Non Alcoholic Fatty Liver Disease In Children

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Introduction

Non alcoholic fatty liver disease (NAFLD) is nowadays one of the leading causes of chronic liver disease in children (1). It is defined by hepatic fat infiltration >5% hepatocytes, as assessed by liver biopsy, in the absence of excessive alcohol intake (<20 g/day), evidence of viral, autoimmune or drug-induced liver disease. It includes a spectrum of liver disease ranging from simple intra-hepatic fat accumulation (steatosis) to different degrees of necrotic inflammation and fibrosis (steatohepatitis [NASH]) (2). NAFLD growing incidence reflects the worldwide annual increase in the number of obese individuals. In fact, it is typically associated with metabolic dysfunctions, which determinates an increased risk of developing type 2 diabetes mellitus, metabolic syndrome (MS) and cardiovascular diseases, even in children.

The scientific literature does not give at the moment long-term follow up data on the natural history and prognosis of pediatric NAFLD, but it is known that, in susceptible individuals, it can evolve to cirrhosis and hepatocellular carcinoma (3).

Epidemiology and pathophysiology

Pediatric NAFLD prevalence is estimated to be between 3% and 10%. This large interval of prevalence is influenced by the diagnostic method used to detect fatty liver: liver histology is the gold standard for diagnosing NAFLD, but slightly elevated liver enzyme values (aspartate amino¬transferase [AST], and alanine aminotransferase [ALT]) in the absence of excessive alcohol consumption and other causes of steatosis, together with the evidence of bright liver at abdominal ultrasound, are commonly used as a noninvasive test to screen for pediatric NAFLD.

NAFLD in children is associated with common features of the MS, especially insulin resistance, central obesity and type 2 diabetes mellitus. The prevalence of NAFLD increases in hyperglycemic patients, and insulin resistance is more severe in individuals with NASH than in those with simple steatosis. NAFLD, and particularly NASH, is actually considered as the hepatic component of the MS.

The consumption of soft drinks can increase the prevalence of NAFLD independently of metabolic syndrome. During regular soft drinks consumption, fat accumulates in the liver by the primary effect of fructose which increases lipogenesis and potentially increase insulin resistance and inflammation (4).
NAFLD is more prevalent in adolescents, especially if overweight (5). Factors that can explain the higher rate of NAFLD in adolescents include sex hormones and insulin resistance in puberty, or their increased control over unhealthy food choices and sedentary physical activity. It is more common in boys than in girls with a male to female ratio of 2:1. It has been hypothesized that estrogens can be potentially liver-protective; or indicate that androgens may aggravate NASH. Ethnicity can also affect the prevalence of NAFLD: fatty liver is more common in Hispanic than in Caucasian children. Ethnic differences could possibly be due to higher rates of insulin resistance, and to visceral adiposity at equivalent body mass index (BMI), but also as a result of socio-economic factors. However, how age, sex and ethnicity influence NAFLD development and progression in obese and/or insulin-resistant children is still unclear (6-11).

Evidence that only part of patients with NAFLD progress to NASH suggests that disease progression is likely to depend on an interplay between environmental factors and genetic predisposition. Multiple factors are involved in the pathogenetic mechanisms. Since a decade ago, the so called "two hits hypothesis" has been used to explain the NAFLD/NASH pathophysiology, but this model was not entirely sufficient to explain NAFLD/NASH development, and actually most authors consider more plausible the so called "multiple hit" hypothesis. Hepatic steatosis is the result of a more complex interplay than that described between "two-hits", since this interplay involves the diet, the metabolic system and also host responses and its inflammatory environment. In fact, adipose tissue is a metabolically active endocrine organ that causes the release of proinflammatory cytokines such as TNF-alpha and IL-6, whereas beneficial adipokines, such as adiponectin, become suppressed. This situation leads to the development of peripheral insulin resistance and hyperinsulinemia and increased fatty acid delivery to the hepatocyte. The disruption of normal insulin signaling in the hepatocyte and increased abundance of fatty acids leads to disordered lipid metabolism, characterized by the over-activation of de novo lipogenesis (DNL) transcriptional factors, causing more fatty acid and glucose products to be shunted into these lipogenetic pathways. Beta-oxidation in the mitochondria is also inhibited, as well as very-low-density lipoprotein (VLDL) packaging and export, leading to build up of triglycerides in the hepatocytes. Gluconeogenesis is not suppressed despite hyperinsulinemia in the insulin-resistant hepatocyte, and increased glucose levels provide more substrate for DNL in a positive feedback loop (12-14).

The role of the gut has been recently considered within this metabolic dysregulation. It has been demonstrated that a diet-dependent increase of intestinal bacteria products (i.e. endotoxins, proteins, DNA, metabolites) and the subsequent activation of the Toll like Receptor pathway, may act as inductors of inflammation and progression of hepatic steatosis to NASH and fibrosis. This process seems also aggravated by the increased intestinal permeability that has been demonstrated in subject with liver disease, where the gut appears to go through a tight junction disruption process, eventualluy reversed by modifications of gut microbiota (15) (see therapy section).

Diagnosis

A recent position paper by the ESPGHAN Hepatology Committee (16) has clarified the diagnostic approach to NAFLD in childhood. NAFLD is more frequent in children aged more than 10 years, and is usually present with overweight/obesity. The diagnosis of NAFLD needs the recognition of fatty liver, and the exclusion of other causes of steatosis (Table 1).

Liver biopsy is the current gold standard for the diagnosis of NAFLD, and it is the only way to distinguish between NASH and simple steatosis, and to determine fibrosis and the severity of liver damage. However, since liver biopsy is an invasive procedure, its use should be limited to patients with real signs of NASH. First-line noninvasive approaches (biochemical parameters, imaging tests and serum biomarkers) are used as initial tools to confirm the diagnosis of fatty liver disease. Liver function blood tests, together with imaging techniques, are commonly used as indirect markers of liver steatosis. None of these have proven to be reliable, and the sensitivity and the specificity are undetermined. Aminotransferases are used, together with the measurement of accessible serum parameters such as glucose, triglyceride, cholesterol, lipoproteins, glucose/insulin levels after tolerance tests, and glycated

hemoglobin HbA1c (Table 1), to assess NAFLD diagnosis and to screen children from possible hepatopathy-related metabolic complications, such as MS. These measurements must be combined with the evaluation of anthropometrical parameters – BMI, abdominal circumference – and with other information such as the patient's gender and the health state and lifestyle of the relatives. Generally, the AST:ALT ratio is less than 1, but this value can increase as fibrosis progresses. Normal levels of serum aminotransferases do not exclude the presence of fibrosis or even cirrhosis. Identifying and validating potential novel noninvasive biomarkers of NAFLD and NASH is a central area of research. The pediatric NAFLD fibrosis index (PNFI), which is obtained from three simple measurements — age, waist circumference and triglyceride levels — has been developed to predict liver fibrosis in children with NAFLD (17).

***Table 1**: Laboratory Tests to Rule out Other Causes of Liver Disease in Children with Suspected NAFLD*

Basic laboratory profile	*Full blood count, Liver Function Tests, Fasting Glucose and Insulin, Urea, Coagulation Tests, Uric acid*
Causes of Liver Disease to Rule Out	**Laboratory Tests to perform**
Dyslipidemia/Familial hypercholesterolemia/ Cholesterol ester storage disease	Lipid Profile
Abetalipoproteinaemia	Lipoproteins
Insulin resistance/Type 2 Diabetes Mellitus (DM2)	Glucose Tolerance Test, Glycosylated Hemoglobin
Hypothyroidism	Thyroid Function Tests
Wilson Disease	Ceruloplasmin
Viral – hepatitis (HBV, HCV)	Viral Hepatitis Panel
Iron storage diseases	Iron, Ferritin
Acute systemic disease	C-Reactive-Protein + consider EBV, CMV immune state profile
Cystic Fybrosis	Sweat Test
Coeliac disease	Anti-Transglutaminase IgA and total IgA
Muscular Dystrophy	CPK
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin serum level
Metabolic diseases (Galactosaemia -in infants-, hereditary fructose intolerance, glycogen storage disease (Type VI and IX), others	Serum Lactate +/- Amino and Organic Acids +/- Plasma-free Fatty Acids +/- Acyl Carnitine Profile
Autoimmune hepatitis	Serum Immuniglobulin, Liver Autoantibodies
Drug toxicity, Parenteral Nutrition, Protein malnutrition, others	Specific Tests as Suggested by History

Liver ultrasonography is the most commonly used imaging diagnostic modality, because it is relatively inexpensive and widely available. Liver ultrasonography can provide a good estimate of the degree, or the extent of hepatic steatosis, based on a series of ultrasonographical characteristics. Unfortunately, the diagnostic accuracy of ultrasonography decreases, either when the liver contains <30% of fat, or in individuals with a BMI of 40 or more. Furthermore, ultrasonography cannot rule out the presence of steatohepatitis or fibrosis. Overall the sensitivity of ultrasound in NAFLD ranges from 60% to 94%, with specificity from 84% to 100% (18).

Histological pattern

Histological assessments play an important role in the diagnosis and management of NAFLD in children. Thus it is important to carefully evaluate and discriminate among the different histological features which characterize NAFLD/NASH.

The main histological characteristics in NAFLD/NASH are macrovescicular fatty changes of hepatocytes, ballooning degeneration, a mixed lobular inflammation, and fibrosis, but other liver lesions may also be present. Other histologic findings in NASH may include: acidophilic bodies, which result from hepatocyte apoptosis; megamitochondria; and vacuolated, glycogen-filled nuclei, which may also be seen in Wilson's disease or in diabetic liver disease (Figure 1).

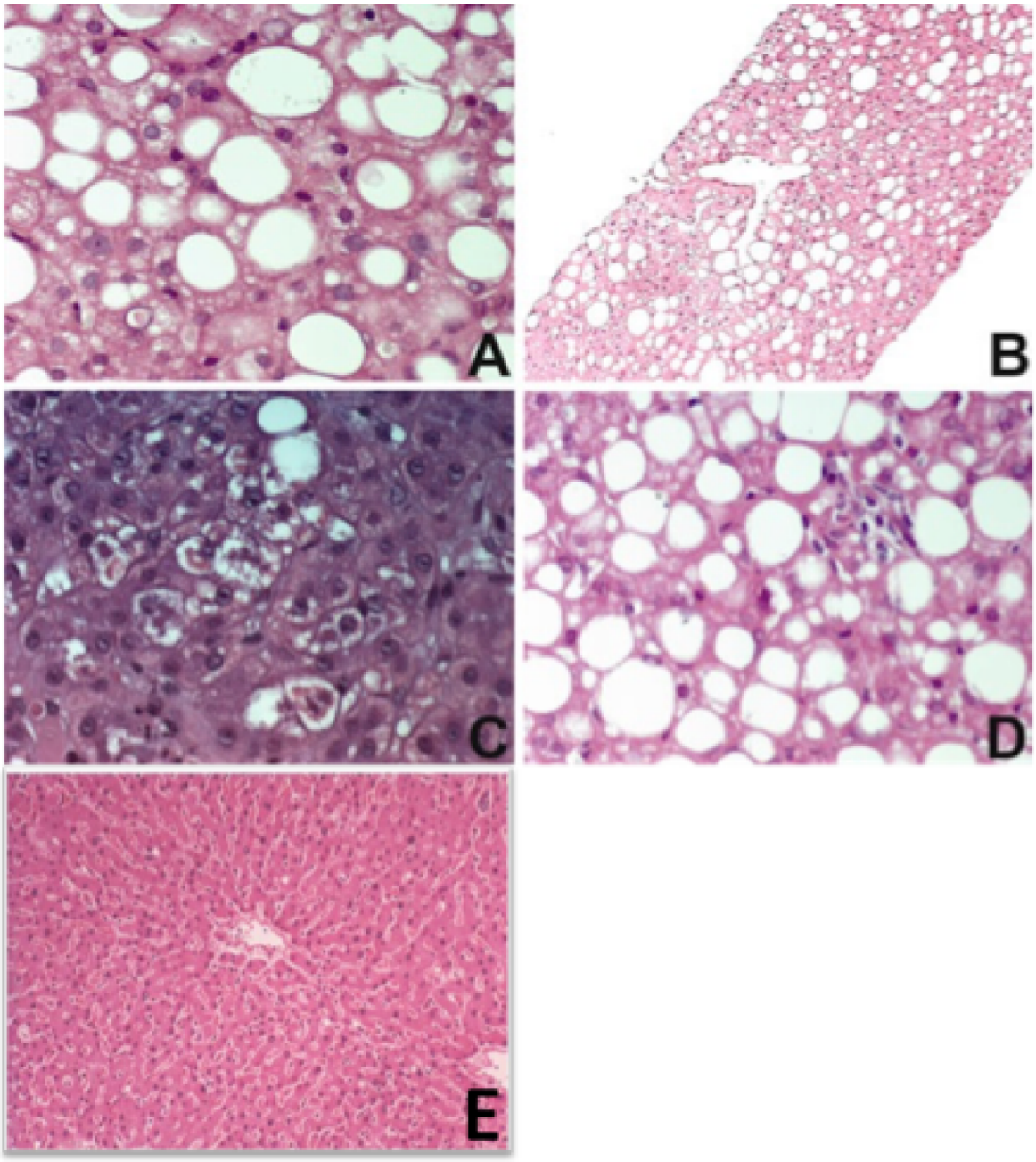

Figure 1. *Major histological features of paediatric NAFLD/NASH. Steatosis is evident in (a) (40× magnification) and (b) (10× magnification); ballooning and lipogranulomas are present in (c) and (d), respectively (40× magnification); normal liver histology -for comparison purposes (e).*

Steatosis

Hepatocellular steatosis, the principal hallmark of NAFLD, is the accumulation of lipids within the cytoplasm in > 5% of hepatocytes. Typically, the steatosis pattern is macrovescicular, the hepatocytes are distended by single large fat droplets that eccentrically displace the nucleus. Macrovacuolar steatosis can

be associated with microvacuolar steatosis (mixed pattern), in which groups of hepatocytes contain numerous minute lipid droplets in the cytoplasm, without nucleus dislocation. The pattern of distribution of fat in the liver is peculiar in children and it typically starts in the periportal zone (acinar zone 1) or shows azonal distribution, differently from adulthood in which the steatosis is mainly localized in zone 3. The severity of steatosis is determined by the extent of parenchymal involvement. Semiquantitative methods based on the percentage of surface area involved is the most useful means of grading the steatosis (19).

Ballooning

Ballooning is a degenerative modification of hepatocytes, that lose their normal polygonal shape, becoming swollen and round (20,21). It is considered the consequence of intracellular fluid accumulation due to microtubule dysfunction and impaired protein secretion (21,22).
The cytoplasm of ballooning cells is rarefied and vacuolated and can contain Mallory–Denk bodies (perinuclear clumps of amorphous eosinophilic material). Loss or marked diminution of immunohistochemical cytoplasmic staining of Keratin 8/18 may be utilized as a marker of ballooning degeneration (20,21).

Ballooning represents the most relevant sign of hepatocytes damage, and is the sign of the increased risk of disease progression (23).

Inflammation

Inflammatory infiltrate, constituted by a mix of lymphocytes and histiocytes, is mainly localized in lobules or in portal tracts. Polymorphonuclear leukocytes may localize in the sinusoids or may cluster around ballooned hepatocytes containing Mallory–Denk bodies (satellitosis) (24). Portal chronic inflammation is not required for the diagnosis of NASH even if it may be presented in liver biopsies in varying degrees (25).

Fibrosis

The fibrosis represents the manifestation of advanced form of liver damage. In children NASH is generally characterized by a pattern of portal-periportal fibrosis, with the possible presence of perisinusoidal fibrosis. The progression of portal–periportal fibrosis results in septal linkage with vascular structures, which remodel the hepatic architecture and can lead to cirrhosis (26). Hepatic stellate cells, the principal collagen-producing cells in the liver, are considered responsible for the development of fibrosis in NASH, even though the exact pathogenetic mechanism is not still clear.

Scoring system

Currently, two main scoring systems exist to evaluate histological activity in NAFLD and NASH, and are used both in children and adults. The Brunt score, specifically developed for assessment of response to therapeutic intervention, is based on the semi-quantitative assessment of macrovacuolar steatosis, ballooning, lobular and portal inflammation (PI) (mild or grade 1; moderate or grade 2; severe or grade 3)

(27). Also, the NASH–CRN system generates a numeric score for grading the disease (NAFLD activity score). NAS (range, 0-8) results from the sum of steatosis, lobular inflammation, and ballooning degeneration scores. A NAS score ≤ 2 corresponds to 'not NASH', while a score ≥ 5 corresponds to 'definite-NASH'. NAS scores of 3 or 4 are considered borderline for a diagnosis of NASH, and these cases may benefit from assessment of the entire biopsy specimen, using other features of NASH histology (28).

When NAS is applied to the pediatric population, only about half of patients can be categorized into a clear-cut pattern while the other half fall into the ''borderline'' category, supporting the need for a more reproducible scoring system to interpret liver histology in pediatric cases of NAFLD. Therefore, recently, Alkhouri et al have proposed a new grading score for pediatric NAFLD to be used in clinical trials, which took into account the presence of PI and the weight of histological features (29). This score was called Pediatric NAFLD Histological Score (PNHS). Histological features were scored: steatosis (0-3), lobular inflammation (0-3), ballooning (0-2), and PI (0-2). In this paper an excellent correlation between PNHS scores and the presence of NASH was showed (29).

Treatment

Several studies have demonstrated that lifestyle modifications, based on a dietary restriction and the promotion of physical activity, lead to an improvement of NAFLD (30-32). In fact, because of the limited knowledge of the molecular pathogenesis of NAFLD, the current NAFLD therapeutic modalities consist of strategies aiming to decrease the incidence of risk factors (i.e., insulin resistance, dyslipidemia), and only in minority, to act on major molecular pathways potentially involved in the development of this disease (33, Table 2).

Table 2. *Pharmacological studies on children with Non-alcoholic fatty liver disease (NAFLD)*

Author	Population type	n	Type of study	Treatment	Time	Outcome	Response
Nobili et al.	Overweight or obese, biopsy proven NAFLD	60	Open-label with control group	Metformin 1.5 gr/day vs antioxidants; lifestyle intervention in both arm	24-months	Serum ALT, Liver histology, dyslipidemia and resistance insulin	Mild improvement
Lavine et al	Overweight or obese, biopsy proven NAFLD	173	RCT	Vitamin E 800 IU vs Metformin 1000 mg o	24-months	Serum ALT, Liver histology	Significant improvements
Nobili et al	Overweight or obese, elevated ALT, biopsy proven NAFLD	60	RCT	Docosahexaenoic acid (DHA) 250 mg/day and 500 mg/day	24-months	Serum ALT, liver fat by ultrasonography	Significant improvements
Vajro et al	Hypertransaminasemia and ultrasonographic bright liver	20	Double blind-placebo-control	Lactobaciluss GG (12 billion CFU/day)	8 weeks	Serum ALT	Significant improvements

RCT: randomized controlled study

Diet and lifestyle changes (34,35)

Weight loss improves hepatic and extra-hepatic insulin sensitivity by reducing the delivery of free fatty acids (FFA) and through better peripheral glucose utilization. It also promotes a reduction of reactive oxygen species (ROS) and adipose tissue inflammation (36). Nobili et al (37) reported that a 2-yrs lifestyle intervention, including personalized diet and increased physical activity, resulted in a significant decrease of serum lipid levels, transaminases, and insulin resistance and a significant improvement of liver histology. Ongoing studies will better clarify the impact of weight loss in NAFLD improvement (38,39).

The ESPGHAN Committee on Nutrition (16) suggests that energy intake should be individually determined, and slowly rather than rapidly absorbed carbohydrates should be preferred. A low-carbohydrate diet free of soft drinks – that are rich in fructose (4) - decrease insulin resistance (IR) and lipogenesis, and seem to have hepatic anti-inflammatory and anti-fibrogenetic effects (39). Increasing physical activity is associated with reduced central adiposity, insulin resistance and the metabolic syndrome (40).

Antioxidants

Oxidative stress is considered a major contributor to NAFLD pathogenesis and its progression to NASH. Antioxidants, such as vitamin E, are therefore potentially valuable as a NAFLD/NASH therapy, breaking

the chain reaction of lipid peroxidation and restoring the endogenous antioxidant/oxidant balance. Alpha-tocopherol (Vitamine E) has been extensively studied. The large TONIC trial evaluated the effect of a 96-week with Vitamine E (400 UI twice daily), metformin (500 mg twice daily), or placebo, in children with biopsy-proven NAFLD. It was observed that the addition of vitamin E to a lifestyle intervention caused only a moderate beneficial effect on hepatocyte ballooning (41). Other 2 studies confirmed that (37, 42) vitamin E did not improve NAFLD much more than lifestyle intervention alone.

Insulin sensitizing agents

Metformin has also been well studied in the field of pediatric NAFLD (43, 44). Its use did not appear to be more effective than lifestyle interventions alone in ameliorating serum levels of ALT, steatosis, and liver histology. The large TONIC study [evaluating, as above reported, the effect of a 2 years therapy with Vitamin E (400UI twice daily) or insulin sensitizer metformin (500 mg twice daily) or placebo in 173 children with biopsy confirmed NAFLD] substantiated its scarce effectiveness in lowering serum ALT, with only marginal effects on hepatic histology (42).

Omega-3 long chain polyunsaturated fatty acids

Dietary supplements such as long-chain omega-3 polyunsaturated fatty acids have been used in adults with NAFLD (45,46). Studies on NAFLD experimental models have shown that long-chain omega-3 fatty acids, known as important regulators of hepatic gene transcription, can decrease liver steatosis, improve insulin sensitivity and decrease markers of inflammation (45-47). Nobili et al (41) reported the results of a randomized clinical trial on ω-3 fatty acid (docosahexaenoic acid - DHA) in children with NAFLD. At 6 and 24 months of follow up, DHA supplementation associated with diet and exercise improved serum ALT and triacylglycerol levels, body mass index, insulin sensitivity index and ultrasonography liver, without significant differences between doses of 250 mg and 500 mg/day.

Hepatoprotective agents

Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid that might theoretically antagonize the progression of NAFLD/NASH, possibly through protection of hepatocytes from bile salts-mediated mitochondrial injury, immunomodulatory function and antiapoptotic effect. A pilot pediatric RCT involving 31 children with NAFLD (48, 49) showed that conventional dose UDCA was ineffective alone or combined with diet in decreasing serum ALT or the ultrasonographic appearance of steatosis (49). These data have been confirmed also in several studies conducted in adulthood.

Probiotics

Recently, a new treatment strategy using probiotics was proposed for treatment of NAFLD. In fact, Small Intestinal Bacterial Overgrowth (SIBO), a frequent condition in obese individuals, seemed to promote NAFLD progression to NASH, by enhancing the intestinal permeability to bacterial endotoxins, activating an immune-mediated inflammatory response of liver resident cells, leading to a profibrogenic phenotype (50). Miele et al (51) provided the first evidence in humans of such mechanism. Probiotic therapies seem able to reduce liver aminotransferases, total-cholesterol, TNF-α, and improve insulin

resistance in NAFLD patients. Indeed, Loguercio et al (52) demonstrated that a chronic therapy with a probiotic (VSL#3) in patients affected by several types of chronic liver diseases, including NAFLD, may reduce liver damage and improve serum levels of various biomarkers. Also, a double-blind RCT study, treatment with Lactobacillus GG (12 billion CFU/day) in a group of obese adolescents with NAFLD, showed that after 8 weeks of treatment, patients attained a significant changes in BMI and visceral fat, with a significant decrease in alanine aminotransferase and a reduction of markers of bowel inflammation (53). These results suggest that the use of probiotics is a promising therapeutic tool in paediatric NAFLD (54-57). However, to confirm these results, further larger randomized studies are still needed.

Other promising novel therapeutic approaches

Recent studies on the pathogenesis NAFLD have highlighted several potential targets for novel pharmacologic therapies. Farnesoid X receptor (FXR) agonists is strongly expressed in bowel and liver and it may induce a reduction of hepatic inflammation trough different mechanisms, acting on glucose and lipids homeostasis and controlling bacterial flora growth (58). Incretin mimetics (exenatide and liraglutide) are the most recent diabetic medications that seem promising for the treatment of NASH. These glucagon-like peptide-1 receptor (GLP-1R) agonists are cardioprotective agents that decrease inflammation, lipogenesis and improve hepatic glucose metabolism. Toll Like Receptors (TLRs) stimulation results in activation of the trascriptional factor NF-KB, crucial for the inflammatory response. Therefore, for their ability to antagonize TLRs pathway, antagonists of TLRs may represent a novel tool in NAFLD therapy, but further study are necessary (59).

Conclusion

With the increasing burden of obesity, escalation of the incidence of NAFLD seems to be particularly dangerous in children. During the past decade, our understanding of pediatric NAFLD in terms of epidemiology and risk factors has improved considerably, but more investigations are required to unravel its pathophysiology and identify novel therapeutic targets.

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During his Specialisation Course he worked diligently in the Department of Pediatric Clinic of the General Hospital Umberto I carrying on activities of caring and research.

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From September 1995 to July 1998 he has carried on his professional activity in Neonatology Department and in Neonatal Patology of Aurelia Hospital.

From September 1995 to 30/04/1999 he has worked as Assistant in the Pediatric Department of S. Pietro Hospital in Rome.

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He is reviewer for the following medical Journal: Hepatology, GUT, Journal Gastroenterology and Hepatology, Journal Pediatric Gastroenterology and Nutrition, World Journal Gastroenterology, Journal of Hepatology, Liver International, Pediatric Transplantation, Expert Review of Molecular Diagnostics, Journal of Hematology, Journal of Internal Medicine, Journal of Clinical Rheumatology, Clinical Endocrinology

He has published many works in international reviews (more than 200) and he has attended many national and international Congresses as reporter.

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