cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

# Parenteral Nutrition Associated Hepatic Steatosis and NAFLD Intersect at AMPK

Parenteral nutrition (PN) is a life-saving treatment for children and adults that are unable to consume enteral feeding because of intestinal injury and resection, immaturity, or impaired function. During long-term PN, liver disease can develop that is characterized by hyperbilirubinemia, cholestasis, steatosis, and hepatic fibrosis.[1] Transition to enteral feeds can resolve hyperbilirubinemia and cholestasis; however, in 45% of children, steatosis does not resolve with enteral feeds.[2] Currently, most research in the field of PN-associated liver disease focuses on the mechanisms leading to cholestasis and treatments to resolve cholestasis. Research into the mechanisms of PN-associated hepatic steatosis (PNAHS) and potential treatment options have been greatly underrepresented in the field of PN research. Given this, much of the understanding of steatosis during PN comes from research on nonalcoholic-associated fatty liver disease (NAFLD).[3] Whereas this is a good starting point, the mechanisms that drive the development of steatosis during PN are possibly different than the mechanisms that drive NAFLD. Early studies in PN showed that administration of high dextrose with minimal lipid, or absent of any lipid component, increases hepatic lipid synthesis, driving the development of steatosis.[4] Even with controlled dextrose administration, the lipid emulsions present in PN can lead to hepatic steatosis. Lipid emulsions do not follow the same circulatory path as micelles during enteral absorption, making the liver the first pass for digestion and potentially increasing deposition of hepatic lipid.[5] Therefore, the mechanism of hepatic steatosis during PN can be conditionally dependent on either de novo lipogenesis or impaired mobilization of lipolytic enzymes. In NAFLD, there is convincing evidence that these lipid-centric events are mediated through AMP-activated protein kinase (AMPK) suppression.[6] However, it has yet to be understood if AMPK-mediated signaling is the same root cause in PNAHS.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Maitiabula et al[7] made the important first steps in identifying the mechanism of PNAHS with the identification of a key protein, protein phosphatase 2a (PP2A). Proteomic analysis of hepatic biopsies from patients diagnosed with PNAHS identified reduced expression of PP2A catalytic subunit alpha isoform (PP2A-C$\alpha$) and PP2A regulatory subunit A beta isoform (PP2A-A$\beta$). Subsequent phosphoproteomic analysis of these samples revealed increased phosphorylation of RAC-beta serine/threonine protein kinase (AKT2) and decreased phosphorylation of AMPK subunit gamma 2 (PRKAG2). These initial protein expression findings fit well with a mechanistic overlap between NAFLD and PNAHS, because the key intermediate, AMPK, is suppressed in both syndromes, and PP2A, a key upstream regulator of AMPK phosphorylation, was identified in the analysis of altered proteins. Maitiabula et al[7] followed up these findings in a mouse model of PN that has previously been shown to recapitulate the clinical development of PNAHS.[8,9] Mice receiving PN for 14 days had suppressed expression of PP2A-C$\alpha$ and increased phosphorylation of AKT2. To confirm the relevance of PP2A-C$\alpha$ in the progression of PNAHS in the mice, liver-specific knock-out of PP2A-C$\alpha$ (PP2ca-LKO) were generated. PP2ca-LKO-PN mice had even greater histopathologic signs of liver injury and lipid accumulation compared with wild-type (WT)-PN mice. By re-expressing PP2A-C$\alpha$, through adenoviral transduction (Ad-PP2A), the phenotype of PP2ca-LKO mice was rescued and AKT2 phosphorylation reduced in the liver; thereby, showing that PP2A-C$\alpha$ plays a central role in PNAHS progression. Importantly in this study, use of pharmacologic inhibitor of AKT2, MK-2206, suppressed the development of liver steatosis in WT-PN mice. A deeper dive into the pathway altered when PP2A-C$\alpha$ is suppressed during PNAHS found suppression of the $\beta$-oxidation pathway and activation of lipogenesis. Phosphorylation of the lipogenic enzyme acetyl coa carboxylase 1 (AAC1), which negatively regulates ACC1 activity, was significantly decreased in WT-PN and strongly trended toward a decrease in PP2ac-LKO mice. Accordingly, ACC1 activity was increased in these animals, and predictably, this raised levels of malonyl-coa, an indicator of increased lipogenesis.

With the elevation of ACC1, AMPK phosphorylation was suppressed as was the abundance of $\beta$-oxidation intermediate carnitine palmitoyltransferase I. Taken in full, this study makes a strong and compelling case for the role of PP2A in driving signaling pathways that culminate in suppression of $\beta$-oxidation and enhancing lipogenesis, resulting in the development of PNAHS.

There are intriguing questions that arise from the findings in this study by Maitiabula et al.[7] First, the mouse model suggests that cotreatment of AKT2 inhibitors during PN administration can prevent the development of hepatic steatosis, but can treatment after the development of hepatic steatosis resolve the excess lipid while still receiving PN? Second, this study examined adults with hepatic steatosis and performed experiments using adult mice. Although steatosis is a primary outcome in adults receiving PN, a major study in infants that developed steatosis suggests that infants have impaired ability to resolve steatosis after enteral nutrition transition feeding.[2] Does this mechanism hold true in the pediatric population, which have a high prevalence of liver injury following long-term PN? It is

hoped that fellow researchers in the field can take these findings and help further progress the understanding of steatosis during PN and most importantly, find targeted treatments for patients on PN that cannot be transitioned to enteral feeds.

*GREGORY GUTHRIE, PhD*
USDA-ARS Children's Nutrition Research Center
Department of Pediatrics, Baylor College of Medicine
Houston, Texas

## References

1. Hojsak I, Colomb V, Braegger C, Bronsky J, Campoy C, Domellof M, Embleton N, Fidler Mis N, Hulst JM, Indrio F, Lapillonne A, Mihatsch W, Molgaard C, van Goudoever J, Fewtrell M. , Nutrition ECo. ESPGHAN Committee on Nutrition Position Paper. Intravenous lipid emulsions and risk of hepatotoxicity in infants and children: a systematic review and meta-analysis. J Pediatr Gastroenterol Nutr 2016; 62:776–792.
2. Mutanen A, Lohi J, Heikkila P, Koivusalo AI, Rintala RJ, Pakarinen MP. Persistent abnormal liver fibrosis after weaning off parenteral nutrition in pediatric intestinal failure. Hepatology 2013;58:729–738.
3. Kyrana E, Dhawan A. Omega-3 fatty acid-rich parenteral nutrition: is it a double-edged sword? J Pediatr Gastroenterol Nutr 2015;61:469–471.
4. Buchmiller CE, Kleiman-Wexler RL, Ephgrave KS, Booth B, Hensley CE 2nd. Liver dysfunction and energy source: results of a randomized clinical trial. JPEN J Parenter Enteral Nutr 1993;17:301–306.
5. Wichman BE, Nilson J, Govindan S, Chen A, Jain A, Arun V, Derdoy J, Krebs J, Jain AK. Beyond lipids: novel mechanisms for parenteral nutrition-associated liver disease. Nutr Clin Pract 2022;37:265–273.
6. Smith BK, Marcinko K, Desjardins EM, Lally JS, Ford RJ, Steinberg GR. Treatment of nonalcoholic fatty liver disease: role of AMPK. Am J Physiol Endocrinol Metab 2016;311:E730–E740.
7. Maitiabula G, Tian F, Wang P, Zhang L, Gao X, Wan S, Haifeng S, Yang J, Zhang Y, Gao T, Xue B, Li C, Li J, Wang X. Liver PP2A-C$\alpha$ protects from parenteral nutrition-associated hepatic steatosis. Cell Mol Gastroenterol Hepatol 2022;14:669–692.
8. El Kasmi KC, Anderson AL, Devereaux MW, Vue PM, Zhang W, Setchell KD, Karpen SJ, Sokol RJ. Phytosterols promote liver injury and Kupffer cell activation in parenteral nutrition-associated liver disease. Sci Transl Med 2013;5:206ra137.
9. Tian F, Wang J, Sun H, Yang J, Wang P, Wan S, Gao X, Zhang L, Li J, Wang X. N-3 polyunsaturated fatty acids ameliorate hepatic steatosis via the PPAR-alpha/CPT-1alpha pathway in a mouse model of parenteral nutrition. Biochem Biophys Res Commun 2018;501:974–981.

**Correspondence**
Address correspondence to: Gregory Guthrie, Baylor College of Medicine, 1100 Bates Street, Houston, Texas 77030. e-mail: gguthrie@bcm.edu.

**Conflicts of interest**
The author discloses no conflicts.


**Most current article**


2352-345X
https://doi.org/10.1016/j.jcmgh.2022.06.005