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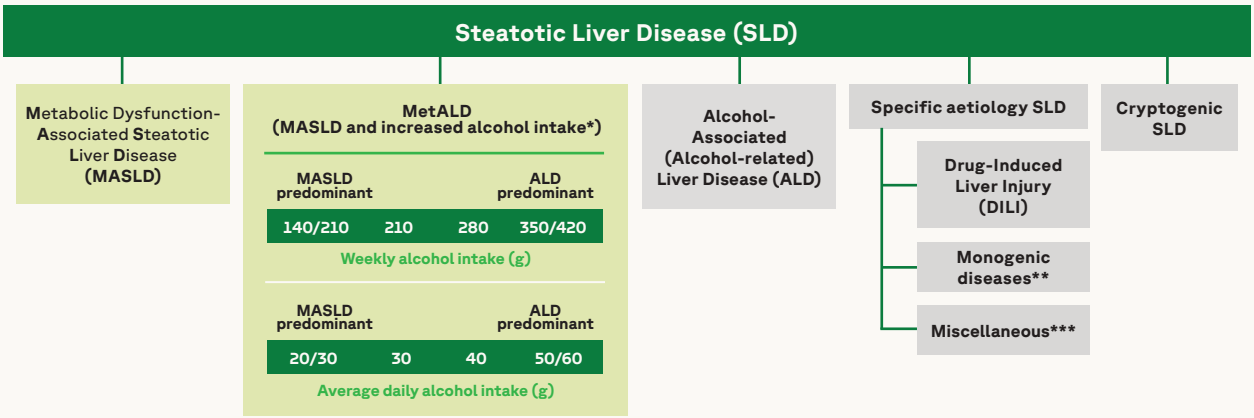
Conducting pediatric trials in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD).

Introduction

Important recent updates of terminology

Ever since the introduction of the term nonalcoholic fatty liver disease (NAFLD), there have been discussions around changing the name to better reflect the disease process and extending the terminology beyond the superficial histopathological similarities to alcohol-related liver disease. After an international consensus process, multinational liver societies, including the Latin American Association for the Study of the Liver (ALEH), the American Association for the Study of Liver Diseases (AASLD), and the European Association for the Study of the Liver (EASL), along with the co-chairs of the NAFLD Nomenclature Initiative, announced a novel nomenclature for "fatty" liver diseases at the EASL Congress in June 2023 (figure 1).[1] The previously named Nonalcoholic Fatty Liver Disease (NAFLD) has now been replaced by Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). There was consensus to change the definition to include the presence of at least one of five cardiometabolic risk factors, e.g., presence of impaired glucose regulation, type 2 diabetes, overweight or obesity, hypertension, or dyslipidemia (figure 2). Those with no metabolic parameters and no known cause were deemed to have cryptogenic steatotic liver disease (SLD). A new category, outside pure MASLD, termed MetALD was selected to describe those with MASLD who consume greater amounts of alcohol per week (between 20 to 50 and 30 to 60 g/day in females and males, respectively). Metabolic dysfunction-associated steatohepatitis (MASH) is the replacement term for nonalcoholic steatohepatitis (NASH).

Figure. 1: New nomenclature of steatotic liver disease[1]



*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease

Figure 2: Cardiometabolic criteria[1]

Adult criteria

At least 1 out of 5:

- ☐ BMI ≥ 25 kg/m² [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnicity adjusted
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment

Pediatric criteria

At least 1 out of 5:

- ☐ BMI ≥ 85th percentile for age/sex [BMI z score ≥ +1] **OR** WC > 95th percentile **OR** ethnicity adjusted
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [≥ 100 mg/dL] **OR** serum glucose ≥ 11.1 mmol/L [≥ 200 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol [140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** already diagnosed/treated type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure age < 13y, BP ≥ 95th percentile **OR** ≥ 130/80 mmHg (whichever is lower); age ≥ 13y, 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides < 10y, ≥ 1.15 mmol/L [≥ 100 mg/dL]; age ≥ 10y, ≥ 1.70 mmol/L [≥ 150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [≤ 40 mg/dL] **OR** lipid lowering treatment

Recently published adult data showed that almost all patients with NAFLD met the MASLD criteria[2], suggesting that previous natural history data can be used. Similar data in pediatric patients are still lacking.

Steatotic liver disease in the pediatric population

Since its first description in 1983, the prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) in the pediatric population increased steadily over the past decades.[3] It included a spectrum of diseases, ranging from the relatively benign non-alcoholic fatty liver to the aggressive non-alcoholic steatohepatitis (NASH), to fibrosis and cirrhosis. The prevalence of NAFLD in the general US pediatric population was estimated around 10%, with higher numbers in adolescents (approximately 17%) and children of Hispanic descent (approximately 12%). The prevalence was much higher among obese children (38%).[4] The role of insulin resistance and obesity as risk factors in the development of pediatric NAFLD was well recognized and the growing "epidemic" of obesity and type 2 diabetes in children and adolescents around the globe was contributing to the increasing prevalence.[5] Because of its close association with obesity, NAFLD had become the most common liver disease in children and adolescents.[6] Unfortunately, NAFLD could progress to NASH, resulting in progressive fibrosis leading to end-stage liver disease. NAFLD in children and adolescents appeared to be more severe compared with adults.[7]

At present, there is no approved therapy for MASH (previously NASH). Dietary interventions and increasing physical activity (lifestyle modifications) are the primary treatment for pediatric MASH. Clinical trials in pediatric MASH patients are scarce due to a unique set of challenges, which adds to the complexity in finding therapies to treat these patients.

In this white paper, we aim to present some of the key challenges this field faces as well as some potential solutions to support successful trial conduct.

Major challenges for trials in pediatric MASH patients

Diagnosing MASH in pediatric patients

NASH/MASH is often asymptomatic and remains clinically silent for a long period of time. In many cases, both in adults and in children, NASH/MASH is identified incidentally due to blood liver biochemistries or abdominal imaging, such as ultrasound or computed tomography (CT), ordered for other indications. Diagnosis can be suspected when elevated liver enzymes are seen and other causes of steatosis and chronic liver diseases have been excluded, but a definite diagnosis of NASH/MASH can only be made with a liver biopsy. Due to its invasive nature, liver biopsy is restricted to children who have increased risk of NASH/MASH (e.g., panhypopituitarism and type 2 diabetes) and/or advanced fibrosis. Potential clinical signs of increased risk of advanced fibrosis in children with NASH/MASH may include higher ALT (> 80 U/L), splenomegaly and AST/ALT > 1. It should be noted that the above described new nomenclature has added cardiometabolic risk factors not only for adults but also for the pediatric population (figure 2).

Screening for pediatric patients

The North American Society for Pediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN) suggested in their guideline in 2017 the screening with ALT between the ages of 9 and 11 years in all obese (BMI ≥ 95th percentile) and overweight (BMI ≥ 85th and < 94th percentile) children with additional risk factors (such as central adiposity, insulin resistance, pre-diabetes or diabetes, dyslipidemia, sleep apnea or family history of NAFLD/NASH).[8] This initial screening could, for example, be completed during the yearly checkups at the office of the primary care pediatrician. Interpretation of ALT should be based upon gender-specific upper limits of normal in children (22 U/L for girls and 26 U/L for boys). Once elevated ALT levels have been established, other causes of chronic liver disease or hepatic steatosis should be excluded. For the diagnosis of NAFLD, the cutoff of two times the gender-specific ALT (ALT ≥ 50 for boys and ≥ 44 for girls) in overweight and obese children age ≥10 would be used. NASH is more common in children with ALT ≥ 80 U/L compared to those with ALT < 80 U/L (41% compared to 21%, respectively).

When diagnosis is unclear or in patients with an increased risk of NASH (higher ALT levels, splenomegaly, AST/ALT > 1 or type 2 diabetes), a liver biopsy should then be considered and the patients would, in this case, be referred from their primary care pediatrician to a specialist in pediatric hepatology who is usually affiliated with children's hospitals/ academic institutions and who will also follow-up with these patients.

Several non-invasive tests to identify NASH patients with significant or advanced fibrosis have been developed and validated in the adult population, such as vibration-controlled transient elastography (VCTE) and magnetic resonance elastography (MRE). These techniques have been used in the pediatric population with excellent results, but there is an urgent need to establish, for example, specific cut-off values for children with NASH before the wide use of these non-invasive techniques can be recommended in the clinical setting as well as in clinical trials.[9]

Liver biopsy remains a critical tool for diagnosis of NASH in children and adolescents. Pediatric NASH has different histological characteristics when compared to adult NASH with more frequent presence of periportal inflammation and fibrosis and lack of balloon cells, mainly in children. Therefore, when the adult NAFLD score (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 applicable scoring system to interpret liver histology in pediatric cases. In an attempt to overcome these challenges, the Pediatric NAFLD Histological Score (PNHS) was developed which showed an excellent correlation with the presence of NASH.[10]

Site selection

To identify pediatric patients with MASH for potential clinical trials, pediatric hepatologists should be approached as well as primary care pediatricians. Primary care pediatricians have a critical role in early screening and identification of patients as well as their referral to pediatric hepatologists for further evaluation and follow-up. Pediatric hepatologists not only have a deep understanding of the condition of MASH and broad experience in following these patients, but also have access to techniques necessary for the conduct of the trial, such as fibroscan, MRI-PDFF and liver biopsy. However, pediatric hepatologists are not easily available in the US compared to other pediatric specialties. Currently, the number of sites fully capable of conducting a pediatric MASH trial is very limited in comparison to adult sites. Challenges for site selection go beyond having the necessary equipment and skill for utilizing these assessments and procedures. As the number of pediatric MASH trials increases, there will be much greater competition for sites and resources at each site, having the downstream effect of lowering enrollment rates. Based on data from Citeline, the US, Canada and United Kingdom have a greater amount of pediatric MASH industry-funded trial experience compared to the rest of the world. In terms of pediatric sites utilized for these trials, the US has been employed the most frequently and has the largest number of experienced sites. The low number of trial-ready sites compared to adult sites, even in the US, needs to be addressed proactively through awareness and education campaigns to build a larger number of sites with relevant capabilities. Increased numbers of pediatric sites will certainly be required when mandatory pediatric MASH trials follow from the success of adult MASH drug development programs.

Recruitment and retention

Patient recruitment for pediatric MASH trials will be a growing challenge as more therapies are ready to be evaluated to treat MASH in pediatric patients. As mentioned earlier, it will be paramount for sponsors of upcoming pediatric MASH studies to raise awareness of the disease among both primary care pediatricians and pediatric hepatologists to improve diagnosis rates, identify potential study subjects and build research capabilities.

Nine American specialists treating pediatric MASH patients shared insights into barriers to recruitment such as logistical challenges of travel as well as time off school and work to be at the site, cultural mistrust, challenges understanding the benefit to the patient participating in a clinical trial and fear of pain or complications. Mitigating these barriers via detailed explanations regarding pain management and the very low risk of complications in the language most comfortable for the patient and family reduces anxiety and increases study participation. Detailed explanation of pain management during and after liver biopsy in a child-friendly manner is an essential component for reducing the rate of patient drop out, as is careful selection of study personnel that have the ability to overcome patient and family language barriers. The use of age-appropriate explanations supplemented with visual aids that include ways in which the child may benefit from participating in the clinical trial should also be considered.

Biopsy as a barrier to study participation

As discussed above, liver biopsy remains the "gold standard" to diagnose MASH in pediatric patients and to determine the stage of liver fibrosis. This was perceived as a barrier to the conduct of previous studies in pediatric MASH patients; however, the acceptance of biopsy in the "Treatment of NAFLD in Children" (TONIC) trial was higher than initially expected.[11] These challenges can be overcome by careful explanation of the procedure and related risks to both the pediatric patient and parents, the use of standard of care biopsies where possible or the appropriate timing of biopsies. The FDA has provided pediatric considerations on the topic of pediatric trials in their "Guidance for Industry: Noncirrhotic Nonalcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment" and plans to provide a pediatric guidance document in the future.[12]

Family and pediatric patient considerations for participation in a MASH trial

In general, pediatric studies require the enrollment of the entire family, not only the pediatric patient. There are several challenges related to the enrollment of patients into pediatric studies, such as the potential of extended time away from school and work. This barrier can be reduced by flexible visit scheduling, allowing for study visits after school or work hours and by offering financial remuneration to offset travel expenses as well as show appreciation for the family's participation. The inclusion of adolescents (privacy and autonomy considerations), family (needs of siblings and other family members), placebo design of trial and high study burden (frequent visits with complex study procedures and medications, long travel to study sites) are all barriers that should be addressed proactively. These challenges can be overcome by allowing for ample time during the assent and consent process to explain clearly the design and risk-benefit of the study, but also to set realistic expectations, clear guidance and education for patients as well as their family members.

As younger patients and adolescents will be required to provide their assent to participate in the MASH trial, it will be important for them to fully understand the details of the study, commit to the study procedures and, particularly with adolescents, ensure they feel the sense of autonomy in making their own decisions. All these factors will ultimately support strong compliance to study procedures and dosing. These tools and tactics must be provided in an age-appropriate manner, utilizing multimedia delivery to help them best understand in this tech-savvy world. For the younger children, providing simple pictorial tools, such as printed materials, might be sufficient. For the older pre-adolescent/adolescent population, more interactive videos with question-and-answer sections will be more engaging and appreciated. During the treatment period, for instance, where multiple blood draws might be required, consideration must be made to help alleviate any anxiety on behalf of the patients. Implementing distraction tools such as stuffed animals or "loveys" to help calm the younger children, or even meditation or calming apps for the older children to listen to, will be quite helpful.

Use of technology and building trust with families

Another potential means of reducing study burden on patients and sites is deploying decentralized clinical trial (DCT) solutions. A well-designed DCT strategy may integrate elements such as home healthcare visits from a study-educated nurse or telehealth check-ins between patients, caregivers and the investigator. An app-based approach that turns the trial into a "game" for the pediatric and adolescent patients is also a potentially valuable way to connect with patients and keep them engaged in the clinical trial. The game can help them track the study procedures and clinic visits so they may watch their progress within the trial while earning virtual badges along the way.

Additionally, patients and families might not only have a lack of understanding of the disease under study, but they might not be aware of the presence of the disease, its potential complications or treatment options, and be quite distrustful of clinical trials as a whole. Raising awareness of pediatric MASLD and MASH and educating patients is, therefore, critically important in getting them to accept the diagnosis, recognize the importance of clinical trials, supporting enrollment and keeping compliance high.

Summary

Pediatric MASH is a growing medical challenge and is now considered the most common chronic liver disease in pediatric patients. There are still many hurdles to overcome when planning and executing pediatric MASH clinical trials. While there are several non-invasive tools available to support a diagnosis of MASH, a liver biopsy is still necessary to formally confirm MASH and to determine the stage of liver fibrosis. There is also a great need for more pediatric investigators to participate in upcoming trials as adult MASH trials complete and pediatric studies will follow. Furthermore, special strategies are necessary to enroll not only the pediatric patient but the whole family in pediatric MASH trials and to gain acceptance of their trial participation with all requested study elements, including liver biopsy. Resistance to liver biopsy during a trial can be overcome by careful explanation of the procedure and related risks to both pediatric patient and parents, the use of standard of care biopsies for the trial, where possible, or the appropriate timing of biopsies. During the course of the trial, both home healthcare and telehealth visits can greatly reduce study burden for families and patients. Lastly, disease and trial awareness need to be raised among more families, patients and pediatric specialists in order to successfully complete pediatric trials in this indication.

References

1. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, Romero D, Abdelmalek MF, Anstee QM, Arab JP, Arrese M, Bataller R, Beuers U, Boursier J, Bugianesi E, Byrne C, Castro Narro GE, Chowdhury A, Cortez-Pinto H, Cryer D, Cusi K, El-Kassas M, Klein S, Eskridge W, Fan J, Gawrieh S, Guy CD, Harrison SA, Kim SU, Koot B, Korenjak M, Kowdley K, Lacaille F, Loomba R, Mitchell-Thain R, Morgan TR, Powell E, Roden M, Romero-Gómez M, Silva M, Singh SP, Sookoian SC, Spearman CW, Tiniakos D, Valenti L, Vos MB, Wai-Sun Wong V, Xanthakos S, Yilmaz Y, Younossi Z, Hobbs A, Villota-Rivas M, Newsome PN, on behalf of the NAFLD Nomenclature consensus group. A multi-society Delphi consensus statement on new fatty liver disease nomenclature, *Journal of Hepatology* (2023), https://www.sciencedirect.com/science/article/pii/S1665268123002375.
2. Hannes Hagström, Johan Vessby, Mattias Ekstedt, Ying Shang. 99% of patients with NAFLD meet MASLD criteria and natural history is therefore identical. *Journal of Hepatology* (2023.09.05). https://www.journal-of-hepatology.eu/article/S0168-8278(23)05080-8/fulltext.
3. Moran JR, Ghishan FK, Halter SA, Greene HL. Steatohepatitis in obese children: a cause of chronic liver dysfunction. *Am J Gastroenterol*. 1983; 78(6):374-377.
4. Alkhouri N, Kohli R, Feldstein AE. Designing Clinical Trials in Pediatric Nonalcoholic Steatohepatitis: Tips for Patient Selection and Appropriate Endpoints. *Hepatology Communications*, Vol. 3, No. 12, 2019, 1563-1570.
5. Roberts EA. Pediatric nonalcoholic fatty liver disease (NAFLD): a "growing" problem? *J Hepatol*. 2007; 46(6):1133-1142.
6. Yu EL, Golshan S, Harlow KE, Angeles JE, Durelle J, Goyal NP, et al. Prevalence of nonalcoholic fatty liver disease in children with obesity. *J Pediatr.* 2019; 207:64-70.
7. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases [published online July 2017]. *Hepatology*. doi:10.1002/hep.29367.
8. Vos MB, Abrams SH, Barlow SE, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the expert committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) *J Pediatr Gastroenterol Nutr*. 2017; 64(2):319–334.
9. Alkhouri N. Putting It All Together: Noninvasive Diagnosis of Fibrosis in Nonalcoholic Fatty Liver Disease in Adults and Children. *Clinical Liver Disease* 2017; 9(6): 134-137.
10. Alkhouri N, De Vito R, Alisi A, Yerian L, Lopez R, Feldstein AE, Nobili V. Development and validation of a new histological score for pediatric non-alcoholic fatty liver disease. *J Hepatol* 2012 Dec;57(6):1312-8. doi: 10.1016/j.jhep.2012.07.027. Epub 2012 Aug 4.
11. The NASH CRN Research Group. Treatment of Nonalcoholic Fatty Liver Disease in Children: TONIC Trial Design. *Contemp Clin Trials*. 2010 Jan; 31(1): 62–70. doi: 10.1016/j.cct.2009.09.001. Retrieved at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2936451/.
12. Guidance for Industry: Noncirrhotic Nonalcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment (2018). Retrieved at: https://www.fda.gov/media/119044/download.

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