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

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. A dramatic rise in the prevalence and incidence of obesity is now increasingly being identified in developing nations as well. 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. 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. 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. The techniques involved in this study included a blinded assessment of liver histology by pathology committee review coupled with quantitative PCR studies of 36
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. 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. 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. 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 (FLINT) clinical trial results, which did show a significant amount of resolution of histologic NASH within their treatment group. Extension of the results of those trials to 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. These trials tested agonists toward PPARα/γ/δ and FXRα. Agonists directed toward 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. Similarly, an agonist directed toward FXRα was studied in the FLINT clinical trial mentioned previously. 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 elafibranor, 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.

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REFERENCES

1) Alisi A, Feldstein AE, Villani A, Raponi M, Nobili V. Pediatric nonalcoholic fatty liver disease: a multidisciplinary approach. Nat Rev Gastroenterol Hepatol 2012;9:152-161.

2) (NCD-RisC) NRFC. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet 2017;390:2627-2642.

3) Crespo M, Lappe S, Feldstein AE, Alkhouri N. Similarities and differences between pediatric and adult nonalcoholic fatty liver disease. Metabolism. 2016;65:1161-1171.

4) Elbel E, Lavine JE, Downes M, Van Natta M, Yu R, Schwimmer JB, et al. Hepatic nuclear receptor expression associates with features of histology in pediatric nonalcoholic fatty liver disease. Hepatol Commun 2018;2:1210-1223.

5) Lavine JE, Schwimmer JB, Van Natta ML, Molleston JP, Murray KF, Rosenthal P, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. JAMA 2011;305:1659-1668.

6) Cave MC, Clair HB, Hardesty JE, Falkner KC, Feng W, Clark BJ, et al. Nuclear receptors and nonalcoholic fatty liver disease. Biochim Biophys Acta 2016;1859:1083-1099.

7) Pawlak M, Lefebvre P, Staels B. Molecular mechanism of PPARalpha action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease. J Hepatol 2015;62:720-733.

8) Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 2015;385:956-965.

9) Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362:1675-1685.

10) Ratziu V, Harrison SA, Francque S, Bedossa P, Lehert P, Serfaty L, et al. Elafibranor, an agonist of the peroxisome proliferator-activated receptor-alpha and -delta, induces resolution of nonalcoholic steatohepatitis without fibrosis worsening. Gastroenterology 2016;150:1147-1159, e1145.