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Similarities and differences between pediatric and adult nonalcoholic fatty liver disease

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ABSTRACT

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.

Abbreviations: NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis;; HCC, hepatocellular carcinoma; ALT, alanine aminotransferase; NHANES, National Health and Nutrition Examination Survey; BMI, body mass index; FFAs, free fatty acids; ROS, reactive oxygen species; GWAS, genome-wide association studies; PUFA, polyunsaturated fatty acids; PNPLA3, patatin-like phospholipase domain-containing 3; AST, aspartate aminotransferase; MRS, magnetic resonance spectroscopy; CAP, controlled attenuation parameter; VOCs, volatile organic compounds; CK18, cytokeratin-18; sFas, soluble Fas; sFasL, soluble Fas Ligand; NFS, NAFLD fibrosis score; APRI, AST/platelet index ratio; PNFS, pediatric NAFLD fibrosis score; TE, transient elastography; MRE, MR elastography; ARFI, acoustic radiation force impulse imaging; AUC, area under the ROC curve; PIVENS, The Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with NASH trial; TONIC, Treatment of NAFLD in Children trial; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid;; FXR, farnesoid X receptor; FLINT, Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment trial; LDL, low-density lipoprotein.

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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 keyword 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]