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Comparison of the Phenotype and Approach to Pediatric vs Adult Patients With Nonalcoholic Fatty Liver Disease




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Nonalcoholic fatty liver disease (NAFLD) is one of the main chronic noncommunicable 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 the patient's lifetime. We review the similarities and differences of NAFLD between children and adults.

Keywords: Nonalcoholic Fatty Liver Disease; Nonalcoholic Steatohepatitis; Children; Adults.

Concurrent with the sharp increase in obesity rates, nonalcoholic fatty liver disease (NAFLD) has become one of the main chronic noncommunicable 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 histologic features, including hepatocellular steatosis and injury, necroinflammation, and eventually fibrosis.[4] Since the first evidence of pediatric NAFLD in 1983, reported by Moran et al,[5] we have developed an understanding of its 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 extrahepatic organs, including adipose tissue and intestines.[2] Although a few studies have demonstrated that NAFLD can 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

Epidemiologic 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] and 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]

Abbreviations used in this paper: **ALT, alanine aminotransferases; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey; NAS, NAFLD Activity Score; NASH, nonalcoholic steatohepatitis; SNP, single nucleotide polymorphism.**

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The prevalence of NAFLD in both children and adults varies widely across the world in terms of ethnicity and population studied. In addition, it is important to consider that the methodology used for assessing prevalence can profoundly affect the estimate. Most epidemiologic 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 United States 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 during the last 20 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 1543 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 1990s, 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 1990s 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 on evaluation with ultrasound.[18] Multicenter population studies in Europe estimated a higher prevalence of NAFLD based on 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 to both ALT and ultrasound, which can under diagnose 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, the macrogeographical regions of Europe, Asia, Middle East, North America, and South America are represented by different colors.[21] In children, estimates for the prevalence of NAFLD range from 5.0% to 25.1% in different populations, including North American, South American, European, Asian, Middle Eastern, and Oceanian 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 histologic 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 with 0.7% in children aged 2–4 years old, 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 aged from 20 to 39 years old.

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 4.6% in women.[14,26] Reasons for this difference may include sex differences in seeking health care and greater use of alcohol among men. In addition, studies have consistently reported that Hispanic 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% 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 histologic sublesions include Mallory-Denk bodies; iron deposition within hepatocytes and/or the cells of the reticuloendothelial system; ductular reaction; megamitochondria observed in hepatocytes; and glycogenated hepatocyte and vacuolated nuclei.[28]

In 2005, a study evaluated the histologic appearance of 100 children with NAFLD, and categorized 2 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%), an overlap pattern with a variable combination of features of the type 1 and type 2 NASH was found, which was confirmed in subsequent clinicopathologic series.[29–31] Notably, children with portal-based NASH have more severe fibrosis.

In an attempt to standardize and grade the histologic criteria for the diagnosis of NAFLD and NASH, different methods have been elaborated. Currently, the most widely