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Pediatric nonalcoholic fatty liver disease: a report from the Expert Committee *on* Nonalcoholic Fatty Liver Disease (ECON)

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Fatty liver disease in children has been increasingly recognized as an important pediatric health problem over the last two decades. Obesity is strongly associated with nonalcoholic fatty liver disease (NAFLD), with high rates of NAFLD reported among obese cohorts, and even higher rates among morbidly obese adolescents[1, 2]. Data from multiple sources, including the United States National Health and Nutrition Examination Survey (NHANES), suggest the overall prevalence of children suspected to have NAFLD has more than doubled in the last two decades [3, 4, 5]. The prevalence of pediatric NAFLD may be as high as 9.6% in the general population,[6] and NAFLD is now the most common cause of chronic pediatric

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liver disease in the developed world and is increasing in prevalence across the developing world as well[7, 8-11]. The primary care provider is at the forefront of this epidemic of childhood obesity and will see many children at risk for NAFLD. Given their frontline status, the primary care provider has the potential to both detect and intervene in the natural history of childhood NAFLD.

NAFLD is not a single entity but reflects a series of disease states across a spectrum of severity. These distinctions have been established based on histologic definitions wherein NAFLD is the umbrella diagnosis, with a threshold of macrovesicular steatosis being present ≥ 5% of hepatocytes, and nonalcoholic steatohepatitis (NASH) is the severe subset of NAFLD spectrum patients wherein the liver histology has inflammation and cellular injury with or without fibrosis in addition to the steatosis [12]. The long-term prognosis for children with NAFLD is determined by the liver histology at diagnosis; specifically, whether they have the mildest form (isolated hepatic steatosis) or the more severe form, NASH. These distinctions are not merely semantics, as NASH related fibrosis can progress to cirrhosis as early as childhood [13]. We now understand that all-cause mortality and liver transplant free survival are different in patients with NASH compared with individuals with steatosis alone or the non-NAFLD background population[14, 15]. Over the past decade, the scientific community has garnered strong evidence implicating NASH as a key contributor in the development and severity of extra-hepatic co-morbidities of the metabolic syndrome[16, 17, 18, 19].

Under the guidance of the North American Society's Pediatric Gastroenterology Hepatology and Nutrition Foundation's NAFLD initiative, we constituted an expert group of pediatric gastroenterologists from across the United States and Canada with a common research and clinical focus in NAFLD. The authors of this report are all members of this Expert Committee on NAFLD (ECON), and aim to provide the readership insight into recent advances in the field of pediatric NAFLD, dispel common misconceptions regarding the use of ALT in NAFLD, and highlight existing knowledge gaps in identification and assessment of children with NAFLD, as well as research. The contents of this report do not represent the official guidelines of North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.

Understanding the Role and Safety of Liver Biopsy in NAFLD

Liver histology is the reference standard for both the diagnosis and staging of NAFLD. Liver biopsy is the only means to definitively rule out chronic liver diseases such as autoimmune hepatitis (high false positive serum auto-antibodies [20]) and Wilson disease (despite normal ceruloplasmin levels [21, 22]) in obese individuals. Liver biopsies are also critical as entry and primary end points in clinical research studies of NAFLD/NASH. Recent safety data from multiple cohorts, including a significant number of obese patients with NAFLD, shows that percutaneous liver biopsy is a safe procedure whether performed with or without ultrasound guidance [23-25]. Specifically, one such review of the medical records of 249 children who underwent 294 ultrasound-guided percutaneous liver biopsies identified only four adverse events with no serious adverse events and one case with an inadequate sample. Similarly, another study examined 255 with suspected NAFLD who underwent ultrasound-guided

percutaneous liver biopsies without any reported serious adverse events [25]. Therefore, liver biopsy is a safe procedure that should be utilized both clinically and as a research tool in the field of pediatric NAFLD.

Role of Non-Invasive Imaging in NAFLD

Significant recent progress has occurred in the area of non-invasive imaging of NAFLD. The focus of these imaging evaluations has been the assessment of hepatic steatosis alone or identification of the degree of liver fibrosis or fibro-inflammatory injury. The limitations of ultrasound based technologies and the superiority of magnetic resonance based technologies, are more pronounced with regards to isolated steatosis. Traditional ultrasound is a sub-optimal technique of assessing steatosis due to a poor positive predictive value (47% to 62%) and inability to reliably distinguish between grades of steatosis or determine the presence of fibrosis [26]. Although ultrasound based transient elastography (TE) can theoretically better assess the degree of fibrosis, it has a high failure rate in obese patients because of limitations in sound wave penetration through subcutaneous fat [27-29]. Specifically, ultrasound based TE has a significant variation of the Young's elastic modulus when overlaying fat layers exceed a 45 mm thickness, yielding unreliable results in 5% to 15% of patients. Studies highlighting correlation between ultrasound based TE liver stiffness measurement and fibrosis stage have been performed primarily in study populations with relatively low mean BMIs. Therefore, with a large percentage of our at risk population being obese, the failure rates for both traditional and TE based ultrasound technologies limit their practical use in our population of interest.

In contrast to ultrasonography, magnetic resonance (MR) based technologies are more promising. MRI-based techniques, including steatosis estimation by proton density fat fraction (PDFF), are a promising approach for the accurate and reproducible assessment of hepatic steatosis in children. A recent study including 174 children with biopsy proven NAFLD showed good correlations between histological steatosis grade and liver PDFF measurements by MRI. Interestingly, this correlation varied significantly by sex and fibrosis stage, with girls (0.86) and those with lower fibrosis stage (0.76-0.78) having stronger correlations. [30] MR-based elastography (MRE) has shown potential for detecting significant hepatic fibrosis in a case series of children with chronic liver disease, including severely obese children. [31-33] Thus, in contrast to the ultrasound-based technologies, MR-based technologies, though still experimental, hold great potential for clinical use in the future.

The Relationship of Co-morbidities of Obesity and NAFLD

Beyond hepatic outcomes, children with NAFLD are at increased risk for numerous other significant health problems. Among the most important long-term risks is that of atherosclerotic heart disease. Risk factors that may impact the development of atherosclerotic heart disease in NAFLD include increased carotid intimal medial thickness (CIMT), higher total cholesterol, higher low-density lipoprotein levels, lower high-density lipoprotein (HDL) cholesterol, higher plasma triglycerides and higher systolic blood pressure (BP) [16, 17,15]. NAFLD patients with higher BPs are also more likely to have worse steatosis than children without high blood pressure [34]. Global cardiac dysfunction appears to

occur earlier in children with NAFLD, including left ventricular hypertrophy, persistently raised BPs, and increased CIMT [16] which in turn correlate with higher levels of plasma triglycerides and low HDL cholesterol and secondary liver damage [35].

Pulmonary co-morbidities, including hypoxia induced by sleep apnea, are increasingly recognized in pediatric NAFLD [36, 37]. Obstructive sleep apnea syndrome (OSAS) and hypoxia was found to affect 60% of children with NAFLD and is more severe in the subset of children with NASH. Even though children with and without sleep apnea and hypoxia had similar aminotransfearases and fasting lipids, worsening oxygen saturation nadirs and percent time spent with saturations less than 90% during sleep were associated with worsening hepatic fibrosis stage[36].

NAFLD has been linked directly with poor bone health as reflected by lower bone mineralization when compared with children of similar BMI without NAFLD. [18, 38] Furthermore, those with NASH had lower dual energy X-ray absorption (DEXA) z-scores then children with NAFLD, but not NASH. Children with NAFLD also have impaired health related quality of life (overall, physical and psychosocial health) scores when compared with healthy children. [19] Therefore, the presence of NAFLD portends numerous and significant extra-hepatic consequences in addition to implicit liver damage.

Misconception Regarding Use of ALT levels as a marker of NAFLD

An ongoing and controversial area has been the utility of using alanine aminotransferase (ALT) as a surrogate measure of NAFLD. An increased level of plasma ALT is the laboratory investigation that is most often associated with NAFLD. Furthermore, recent investigations have better defined the normative values for ALT. The Screening ALT for Elevation in Today's Youth (SAFETY) study compared normative values used for ALT in the laboratories of pediatric hospitals across the United States to age and sex matched lean children free of liver disease using the National Health and Nutrition Examination Survey (NHANES) dataset. This study found that the upper limit for normal ALT used in children hospital laboratories across the North America is more than twice what is predicted when using controls from NHANES data [39]. Specifically, the 95th% for ALT in healthy weight, metabolically normal, liver disease-free, NHANES pediatric participants were 25.8 U/L (males) and 22.1 U/L (females). The American Academy of Pediatrics Expert Committee Recommendations[40] and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) [41], have both advocated for the use of ALT as a screening measure for pediatric NAFLD in the obese child. Having said that, in our combined opinion, an isolated elevation in ALT is alone not sufficient to conclude whether a child has NAFLD and also some patients with NAFLD may have completely normal ALT levels. Furthermore, the level of ALT elevation does not reflect the stage or grade of NAFLD[1,42]. Another report from the NASH Clinical Research Network highlights that there can be significant histological NAFLD even with mild ALT elevation. Specifically, in this study of 91 children with NAFLD, 74 (81%) had only a mild elevation in their ALT levels. Of those children with mildly elevated ALT, 50% had marked steatosis and 9% actually had advanced (stage 3/4) fibrosis [12]. Thus these data emphasize that there is more to the NAFLD umbrella "than just an elevated ALT" [43]. In summary therefore, when used with the appropriate cut off values,

ALT maybe a helpful, albeit not perfect, tool for the identification and assessment of NAFLD.

Current research challenges in pediatric NAFLD

Below we highlight three broad areas of research necessary to advance the care of children with NAFLD:

Non-invasively distinguishing isolated steatosis from NASH

The distinction between isolated steatosis and NASH currently requires examination of liver histology. There is a critical need to reduce the dependence on liver biopsy in the diagnosis, staging and monitoring of NAFLD progression. Although it has been perceived as risky due to the potential complications of bleeding, perforation, or infection, recent data have demonstrated that liver biopsy is a safe procedure when performed using appropriate personnel and equipment [23, 25]. Nevertheless, given the large proportion of the general pediatric population this disease effects, we are faced with an ongoing challenge of numbers that precludes the use of liver biopsy as a screening tool for NASH. Thus, the development and validation of non-invasive biomarkers and surrogate end-points will decrease the need to perform routine liver biopsies. These studies will require careful and appropriate selection of study design, sample size, and validation in appropriate populations of interest. Until such a time as these bio-markers are successfully validated, liver histology will remain important for diagnosis, staging, and assessment of treatment response in clinical trials [44]. Although there has been progress on blood based biomarkers and biomarker panels, their practical and clinical use are currently premature. The push to develop and improve existing imaging technologies, including novel MRI and ultrasound based methodologies present yet unproven potential opportunities. With an ever present and increasing prevalence of disease and disease burden, the critical need to find an adequate replacement for liver biopsy as an assessment tool must remain a research priority.

Preventing NASH progression to cirrhosis and liver transplantation

NASH is an increasingly common cause of cirrhosis and resultant hepatocellular carcinoma (HCC), with the downstream effect of increasing the demand for liver transplantation while simultaneously decreasing the healthy donor pool. [45]. Cases of NASH leading to HCC in the absence of cirrhosis have been reported [46]. HCC is one of the fastest growing causes of cancer and carries a high mortality rate. Given the obesity epidemic, increasing NASH prevalence and the recent availability of easy, safe and effective therapies for Hepatitis C, NASH related cirrhosis is widely predicted to pass Hepatitis C as the leading indication for liver transplantation in adults by 2030, if not sooner [47-50]. The current pharmacologic agents to prevent NASH progression is limited. Novel therapeutics, including agents such as pentoxifylline and obeticholic acid [51-56] have been shown to improve fibrosis in adults. Similarly, vitamin E and thiazolidinediones have been shown to improve ballooning degeneration in adults patients with NASH. However other than vitamin E and metformin and a smaller study with cysteamine, most of these agents have not been tested in children with NASH [57-60]. Hence, short of reversing the obesity epidemic, *another* critical need is to discover, test, and introduce NASH halting therapeutics in children.

Preventing or reversing extra-hepatic morbidities associated from NASH

Cardiovascular, diabetic, pulmonary, and bone health outcomes (outlined above) are all negatively impacted in individuals with NASH. Therefore once NASH is identified, resources in these areas should be preferentially directed towards these individuals. *Heightened screening* for extra-hepatic consequences should occur in all children with NASH and referrals to relevant specialists made as appropriate. Although we have a better understanding of these severe co-morbidities of obesity (sleep apnea, hyperlipidemias) being associated with more severe NASH, we do not know the true mechanisms behind these clinical associations. The challenge to the research community is to identify common underlying pathways that link these co-morbid conditions above and beyond being overweight.

Conclusions

NAFLD and obesity are not synonymous, but rather NAFLD has considerable overlap with obesity. Further, there is a growing concern that the severe co-morbidities of obesity are not only associated, but also causally related to the severe form of NAFLD (ie, NASH). Diagnostic paradigms continue to evolve and, despite the above listed limitations, ALT remains the best readily available screening biomarker for NAFLD. While we await the clinical validation and application of newer biomarkers and imaging technologies, liver biopsy is a safe modality and remains the mainstay for diagnosis and monitoring of NAFLD. Evidence based treatment is a major need and there is a plethora of new therapeutic options that are already in the pharmaceutical pipeline but were not discussed in this report. We trust that in the not so distant future pediatric care providers will be able help guide families in the diagnosis and treatment of this ever growing societal problem.

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