Noninvasive Evaluations of Non-alcoholic Fatty Liver Disease in Pediatric Populations

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Abbreviations: NAFLD: Nonalcoholic Fatty Liver Disease; NASH: Nonalcoholic Steatohepatitis; IHTG: Intrahepatic Triglycerides; HCC: Hepatocellular Carcinoma; MRE: Magnetic Resonance Elastography; VLDL: Very Low-Density Lipoprotein

Mini Review

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in the pediatric population Schwimmer JB et al. [1], Anderson et al. [2] & Le et al. [3]. NAFLD in children is associated with central obesity and insulin resistance Alterio & Vos et al. [4,5]. The prevalence of NAFLD in children with obesity is estimated to be 34.2%. That is significantly higher than the 7.6% among children from the general population Anderson et al. [2]. The understanding of the pathogenesis of NAFLD is essential to finding a reproducible and accurate noninvasive tool to effectively detect the progress of hepatic steatosis Loomba [6]. This mini review focuses on the currently available noninvasive diagnostic modalities that can potentially be applied in children populations.

The natural history of NAFLD progresses from steatosis to nonalcoholic steatohepatitis (NASH) to cirrhosis. The term NASH is specifically associated with inflammation and subsequent fibrosis compared to simple steatosis. The stage of liver fibrosis has been identified as the strongest predictor of overall mortality and liver disease complications in adults Angulo et al. [7]. NAFLD-related cirrhosis is currently the second leading cause for liver transplantation in adults Charlton et al. [8]. The risk of hepatocellular carcinoma (HCC) increases with cirrhosis; however, recent report suggests that HCC can also develop in non-cirrhotic NAFLD Welzel et al. [9]. Patients with NAFLD are at higher risk of having other complications such as type 2 diabetes mellitus, cardiovascular diseases, and cancer compared to the general population Lonardo et al. [10]. Similarly, children with NAFLD also were noted to have increased cardiovascular risk and systemic health complications Baskar [11]. The natural history of NAFLD in pediatric populations has not been well established due to the paucity of prospective longitudinal studies. Available cross-sectional studies suggested that the entire spectrum of NAFLD also occur in children. Nobili et al. [12] However, the prognosis and clinical complications of NAFLD in pediatric populations need to be carefully evaluated by prospective studies.

Simple steatosis, or fatty liver, occurs early in NAFLD and may not be associated with elevated liver enzymes. Moreover, up to 23% of children with NAFLD can have a normal ALT even with the presence of liver fibrosis. Schwimmer, et al. [13], Mencin [14], Schwimmer, et al. [15] & Temple et al. [16]. It is estimated that 25% of pediatric patients with NAFLD will progress to NASH. In a study on pediatric NAFLD patients, 5 had serial liver biopsies over 5 years. Four of them were noted to have progressive advanced fibrosis Feldstein AE et al. [17].

Liver biopsy is considered the gold standard for diagnosing and evaluating the severity of NAFLD. It is, however, an expensive invasive procedure associated with sampling error and potential serious complications. Its acceptance in the pediatric population is, therefore, limited Kalia et al. [18] & Le et al. [3].

Noninvasive modalities to monitor disease progression in pediatric patients with NAFLD are greatly needed. Abdominal ultrasound is readily available but has limited sensitivity. It can only detect moderate to severe fatty infiltration of the liver (≥ 30% steatosis). Furthermore, it is operator-dependent and cannot quantitatively assess fibrosis Bouchi, et al. [19], Jiang ZG, et al. [20] & Mencin [14]. Despite their limitations, abdominal ultrasound and serum aminotransferases remain the first choice in screening NAFLD in children Temple et al. [16]. Magnetic resonance elastography (MRE) can quantify steatosis and fibrosis with high accuracy and reliability in patients with NAFLD but it
has limited availability and is not cost-effective as a screening modality. Temple et al. [16] & Dulai et al. [21]. Transient elastography (Fibro-scan) is another relatively new noninvasive method for the assessment of liver steatosis and fibrosis. It is fast with generally accurate and reproducible results. It is, however, less reliable in pediatric patients with obesity and is not available in most community hospitals in the USA Francavilla [22].

Pathogenesis of NAFLD is complex and is directly associated with the metabolism of lipoproteins. The lipolysis of subcutaneous adipose tissue and intrahepatic and intra-abdominal fat leads to an increase in fatty acids, with an increase in intrahepatic triglycerides (IHTG) content. That subsequently leads to elevated production of VLDL and triglycerides. Fatty acid overload in the hepatocytes results in an impairment of the insulin signal pathway causing decreased insulin action on glycogen synthase with subsequent insulin resistance increase in glucose secretion. Hepatocytes attempt to dispose the excessive triglyceride accumulation in the liver by increasing the VLDL secretion. However, the generation of free fatty acids and VLDL is not balanced, it is actually ineffective and results in inflammation and accumulation of fat in the liver. With the increasing fat deposition in the liver, the processing of intrahepatic fats via various lipoproteins such as low density-LDL, very low density-LDL, high density-HDL is also altered, resulting in change in the serum concentration of these molecules Nobili et al. [12] Fabbrini et al. [23], Jiang ZG et al. [24], Lavine et al. [25] & Perla et al. [26].

Lipoprotein analysis by Nuclear Magnetic Resonance (NMR) is an assay that provides lipoprotein information based on the lipid methyl signals. A given size particle has a constant number of terminal lipid methyl groups and each lipoprotein particle of a particular size has its own NMR signature. NMR spectrum is analyzed to provide particle concentrations for each of the VLDL, LDL, and HDL subclasses. By size VLDL particles, for example, can be divided as large (≥60 nm), medium (42–60 nm), and small (29–42 nm). Likewise, LDL particles can separate into large (20.5–23 nm) and small (18–20.5 nm) particles; HDL particles are classified into 3 categories by size: large (9.4–14 nm), medium (8.2–9.4 nm), and small (7.3–8.2 nm). Some of the advantages of using NMR detection include negligible sample preparation, unbiased detection and its inherently quantitative without the need for control standard.

In adults, it has been shown that the progression of NAFLD is accompanied by distinctive changes in very low-density lipoprotein (VLDL) Jiang ZG et al. [24], Garcia et al. [27] & Amor et al. [28]. In a single center study of adult patients with NAFLD, an increase in VLDL particle size was noted to be association with both NAFLD activity score (NAS) and NASH. In addition, a decrease in small VLDL particle concentration was associated with more advanced liver fibrosis Jiang ZG et al. [24]. Hence, this NMR profile of lipoprotein particles can potentially be used as a reliable method to detect progression of NAFLD in the future. Its availability along with its noninvasive nature could hold a special interest in the pediatric population. These interesting and important observations need to be further validated in both adult and pediatric populations before it can be applied to clinical practice. It is imperative to find noninvasive and cost-effective tools that can accurately monitor progression of NAFLD in the clinical settings of pediatric populations [29-31].

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