Nuclear Receptors: Opening Up New Avenues of Pediatric Fatty Liver Research

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Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are quickly becoming more recognized not only in adult but also in pediatric populations. It is estimated that nearly 3%-10% of children in westernized nations have NAFLD and that the prevalence of pediatric NAFLD reaches nearly 70%-80% in obese patients.[1] A dramatic rise in the prevalence and incidence of obesity is now increasingly being identified in developing nations as well.[2] As NAFLD is linked strongly to obesity, one can expect rates of this disease to rise in proportion. The increasing perception that these entities are linked has led to an expanding awareness of this disease in the pediatric population.

Data regarding differences in the clinical features between the pediatric and adult forms of this disease are scant. The natural history of this disease in the pediatric population is not nearly as well described as it is in adults. There exists significant overlap of risk factors for the development of NAFLD between pediatric and adult populations. One significant distinction between the two groups is pubertal stage. Histological differences have also been identified between pediatric and adult versions of this disease. Pediatric NASH is characterized by hepatic steatosis with portal inflammation with or without fibrosis and without ballooning or perisinusoidal fibrosis. In contrast, adult patterns of NASH include steatosis with ballooning and perisinusoidal fibrosis with portal tract sparing. Despite these findings, there may be a great overlap in the features between adult and pediatric NASH.[3] The current mainstay of treatment remains lifestyle modifications that target gradual weight loss. Vitamin E is the only pharmacologic option available at this time, but little data exist on long-term use. Therefore, there is a great need to design therapeutics directed toward this disease in children. However, much remains unclear about the clinical features of pediatric NAFLD, because so little data exist from which to draw conclusions. Whether the differences between pediatric and adult NAFLD can be exploited to develop therapies for the pediatric population remains unclear. Further studies are required to help guide the management of this special at-risk population.

This study by Elbel et al.[4] investigated the differential expression of liver nuclear receptors in a pediatric population with NAFLD. This study was conducted on 40 pediatric patients with end-of-treatment liver biopsies recruited from the Effect of Vitamin E or Metformin for Treatment of NAFLD in Children and Adolescents trial.[5] The techniques involved in this study included a blinded assessment of liver histology by pathology committee review coupled with quantitative PCR studies of 36

Abbreviations: FLINT, Farnesoid X Nuclear Receptor Ligand Obeticholic Acid for Noncirrhotic, Nonalcoholic Steatohepatitis trial; FXR, farnesoid X receptor; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PPAR, peroxisome proliferator–activated receptor.

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ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Ekihiro Seki, M.D., Ph.D.
Division of Digestive and Liver Diseases
Department of Medicine, Cedars-Sinai Medical Center
8700 Beverly Blvd., Davis Research Bldg., Suite 2099
Los Angeles, CA 90048
E-mail: Ekihiro.Seki@cshs.org
Tel: +1-310-423-6605
Fax: +1-310-423-0157

different nuclear receptors derived from liver mRNA. Subsequent cluster analysis allowed for grouping of both gene expression levels and individual patient data based on histology. Further correlations were derived from direct comparison of liver histology to normalized nuclear receptor expression levels. This approach allowed for simultaneous evaluation of many different nuclear receptors in a population of special interest.

To our knowledge, this paper represents the first profile of differential nuclear receptor expression in the pediatric population of NAFLD coupled with liver histology. Nuclear receptors have been studied extensively in the adult disease and have been the subject of several clinical trials.[6] Fewer such studies have been performed in the pediatric population. Interestingly, the greatest amount of increased nuclear receptor expression correlated primarily with liver fibrosis seen on biopsy. Data are mixed regarding the level of expression of these nuclear receptors in correlation with fibrosis in adults.[6] For example, decreased expression of PPARα (peroxisome proliferator-activated receptor gamma) has been found with increasing amounts of fibrosis, whereas its expression was increased in this study.[7] Interestingly FXRα (farnesoid X receptor) expression did not change with regard to fibrosis, which differs with the results of the Farnesoid X Nuclear Receptor Ligand Obeticholic Acid for Noncirrhotic, Nonalcoholic Steatohepatitis trial (FLINT) clinical trial results, which did show improvement in fibrosis with a agonist directed toward this receptor.[8] Presumably, these differences may be the result of the posttreatment biopsies used in this study or may reflect differences in the pathophysiology of the adult and pediatric versions of this disease. This study raises interesting questions that need further investigation to better understand the role of these nuclear receptors in this disease.

The major limitations of this study include the use of posttreatment biopsies for histological studies as well as the significant number of statistical comparisons that were made. Use of posttreatment biopsies, as noted by the authors, limit the ability to draw conclusions about the cause and effect of the differentially expressed nuclear receptors, as the treatment itself may have altered expression. Finally, the number of comparisons made it extremely likely that statistical significance would be reached for any one comparison. These limitations primarily restrict the ability to draw mechanistic insights into the pathogenesis of this disease. Despite these shortcomings, the main power of this study is the correlation of these receptors to liver histology, from which one can design future experiments to explore these differences in nuclear receptor expression.

Nuclear receptors are well known to play a role in the development of NAFLD, and several agonists toward these receptors have undergone testing in clinical trials.[6] These trials tested agonists toward PPARα/γ/δ and FXRα. Agonists directed toward the PPARγ and PPARα/δ were tested in the Pioglitazone Versus Vitamin E Versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis trial and by the GOLDEN-505 Investigator Study group, respectively.[9,10] Similarly, an agonist directed toward FXRα was studied in the FLINT clinical trial mentioned previously.[8] Improvements in some of the features of NASH were seen in all of these trials. These trials, however, are not without their own shortcomings. For example, the trial conducted to test elafibrinor, a PPARα/δ agonist, did not reach its primary endpoint of resolution of NASH. The FLINT trial similarly also did not show a significant amount of resolution of histologic NASH within their treatment group. Extension of the results of those trials to this study are somewhat difficult to make, given that a pediatric population was not tested. Nevertheless, because significant differential expression of various nuclear receptors appears to overlap at least somewhat with the adult version of NAFLD, there is hope that some of these treatments could be trialed in a pediatric population. This present study will help drive future research into pediatric fatty liver disease and by extension lend some credence to possibly trialing these drugs in this special population.

This relatively large array of data was able to accomplish several things: (1) confirmation of previous nuclear receptor studies showing involvement of these receptors in this disease process; (2) identification of potential new targets for further investigation; and (3) allowance for further grouping of individual patients into possible subcategories. Although one is unable to clearly deduce mechanistic insights from this study, it does offer a starting point for further research. A prospective study designed to categorize patients using the groups in this study and follow

their long-term outcomes would prove useful, given how little is known about this patient population. The morbidity and mortality associated with pediatric NAFLD/NASH is large and is only expected to increase with the rising epidemic of global obesity. Furthermore, there is a dearth of treatment options for this disease entity and this work provides a foundation for the further study of directed therapeutics in this population.

Vijay Pandyarajan
Ekihiro Seki
Division of Digestive and Liver Diseases
Department of Medicine
Cedars-Sinai Medical Center
Los Angeles, CA

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