from NAFLD to NASH remains unclear both in children and adults. It has been reported that approximately 15–20 % of adult patients with NASH will subsequently develop liver fibrosis and cirrhosis, but there are no equivalent long-term follow-up studies in children.[68]

In the past ten years, we have seen an increase in the percentage of liver transplantations associated to NASH. Using the united network for organ sharing database it was reported that approximately 7.7% of all adult liver recipients exhibited NASH-related cirrhosis during the period 2007–2010.[69] In US adults, NASH-associated cirrhosis is the second most common indication for liver transplantation.[70]

In the only long-term outcomes study in 66 children, there was a standardized mortality ratio of 13.6 which included 3% of requiring liver transplantation for decompensated cirrhosis.[6] More recently, a study, including children and young adult patients with NASH cirrhosis who underwent liver transplantation in the US from the 1987–2012, showed that NASH can progress to end-stage liver disease requiring transplant in childhood and young adults[71]. Several cross-sectional studies suggest that NAFLD is also a major risk factor for

hepatocellular carcinoma (HCC) in the adult setting. In fact, recent studies demonstrate that HCC is also frequently associated with a background of obesity and insulin resistance, and may occur in NAFLD patients.[72] Furthermore, since 2004, there has been a rapidly growing body of literature that has reported HCC in histologically-confirmed adults with NAFLD without cirrhosis.[73,74] Although NAFLD is quite prevalent in children, little is known about the risk for HCC in children, and only two cases have been described to date both in a cirrhotic and non-cirrhotic background.[75,76] Furthermore, the extent that NAFLD in childhood increases risk for HCC in adulthood is also not yet known.

Associated Co-morbidities of NAFLD

Over the last decade, there has been increased interest in the determination of possible pathogenic and clinical associations between NAFLD and other obesity-related co-morbidities, including metabolic syndrome features and cardiovascular disease.[77,78] For example, Ekstedt et al[79], showed an increased risk of death from cardiovascular disease in a cohort of adult patients with biopsy-proven NAFLD.

However, although there is abundant literature in adults, the pediatric population has not been as well-characterized. A case-control study in children confirmed that NAFLD is strongly associated with dysregulated glucose metabolism, dyslipidemia, and hypertension and that the association is independent of obesity itself. [80] In addition, the importance of central obesity was shown in Caucasian children with NAFLD including that having a waist circumference ≥90th percentile is correlated with the risk for fibrosis.[81] The association between NAFLD and metabolic syndrome in children has also been shown in several different ethnic groups.[82_67]

There are several lines of evidence suggesting that NAFLD is an independent risk factor for cardiovascular disease in adults, because the disease pattern has been found associated with impaired endothelial function, increased carotid intima media thickness, and a higher prevalence of coronary plaques and atherosclerosis.[88_91] The cardiovascular risk assessment in children with NAFLD, before the expression of overt cardiovascular endpoints, has been achieved via other methods, such as the assessments of vascular structure mainly by evaluation of intima media thickness and function. However, some data are controversial. Manco et al[92] reported no association between intima-media thickness and liver histology in obese children and adolescents with NAFLD; whereas, more recent studies based on surrogate biomarkers of NAFLD or liver biopsy found an increased interventricular septum thickness at end-diastole and at end-systole.[93,94] However, both adult and pediatric studies have shown that NAFLD has been associated with impaired left ventricular function and adverse changes in cardiac geometry, which are well established risk factors for cardiovascular events.[95,96]

Recent studies highlighted that NAFLD may also affect quality of life (QOL) of patients.[97_100] Adults with NAFLD had had worse physical and mental health scores compared to the U.S. population with and without chronic illness.[99] Moreover, among adults with NAFLD, those with NASH reported lower physical health, but not mental health, compared to subjects with fatty liver disease without NASH. Similar to the data in adults,

children with NAFLD had worse total, physical and psychosocial health compared with healthy children.[101] However, unlike in adults, QOL scores did not significantly differ by histological severity of NAFLD. Notably impaired QOL was present in nearly 40% of children with NAFLD. Another study on 48 children and adolescents with NAFLD between 8 and 18 years found higher levels of depression compared to obese children and adolescents without NAFLD.[102] In addition, more frequent emotional and behavioral problems have been noted in children with NAFLD compared to healthy controls.[97] There are important questions that remain regarding how much the psychosocial problems observed are due to NAFLD itself versus the role of obesity and/or other unmeasured factors. However, these data support a need for clinical management to integrate caregivers who can address the psychosocial needs of children with NAFLD.

Management

Diagnosis

Despite the high prevalence of NAFLD, well-defined diagnostic recommendations remain a work in-progress.[103] Clinical practice guidelines are much better developed for adult NAFLD than for pediatric NAFLD.[104–109] Notably screening has not been recommended in adults, but has been recommended for children. In the U.S., the American Academy of Pediatrics recommends screening children for NAFLD who are ≥ 10 years and overweight with risk factors or obese regardless of other risk factors.[110] In Europe, ESPGHAN recommends that NAFLD should be suspected in children who are ≥ 3 years and overweight or obese, especially if they have a high waist circumference and/or a family history of NAFLD.[109] There still is some controversy surrounding screening children for NAFLD. However, the use of serum ALT for screening overweight children for NAFLD in primary care was validated in a study of 347 children identified with suspected NAFLD.[111]

As screening is based on laboratory results, it is important to define what is normal. The Screening ALT for Elevation in Today's Youth (SAFETY) study demonstrated that conventional ALT cutoff values of normal used in children's hospital in the U.S. varies widely and is too high for reliable detection of chronic liver disease.[112] The median upper limit of normal ALT used was found to be 53 U/L, with a range from 30–90 U/L. Using data from NHANES, the 95th percentiles for ALT levels for healthy weight, metabolically normal children without liver disease were 26 U/L in boys and 22 U/L in girls.

Once a patient is known to have suspected NAFLD, it is important to keep in mind that there is a differential diagnosis of other hepatic and non-hepatic conditions which may yield elevated serum aminotransferase activity and/or hepatic steatosis. These conditions include significant alcohol consumption, hepatitis C, autoimmune liver disease, Wilson's disease, parenteral nutrition, medications, inborn errors of metabolisms (e.g. cholesterol ester storage Disease, alpha-1-antitrypsin deficiency, Wolman disease, etc.) and severe malnutrition; however, some of them, such as Wilson's disease, parenteral nutrition and genetic-metabolic diseases are more relevant for children. In a retrospective review of 155 children with steatosis, Hourigan et al reported that etiologies other than NAFLD were common including metabolic diseases (9%), oncologic causes (8%), and viral hepatitis (7%).[113] Of note, the

role of alcohol consumption as confounding factor, although well documented in adults has been understudied in adolescents.[114]

Liver imaging is an increasingly important component to the evaluation of NAFLD. Ultrasound is the most widely used imaging technique for the evaluation of hepatic steatosis. Changes due to scattering and attenuation of the sound wave are used to infer hepatic steatosis. In children, liver ultrasound for fatty liver has a sensitivity of 70 to 85% and specificity of 50–60%.[115] This limitation of traditional ultrasound to accurately classify whether or not a child has fatty liver stems in part from an inherent property of ultrasound; it does not measure fat directly, instead, the relation between ultrasound-derived images and liver fat is intrinsically subjective and non-quantitative. Importantly, there is a new generation of ultrasound based technologies such as controlled attenuation parameter that are more promising for the detection of steatosis.[116] In addition, magnetic resonance imaging proton density fat fraction (PDFF) is a reliable measure of hepatic steatosis in children.[117] Therefore, MRI PDFF is increasingly used in clinical research and additional studies will address issues such as availability and cost of MRI as well as the validation of specific PDFF threshold values required to integrate this tool into clinical use.

In addition, to evaluation of steatosis, progress has been made in the non-invasive imaging of hepatic fibrosis. For example imaging techniques based on elastography assess liver stiffness by the analysis of propagation of shear waves within the liver. Some of these techniques, such as transient elastography, have been shown to detect advanced fibrosis in both children and adults.[118,119]

The diagnosis of NASH requires liver biopsy to perform microscopic evaluation of hepatic damage. Histological evaluation is a comprehensive assessment of numerous aspects of liver disease including patterns of hepatic fibrosis and vascular remodeling.

Liver histology, in both children and adults, still has an important role in the assessment of NAFLD-associated hepatic damage and diagnosis of NASH. Controversy remains over who should have a liver biopsy and when in the diagnostic evaluation a liver biopsy should be used, particularly in children. The European Society of Gastroenterology, Hepatology and Nutrition has suggested that biopsy should be performed when diagnosis is uncertain, in the presence of ultrasonographic evidence of steatosis, or in cases of persistent elevation of ALT levels after 3–6 months of lifestyle intervention.[99] The clinical practice guideline on NAFLD from AASLD, AGA, and ACG states that, “liver biopsy in children with suspected NAFLD should be performed in those where the diagnosis is unclear, where there is possibility of multiple diagnoses, or before starting therapy with potentially hepatotoxic medications. A liver biopsy to establish a diagnosis of NASH should be obtained prior to starting children on pharmacologic therapy for NASH.[120]

Treatment

The mainstay of therapy for NAFLD in both children and adults is centered on optimization of lifestyle with focus on nutrition and exercise. In addition, for many patients with NAFLD weight loss is also an important goal. Clinical studies have demonstrated that hypocaloric diets and regular physical exercise have the potential to induce weight loss with an

improvement of both metabolic effects and liver health status, mainly steatosis, in adult and pediatric obese-subjects with NAFLD.[121,122] However, in children there are not sufficient data to make any conclusions regarding the optimal dietary intervention or program of exercise. Most of the available studies have been conducted in small series of children, often without a control group, and with substantial variations in duration of follow-up and in clinical endpoints.[122–124] Furthermore, there are numerous challenges in achieving persistent lifestyle modification with sustained long-term results, some of which are unique to the population of children with NAFLD.[125]

The overall goal of treatment of NAFLD with pharmacological interventions, both in children and adults, is to stop and eventually reverse liver damage. Therefore, current therapeutic approaches are focused on established mechanisms that are involved in the pathogenesis of disease, including insulin resistance, oxidative stress and dyslipidemia. The pharmacological approaches used in pediatric trials are shown in Table 2.

Metformin, the insulin-sensitizer that is most often used, exerts its action by increasing hepatic lipid and glucose catabolism. Several studies have been conducted in adults and children with good safety profile, but with conflicting results. Although previous studies performed in small-series of children seemed to demonstrate a beneficial role of metformin on laboratory and imaging features of NAFLD[126,127], subsequent clinical trials reported no significant histological effect of metformin with respect to placebo in the treatment of NAFLD.[128] Conversely, in the TONIC trial, there was improvement in ballooning in 38% of children taking metformin, however, there was not an improvement in steatosis, inflammation or fibrosis.[129] Similarly, there was a beneficial effect of metformin on ballooning reported in adult patients.[130]

Nutritional supplements have also been an active area for therapeutic trials in NAFLD, including vitamin E, omega-3 fatty acids, and probiotics. Vitamin E, has been considered a good candidate for NAFLD therapy with its potent anti- oxidant capacity. In children in the TONIC study, there was improvement in hepatocyte ballooning in 37% of children taking vitamin E.[129] However, in several clinical trials, vitamin E was not better than lifestyle interventions only.[122,131,132] Data on vitamin E treatment in adults with NAFLD were more positive; in fact, in the PIVENS trial, a 96-week course of natural vitamin E was associated with a marked decrease of ALT, improvements in steatosis, inflammation and ballooning during the period of treatment.[133]

Data regarding omega-3 fatty acids have been inconsistent in adults and children with NAFLD. In a large study of adults with NASH, ethyl-eicosapentanoic acid had no significant effect on liver histology.[134] In another study in adults with NASH and type 2 diabetes, omega-3 fatty acids (eicosapentaenoic acid (2160 mg) and docosahexaenoic acid (DHA)) were inferior to placebo with respect to liver histology and insulin resistance.[135] In contrast, a study of children with NAFLD reported that the lack of fish intake was associated with portal inflammation, and that after applying adjustment factors, the lack of dietary long-chain omega-3 fatty acid intake was associated with lobular inflammation.[136] Moreover, in children, a double-blind, placebo-controlled clinical trial reported that dietary supplementation with DHA may improve liver steatosis, insulin-sensitivity and

inflammation.[137,138] However, recently, Janczyk et al[139] reported no effect of omega-3 fatty acid on ALT, liver steatosis, or insulin-resistance, and only marginal effects on AST and GGT levels. Therefore, more data are needed to understand the effect of specific omega-3 fatty acids and how and why they may differ between adults and children.

There have also been promising results observed in adults and children with NAFLD in response to treatment with probiotics.[140] A randomized controlled trial reported that 4 months of treatment with VSL#3, a proprietary mixture of eight probiotic strains, resulted in reduced BMI, improvement in abdominal ultrasound score, and no improvement in serum ALT compared to placebo.[141] While, another study found that 8 weeks of Lactobacillus improved serum ALT but not liver ultrasound. [142] Further studies are needed to know whether probiotics are a safe and effective long-term therapy for NAFLD.

To date, in children none of the tested drugs has proved entirely satisfactory *per se* in treating liver damage in NAFLD. Therefore, as shown in Table 2, many newer trials use combination approaches which include different molecules directed towards specific pathogenic targets, or drugs that have shown sufficient potential in adults with NAFLD.

Future Directions

The burden of pediatric NAFLD could reduce life expectancy in countries with a high prevalence of childhood obesity. Diagnosis and treatment of pediatric NAFLD represent a major challenge for physicians. In order to address this challenge, hepatologists, pediatricians, and researchers must collaborate to gain insight into mechanisms of NAFLD development and progression in children. The dissection of NAFLD pathophysiology, in both children and adults, is needed in order to develop tools to improve early detection and treatment of disease as soon as possible. Furthermore, primary prevention of obesity is vital in children because the likelihood of obese youth becoming obese young adults with NASH is expected to increase. In this case, age-appropriate diets may provide children not only adequate nutrition for child's development, but also help to prevent childhood obesity and its co-morbidities.

Acknowledgments

Grant Support: VN and AA are supported by the Italian Ministry of Health funds (Fondi di Ricerca Corrente). KN and JS were supported in part by NIH grants R56DK090350, R01DK088831, and U01DK61734. The funders did not participate in the preparation, review, or approval of the manuscript. The contents of this work are solely the responsibility of the author and do not necessarily represent the official views of the Italian Ministry of Health or the National Institutes of Health.

Abbreviations

ALT	alanine aminotransferases
BMI	Body mass index
CRN	Clinical Research Network
FGF21	fibroblast growth factor 21

HCC	hepatocellular carcinoma
IGFs	insulin-like growth factors
NAFLD	nonalcoholic fatty liver disease
NHANES	National Health and Nutrition Examination Survey
NAS	NAFLD Activity Score
NASH	nonalcoholic steatohepatitis
PNHS	Pediatric NAFLD Histological Score
QOL	quality of life

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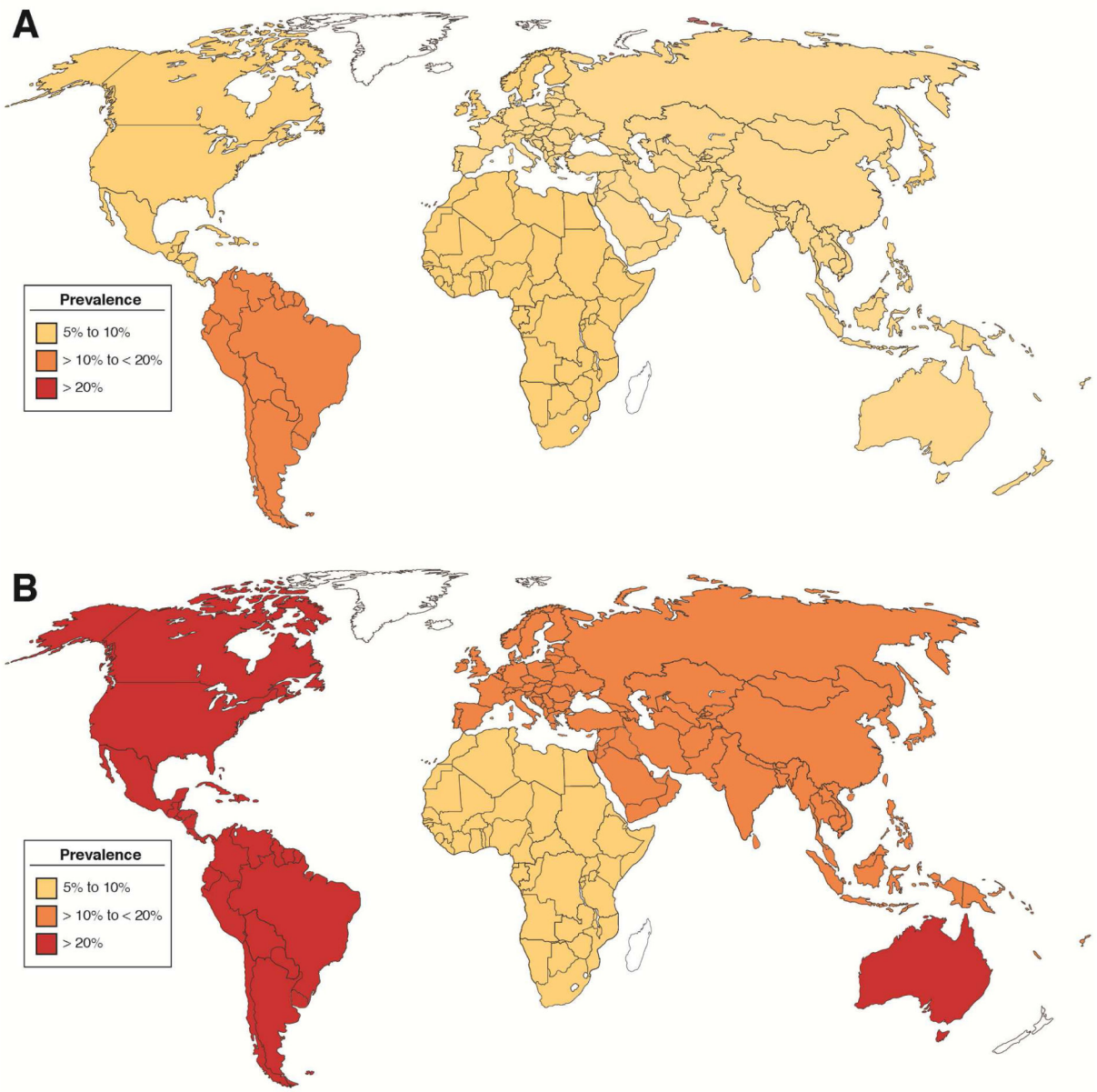

Figure 1.
Estimated general population prevalence of NAFLD is shown for Children (panel A) and Adults (panel B).

Table 1

Similarities and differences between adult and pediatric NAFLD

Adults	***Histological features***	**Children**
Typically mild to moderate. Location typically zone 3 or panacinar	*Steatosis*	Typically moderate to severe. Location panacinar, zone 1, or zone 3.
Common	*Ballooning*	Uncommon
mainly lobular	*Inflammation*	mainly portal
pericellular *chicken wire*	*Fibrosis*	predominantly portal-periportal
	Molecular markers	
Gut miocrobiota dysbiosis	*Fecal*	Gut miocrobiota dysbiosis
Adipocytokines and Hepatokines	*Circulating*	Adipocytokines and Hepatokines
- Macrophage activation - Activation of hepatic progenitors	*Tissue-specific*	- Macrophage activation - Activation of hepatic progenitors
	Genetic variants	
Strongly associated with NAFLD and NASH	*PNPLA3*	associated with NAFLD; association with NASH unclear
Associated with NASH	*GCKR*	Associated with NASH
no correlation with NAFLD	*APOC3*	no correlation with NAFLD
not investigated	*LPIN1*	inverse association with NASH
	Outcome	
5–10%	*Cirrhosis*	1–2%
Strong clinical evidence	*HCC*	Rare
Strong clinical evidence	*Metabolic syndrome*	Strong clinical evidence
Strong clinical evidence	*Cardiovascular disease*	Increased risk

Table 2

Completed and ongoing clinical trials in children with NAFLD.

Ref	Drug	Age range (y)	Type of study	Intervention	Endpoints
Completed					
127	Metformin	8 –17	Single-arm, Open label	Metformin, 500 mg twice daily	Improvement of liver chemistry, liver fat, insulin sensitivity and quality of life
129	Metformin	9 –18	Open-label – preliminary	Metformin, 1500 mg daily	Improvement of inflammation and NAS from baseline
130	TONIC	8 –17	Double blind, RCT	Metformin, 500 mg twice daily Vitamin E, 400 IU twice daily	Improvement of ALT similar to placebo Improvement of ballooning
132	Vitamin E	6 –15	Single blind, RCT	Vitamin E, 400 mg/day	ALT normalization similar to lifestyle intervention
133	Vitamin E + Ascorbic Acid	3 – 20	Double blind, RCT	Alpha tocopherol 600 IU/day plus ascorbic acid 500 mg/d	Improvement serum levels of aminotransferases Improvement liver histology
138,139	Docosahexaenoic acid	4 – 16	Double blind, RCT	1° experimental arm: 250 mg/day 2° experimental arm: 500 mg/day	Improvement of levels of ALT land triglycerides, improvement of liver steatosis and inflammation
140	Omega-3	11 – 16	Double blind, RCT	docosahexaenoic acid and eicosapentaenoic acid, 450– 1300 mg/day	Improvement of aspartate aminotransferase and gamma- glutamyl transpeptidase levels
142	VSL#3	9 – 12	Double blind, RCT	1 sachet/day < 10 years 2 sachet/day > 10 years	Improvement of steatosis and BMI
143	Lactobacillus GG	8 – 13	Open label – preliminary	12 billion CFU/day	Reduction of ALT serum levels No modifications in TNF-α levels and liver ultrasound
Ongoing					
NCT01913470	Losartan	12 – 19	Double blind, RCT	0.4mg/kg/day (max 25mg) for one week and then increased to 0.8mg/kg/day (max 50mg) for 7 additional weeks	Change in ALT from baseline
NCT01529268	Cysteamine Bitartrate Delayed- Release	8 – 17	Double blind, RCT	600 mg/day for patients ≥ 65 kg 750 mg/day for patients 65–80 kg 900 mg/day for patients > 80 kg	Histological endpoints: decrease in NAS of 2 or more no worsening of fibrosis
NCT02098317	DHA + vitamin D	4 – 16	Double blind, RCT	DHA 500 mg/day Vitamin D 800 UI/day	Histological endpoints: Improvement in NAS score Improvement of clinical
NCT01934777	DHA + choline + vitamin E	4 – 16	Double blind, RCT	DHA 500 mg/day Choline 400 mg/day Vitamin E 78 UI/day	Histological endpoints: Improvement in NAS score