Wednesday, October 7, 2015
Washington Hilton
Washington DC

International Ballroom East

Single Topic Symposium

STOPNASH: Symposium on **t**he **O**rigins and **P**athways of **N**on**a**lcoholic **S**teato**h**epatitis

Course Directors: Miriam Vos MD, Ariel Feldstein MD, Joel Lavine MD, Rohit Kohli MD

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in children and is estimated to affect more than 7 million children in the United States. It is a chronic liver disease that occurs in the setting of increased adiposity and systemic lipid dysregulation. Nonalcoholic steatohepatitis (NASH) is the more severe, progressive form of the disease but even the more mild form (NAFL) is associated with adverse health outcomes including type II diabetes and cardiovascular disease. Because the pathophysiology of NAFLD is not isolated to the liver, the science of NAFLD is growing across diverse fields including metabolism, endocrinology, adult and pediatric hepatology as well as lipidology, and more. The diversity of backgrounds has led to inadequate cross-pollination of science in the pediatric NAFLD field because investigators present at separate meetings and have less interaction than desired.

The overall objective of "STOPNASH: **S**ymposium on **T**he **O**rigins and **P**athways of Nonalcoholic Steatohepatitis" is to bring together experts from diverse fields in order to generate synergy in pediatric nonalcoholic fatty liver disease research, to develop consensus regarding priorities in pediatric NAFLD research and to encourage young investigators and investigators from diverse backgrounds to study NAFLD in order to improve prevention and treatment of NAFLD. Specific aims include:

1. Bring together basic, translational, clinical and population NAFLD researchers from the fields of endocrinology, lipidology, metabolism, nutrition, and hepatology to share their work and develop synergy and collaboration.
2. Define, prioritize and widely communicate a future research agenda for pediatric NAFLD.
3. Provide support, networking and potential collaboration to young investigators.
4. Inform the wider community of researchers of the findings from this conference.

8:00-8:05 Introduction: Themes and goals of conference
Miriam Vos MD

Module 1 **Clinical Patterns and Early Influences on NAFLD**
Moderators: Stavra Xanthakos MD and Ajay Jain MD

8:05 – 8:25 Patterns of NAFLD around the world
Jeff Schwimmer MD, University of California, San Diego

8:25 – 8:45 Putting NAFLD in perspective: An overview of the pathophysiology
Brent A. Neuschwander-Tetri MD, St. Louis University

8:45 – 9:05 Genetics plus the environment: The sugar effect on PNPLA3
Michael Goran MD, Keck School of Medicine, University of Southern California

9:05 – 9:25	NAFLD and Type II Diabetes *Sonia Caprio MD, Yale University School of Medicine*
9:25 – 9:45	Panel Discussion
9:45 – 10:00	Break
Module 2	**From "Healthy" Obese to NASH - What Happens?** Moderators: Shikha Sundaram MD and Ariel Feldstein MD
10:00 – 10:20	Maternal insulin resistance and NAFLD development *Jed Friedman MD, University of Colorado School of Medicine*
10:20 – 10:40	Fatty acid dysregulation in NAFLD *Elizabeth Parks MD, University of Missouri School of Medicine*
10:40 – 11:00	Fructose and the liver: More than just extra calories? *Rob Lustig MD, University of California, San Francisco*
11:00 – 11: 20	Microbiome and NAFLD in children *Marialena Mouzaki MD, The Hospital for Sick Children*
11:20 – 11:40	Genetics and NAFLD: What we know so far *Nicola Santoro MD, Yale University School of Medicine*
11:40 – 12:00	Panel Discussion
12:00-1:00	Lunch in Small Groups – Breakout sessions to define research priorities Moderators to lead small groups International Ballroom West
Module 3	**Initiating Mechanisms of Inflammation & Fibrosis** Moderators: Saul Karpen MD and Stephanie Abrams MD
1:10 -1:30	Crosstalk between adipocytes and hepatocytes *Nitika Gupta MD, Emory University*
1:30 – 1:50	Oxidized lipids and linoleic acid in NASH *Christopher Ramsdam MD, National Institutes of Health*
1:50 – 2:10	Sterile inflammation and cell death *Ariel Feldstein MD, University of California, San Diego*
2:10 – 2:30	NASH: What's bile got to do with it? *Rohit Kohli MD, Cincinnati Children's Hospital Medical Center*
2:30 – 2:50	Panel Discussion
2:50 – 3:10	Break

Module 4	**From Bench to Bassinet: Research Informing NAFLD Prevention** Moderators: Regino Gonzalez-Peralta MD and Emily Perito MD
3:10 – 3:30	What dose of exercise reduces insulin resistance in children and application to NAFLD *Catherine Davis MD, Georgia Regents University*
3:30 – 3:50	Interventions and policies to prevent obesity among vulnerable children *Jennifer Woo Baidal MD, Boston Children's Hospital*
3:50 – 4:10	Prevention and treatment of childhood obesity: What can we learn and apply to prevention of NAFLD? *Sarah Barlow MD, Baylor College of Medicine*
4:10– 4:30	Panel Discussion
Module 5	**Moving Forward: Research Priorities** Moderators: Miriam Vos MD and Rohit Kohli MD
4:30 – 4:45	Goals of the NASH CRN and opportunities for collaboration *Joel Lavine MD, Columbia University*
4:45– 5:00	NIDDK priorities and perspectives *Ed Doo MD, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)*
5:05 – 5:15	Opportunities for Collaboration Veronica Miller PhD, Director, Forum for Collaborative HIV Research and The Liver Forum
5:15 – 6pm	Presentation & Discussion of Small Group Results Moderators: Drs. Vos, Kohli, Lavine and Feldstein

CME information

NASPGHAN is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

NASPGHAN designates this live activity for a maximum of 9 AMA PRA Category 1 Credit(s). Physicians should only claim credit commensurate with the extent of their participation in the activity.

Program Evaluation

It is NASPGHAN policy to conduct post activity evaluations. Evaluations must be completed to receive your CMR certificate. The results of these evaluations play a major role in planning future CME activities and are shared with faculty presenters.

Faculty Disclosure

In order to ensure independence, objectivity and scientific rigor in all activities and in accordance with the ACCME, ANCC and ACPE Standards for Commercial Support, all those in a position to control the content of an educational activity are required to disclose their relevant financial relationships. This includes indicating that one has nothing to disclose. Disclosure information will be distributed to the activity attendees.

Prior to the program, all persons involved in the development or presentation of course content are expected to disclose any relevant financial relationships with any entity producing, marketing, re-selling, or distributing health care foods or services consumed by, or used on, patients and related to the content of their presentations. All conflicts have been resolved satisfactorily.

NASPGHAN is grateful for the support from the following:

Alexion Pharmaceuticals

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Intercept Pharmaceuticals

National Institutes of Health

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Takeda Pharmaceuticals International, Inc

NOTES

PATTERNS OF NAFLD AROUND THE WORLD

Jeffrey Schwimmer MD, University of California, San Diego

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in children in the United States and much of the world. NAFLD has been reported in children from over 30 countries in 6 of the world's 7 continents. In children in the U.S., the prevalence of NAFLD is nearly 10%. NAFLD most commonly presents in early adolescence, but can be seen across the entire pediatric age range. NAFLD is associated with obesity and insulin resistance. In the U.S., the highest rates of pediatric NAFLD are in Hispanic and Asian children. NAFLD is also more common in boys than in girls. Nonalcoholic steatohepatitis (NASH) is a distinct subtype of NAFLD. In children, NASH can present in at least two different forms. NASH is present in approximately 25% of children with NAFLD. Advanced fibrosis is seen in > 10% of children with biopsy-proven NAFLD. In addition to the risk for adverse hepatic outcomes, NAFLD is associated with numerous other health problems including cardiovascular, endocrine, psychological and pulmonary disorders in children. Thus, NAFLD is a serious, chronic health problem in millions of children that presents a challenge to the pediatric clinical and research communities.

References

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NOTES

PUTTING NAFLD IN PERSPECTIVE: AN OVERVIEW OF THE PATHOPHYSIOLOGY

Brent A. Neuschwander-Tetri MD, Saint Louis University

Keeping mind that NASH is a phenotype and not a specific disease, the causes of NASH can be understood by focusing on fatty acids in the liver, specifically where they come from and their routes of disposal. Different patients may arrive at the phenotype of NASH by different routes depending on dietary and genetic factors.

The two major sources of fatty acids in hepatocytes are their delivery to the liver by the blood and their formation within the liver by de novo lipogenesis (DNL). Minor sources include uptake and lysosomal breakdown of apolipoprotein remnants and autophagic breakdown of internal cell membrane lipids. Just as the supply of fatty acids to the liver is important in NASH, so is their disposal. The two major fates of fatty acids areoxidation by mitochondria, peroxisomes and cytochrome P450s or formation of triglyceride and its export into the blood as very low density lipoprotein (VLDL). If triglyceride formation exceeds the capacity to secrete it as VLDL, it accumulates as temporary triglyceride droplets (steatosis) which have their own lipolytic mechanisms to return the fat back to the intracellular fatty acid pool.

The primary underlying abnormalities in NASH include an oversupply of free fatty acids to hepatocytes, either by too much lipolysis in adipose tissue or an excessive supply of carbohydrate which promotes the formation of new fatty acids in the liver by DNL.[1-4] This is compounded by any defects in fatty acid disposal such as defects in mitochondrial oxidation or impaired formation and removal of triglyceride from the liver. When the supply of fatty acids exceeds disposal, lipotoxic lipids can be formed that cause hepatocellular stress and injury. These may include lysophosphatidyl choline (LPC), phosphatidic acids and products of cytochrome P450 and peroxisomal oxidation such as dicarboxylic acids. Once cellular injury is initiated, then a complex interplay between the regenerative and inflammatory responses ensues with the outcome determining whether and how much stellate cell activation and extracellular matrix deposition occurs. This ultimately determines the rate of fibrosis progression and whether NASH progresses to cirrhosis.

When considering the pathogenesis of NASH, we must remember that the underlying genetic and environmental causes are likely quite variable among different patients but they all lead to the same phenotype of NASH. Genetic associations with NAFLD are only beginning to be understood[5] but with advances in deep sequencing, more insights into the role of genetic differences in the handling of fat in the liver and the response to lipotoxic injury can be expected. Thus as treatments are developed in the era of personalized medicine, we can expect that different medications or combinations of medications will be needed to target specific abnormalities in patients when lifestyle modification and weight loss are not successful.

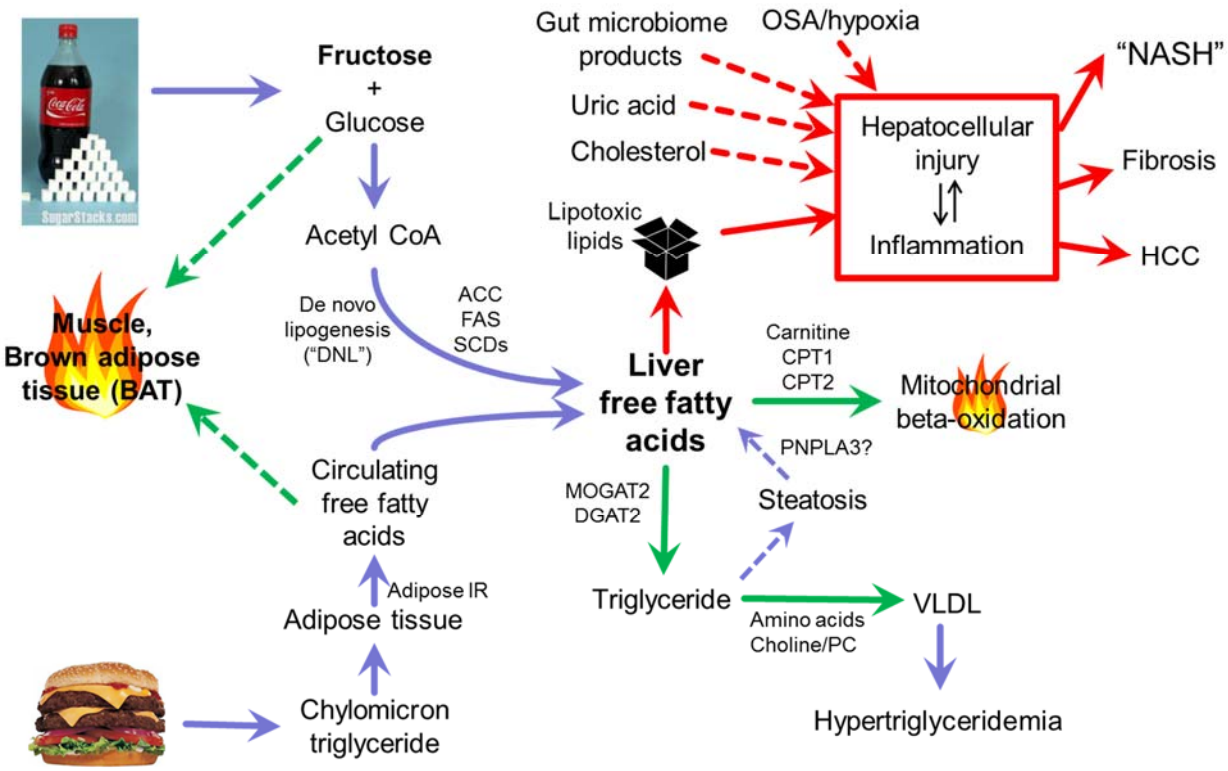

Figure: Comprehensive lipotoxicity paradigm for the pathogenesis of NASH.

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NOTES

GENETICS PLUS THE ENVIRONMENT: THE SUGAR EFFECT ON PNPLA3

Michael Goran MD, Keck School of Medicine

The prevalence of suspected non-alcoholic fatty liver disease (NAFLD) in children has doubled over the last 20 years, and is highest among obese Hispanics (1). Using advanced imaging techniques, our studies have found that 40% of obese Hispanic children and adolescents have a liver fat fraction above 5.5%, a clinical criteria for NAFLD diagnosis (2). Over time, elevated liver fat and NAFLD can lead to cirrhosis, liver disease and eventually liver cancer. This increased susceptibility to high liver fat in Hispanics is due in part to genetic predisposition based on the 50% frequency in this population of a C>G (Ile148Met) polymorphism in the patatin-like phospholipase 3 (PNPLA3) gene (3). Our prior studies, as well as recent studies in animal models, provide compelling evidence that the impact of the PNPLA3 variant on liver fat is exacerbated by high dietary sugar. For example, in previous studies we have: a) Shown that Hispanic children and adolescents who are GG for the PNPLA3 variant have a greater than 2-fold higher liver fat compared to GC and CC individuals, with this effect manifested as young as 8y of age (4); and, b) Demonstrated a significant gene*dietary sugar interaction with a significant association between liver fat and dietary sugar intake in GG subjects with no such association in GC or CC individuals (5). This latter finding is consistent with animal models where it has recently been shown that genetically modified “knockin” mice, in which the isoleucine at position 148 in the mouse PNPLA3 protein was substituted with methionine, exhibited 2 to 3-fold higher liver fat compared to wildtype littermates, but this was only manifested when challenged with a high sugar diet (6). Taken in combination, these studies in humans and mouse models, suggests that different dietary strategies may have differential effects on reducing liver fat, depending on PNPLA3 genotype.

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NOTES

FATTY LIVER: A MARKER OF LOOMING DIABETES AND METABOLIC SYNDROME IN OBESE YOUTH

Sonia Caprio MD, Yale University School of Medicine

NAFLD is emerging as one of the most common metabolic complications of childhood obesity. NAFLD and in particular NASH are biopsies based diagnoses, however, recently two imaging techniques (1H-NMR and Fast-MRI) have been proven to accurately quantitate fatty liver content in both adults and children and thus are increasingly being used to assess fatty liver content in clinical research . Hepatic fat content >5.5% is consistent with the diagnosis of fatty liver (NAFLD). In this presentation evidence will be presented showing that in obese adolescents the prevalence of metabolic syndrome and prediabetes increases with the increases in hepatic fat content. Moreover, we found that fatty liver is associated with increased TG, large VLDL, small dense LDL, and decreased large HDL concentrations (13). *Thus fatty liver, even at this very early stage of life, is a perfect prediabetic and pro-atherogenic state*. Fatty liver, independent of visceral and intramyocellular lipid content plays a central role in the impairment of liver, muscle and adipose insulin sensitivity in obese adolescents. Fatty liver may not only evolve into steatoheaptitis and culminate in cirrhosis, but is also a strong marker of looming T2DM and cardiovascular complications occurring early in youth.

NOTES

MATERNAL INSULIN RESISTANCE AND THE EARLY ORIGINS OF NAFLD IN HUMANS AND NON-HUMAN PRIMATES

Jed Friedman MD, University of Colorado School of Medicine

NAFLD is now the most common liver disease in children and adults. Even more concerning is that the risk factors for NAFLD may start operating in early life. Pregnancy and the postnatal period are crucial windows of opportunity for the prevention of metabolic diseases. In the U.S., 23% of children are already overweight or obese entering kindergarten, and maternal obesity is consistently one of the most powerful predictors of pediatric obesity and its complications (1). Our group has spent the past decade studying developmental programming in humans, non-human primates (NHP), and transgenic mouse models. We have shown that maternal Western-Style Diet (WSD) in NHP mothers results in a NAFLD phenotype in the fetus, beginning in the early 3rd trimester (2). This phenotype persists in juveniles up to 14 months of age despite weaning to a healthy diet (3), and in the absence of obesity. Our compelling human data in neonates born to obese/Gestational Diabetic mothers demonstrate increased intrahepatic fat using MRI/MRS at 2 wks of life (4). However not everyone who is born to an obese mother develops disease, with other potential contributing factors particularly excessive maternal insulin resistance, hypoxia, and mitochondria dysfunction important in the fetal development of NAFLD. Our studies in obese NHP mothers using the anti-oxidant resveratrol (5), as well as switching obese mothers to a healthy diet may be able to mitigate some of these complications to prevent the early complications of maternal obesity on the developing liver.

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NOTES

FATTY ACID DYSREGULATION IN NAFLD

Elizabeth J. Parks, PhD, University of Missouri, Columbia, MO

To develop therapies for nonalcoholic fatty liver disease, it is critical to identify the sources of fatty acids that contribute to lipid stores in the liver. Using stable isotope labeling in humans studies, we have identified three sources of fats that can lead to fatty liver. These are 1) fatty acids originating in the adipose and flowing to the liver through the plasma, 2) dietary fatty acids, which clear to the liver after meals and 3) intrahepatic fatty acid synthesis from dietary sugars through the pathway called de novo lipogenesis (DNL). It is clear that adipose insulin resistance contributes to NAFLD through poor suppression of lipolysis after meals. Further, diets high in fat can increase liver lipid accrual when muscle lipid oxidation and adipose fatty acid uptake are insufficient. Importantly, hepatic DNL has been shown to be a unique characteristic of NAFLD, independent of gender, age or ethnicity. DNL contributes significantly to liver lipid stores both directly by supplying newly-made fatty acids, and indirectly by suppressing fatty acid oxidation.

We have shown that DNL is significantly stimulated by dietary fructose consumption in a dose dependent manner, that lipogenesis is greater when food is taken in as a liquid instead of a solid, and when absorption of dietary carbohydrates occurs very quickly. We propose that the over-consumption of simple carbohydrates contributes to NAFLD and increases cardiovascular risk, since the primary product of DNL is the saturated fatty acid palmitate. Two other fatty acids have been investigated for their connection to liver lipid metabolism. Through the direct labeling of palmitoleic acid (16:1n7), we have shown that this fatty acid can be used as a biomarker of hepatic lipogenesis - a technique that can be used in larger epidemiologic studies in which isotope administration is not feasible. Elevated 16:1n7 is the product of the liver enzyme stearyl-CoA desaturase and our data support the co-regulation of hepatic DNL and desaturase activities. The data also support a model in which elongation and desaturation occur using dietary saturated fatty acids preferentially as substrates, rather than endogenous unlabeled (stored) fatty acids. The essential fatty acid, linoleic acid (18:2n6), may also directly contribute to the pathogenesis of fatty liver. In summary, the present paper will discuss how adipose insulin resistance and variability in the handling of dietary fatty acids and carbohydrates impact tissue fatty acid flux and contribute to fatty liver disease.

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IS SUGAR TOXIC BEYOND ITS CALORIES?

Robert H. Lustig, M.D., M.S.L.

In order to answer this question, we must define “toxic”, which is “the degree to which a substance can damage an organism”. In order to demonstrate toxicity, I must show that sugar is an independent risk factor for disease, irrespective of its caloric content or its effects on obesity, and I must show causation.

Prospective correlative studies support this contention. Yang et al. in 2014 demonstrated increased cardiovascular mortality over two decades based on the percent of calories in the diet as added sugar, and adjusting for weight. The EPIC-Interact Study in 2013 demonstrated that after adjusting for energy intake and weight, each sugar sweetened beverage per day increased risk for diabetes by 29%. Imamura et al. in a systematic review in 2015 showed that sugared beverage (including juice) consumption was correlated over time with an increased risk for diabetes.

Econometric analysis by Basu et al. in 2013 demonstrated that every 150 extra calories per day globally did increase prevalence of diabetes (0.1%), yet if those 150 calories were sugar instead, there was an 11-fold increased prevalence of diabetes (1.1%), unrelated to calories or obesity. This study meets the Bradford Hill criteria for causation, including dose, duration, directionality, and precedence.

Most recently, my group performed an isocaloric glucose-for-fructose exchange for 10 days in 43 children with metabolic syndrome. We demonstrated improvements in virtually all aspects of metabolic health (insulin sensitivity, glucose tolerance, triglycerides, HDL, liver fat, visceral fat, lactate, AST) exclusive of caloric content or weight change. Furthermore, the change in insulin sensitivity over the 10 days correlated with the change in liver fat, not the change in visceral fat or subcutaneous fat.

Thus, prospective correlation, econometric, and interventional analyses firmly establish that sugar causes chronic disease, particularly NAFLD, unrelated to calories or weight gain.

NOTES

MICROBIOME AND NAFLD IN CHILDREN

Marialena Mouzaki MD, The Hospital for Sick Children

Over the past decade, scientific evidence on the role of intestinal microbiota in nutrient digestion, metabolism and host gene expression[1], as well as their involvement in immune regulation and response[2], has increased immensely. It has also become clear that obesity is tightly linked to intestinal dysbiosis, so much so that strategies that alter the intestinal microbiota composition are being researched as treatment options for obesity and the metabolic syndrome.

This presentation will discuss the current knowledge on the effects of intestinal microbiota on the gut barrier, as well as the impact of metabolic endotoxemia and altered nutrient metabolism on the development of insulin resistance, hepatic steatosis, inflammation and fibrosis[3]. The role of bacterial metabolites, such as short chain fatty acids, bile acids[4] and ethanol, in the pathogenesis of non-alcoholic fatty liver disease will be reviewed as well[5]. Lastly, the cross talk between diet, intestinal microbiota and immune system maturation and function will be discussed in brief.

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NOTES

GENETICS OF NAFLD: WHAT WE KNOW SO FAR

Nicola Santoro MD, Yale University School of Medicine

The heritability of fatty liver disease has been estimated to be almost 40%, but so far only few gene variants have been identified as predisposing to NAFLD and very few of those discoveries have been successfully replicated. To date, the strongest variants associated to pediatric NAFLD are the rs738409 in the *PNPLA3* gene, the 1260326 in the *GCKR* gene and the rs58542926 in the *TM6SF2*. All these variants have been identified through genome wide association studies and replicated in multiethnic pediatric populations. Interestingly, the mechanisms by which they cause intra-hepatic fat accumulation is different among the three of them. In particular, the rs738409 seems to affect the lipolytic activity of the *PNPLA3* gene, the rs1260326 in the *GCKR* enhances hepatic de novo lipogenesis and the rs58542926in the *TM6SF2* affects the secretion of lipoproteins from the liver.

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NOTES

CROSSTALK BETWEEN ADIPOCYTES AND HEPATOCYTES

Nitika Gupta MD, Emory University

For the past decade it has been known that Non Alcoholic Fatty Liver Disease develops as a result of insulin resistance, peripherally (1)and locally in the liver. (2) Obesity is independently associated with the development of metabolic syndrome, NAFLD and insulin resistance and it has been shown that this results in a low-grade inflammation in the adipocytes. (3) There is increasing evidence to show that the innate immune system, especially the macrophages in the liver are involved with a (4) a concomitant increase in levels of cytokines such as IL6, TNFα, adiponectin, leptin and resistin in the adipocyte. Additionally, the visceral fat has been shown to be directly associated with liver inflammation (5) and studies have implicated FAS and IL1β signaling from the adipocyte as having an effect on liver steatosis. (6, 7) In a recent study, Sabio et al showed that high fat diet (HFD) fed mice have increased levels of JNK in the liver, adipose tissue along with insulin resistance; and abrogating JNK from the adipose tissue prevented the development of fatty liver in WT mice fed a HFD. (8) Hence hepatocyte-adipocyte crosstalk is an exciting area of research and perhaps shifting the target of treatment of NAFLD, from the liver to the adipose tissue will result in new therapeutic options.

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NOTES

OXIDIZED LIPIDS AND LINOLEIC ACID IN NASH

Christopher Ramsdam MD, National Institutes of Health

Dietary modulation of oxidized linoleic acid metabolites

Linoleic acid (LA) is the most abundant polyunsaturated fatty acid in human diets, a major component of human tissues, and the direct precursor to the bioactive oxidized LA metabolites (OXLAMs), 9- and 13 hydroxy-octadecadienoic acid (9- and 13-HODE) and 9- and 13-oxo-octadecadienoic acid (9- and 13-oxoODE). These four OXLAMs, which have been mechanistically linked to pathological conditions including alcoholic and non-alcoholic steatohepatitis (NASH), have been proposed as biomarkers useful for indicating the presence and severity of NASH. Mammals lack the enzymatic machinery needed for de novo LA synthesis. OXLAMs can be synthesized enzymatically after consumption of dietary LA; preformed OXLAMs can be consumed in foods containing oxidized oils and fats. Therefore, the abundance of LA and OXLAMs in mammalian tissues may be modifiable via diet. To examine this issue in humans, we measured circulating LA and OXLAMs before and after a 12-week LA lowering dietary intervention in chronic headache patients. Lowering dietary LA significantly reduced the abundance of plasma OXLAMs, and reduced the LA content of multiple circulating lipid fractions that may serve as precursor pools for endogenous OXLAM synthesis. These results show that lowering dietary LA can reduce the synthesis and/or accumulation of oxidized LA derivatives that have been implicated in a variety of pathological conditions. Future studies evaluating the clinical implications of diet-induced OXLAM reductions are warranted.

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NOTES

STERILE INFLAMMATION AND CELL DEATH FOR NASH TREATMENT

Ariel E. Feldstein MD

Increase cell death and activation of sterile inflammatory pathways as a key self-perpetuating loop involved in liver injury and fibrosis in NASH (1). While several of the early triggers of hepatic steatosis can be traced to events that occur outside the liver, in distant organs such as the gut, adipose tissue, and muscle among others, excessive hepatocyte cell death by apoptosis, necrosis, and other forms of cell death followed by release of danger or stressed signals by these hepatocytes, and activation of sterile inflammatory pathways can initiate an intra-hepatic, self-perpetuating noxious loop that results in chronic injury and fibrosis as an intrinsic response to this damage that can eventually progress to excessive scarring and liver failure.

Since the original description that caspase activation and TUNEL positive cells are a characteristic pathologic features in the liver of NASH patients,(2) a growth of data have demonstrated that hepatocyte cell death is a key process involved in NASH pathogenesis (3-4). Sustained hepatocyte cell death has also been implicated in the development of hepatic fibrosis (5). In addition to the classical modes of cell death, such as apoptosis and necrosis (oncosis), other forms of hepatic cell death have been more recently described in preclinical models and patients with NASH, including autophagic cell death, pyroptosis, and necroptosis. Apoptosis, a highly organized and genetically controlled process, is the most investigated and best defined form of programmed cell death in NASH. Apoptosis is initiated by either membrane receptors (extrinsic pathway) or intracellular stress leading to organelle dysfunction (intrinsic pathway). Both pathways tend to converge in the activation of effector caspases 3 and 7, which execute the final apoptotic changes. Necrosis, or oncosis, is an accidental form of cell death with the fatal consequence being cellular oxygen deprivation whereby the generation of reactive oxygen species (ROS), leads to mitochondrial dysfunction and a drop in ATP level below the threshold required to maintain cellular integrity. The latter induces membrane rupture with the release of cellular contents. While ROS production and mitochondrial dysfunction is a central feature of NASH, necrotic cell death is a rare histopathological feature of the disease. Necroptosis is induced by the same death receptors that activate the extrinsic apoptotic pathway, namely Tumor Necrosis Factor Receptor-1 (TNF-R1), and Fas. Upon interaction of receptor protein kinases 1 and 3 (RIP1 and RIP3), and a deficiency or absence of caspase 8, cell death that morphologically resembles necrosis occurs (6). Controversy exists on the potential role of this form of cell death in NASH. Pyroptosis is novel caspase 1 dependent form of programmed cell death that has been recently shown to occur in vivo during liver injury that shares features of apoptosis such as DNA fragmentation and necrosis such as plasma membrane permeabilizaton. It is dependent on Inflammasome mediated caspase 1 activation and results in the formation of discretely sized ion-permeable pores in the plasma membrane, which leads to water influx and cell swelling (7). Its potential role in NASH has yet to be explored.

Dying hepatocytes in which a particular molecular cell death pathway is activated are capable of releasing stress signaling molecules called damage-associated molecular patterns or DAMPs that can act on neighboring cells including other hepatocytes as well as non-parenchymal cells of the liver such as immune cells mainly liver macrophages or Kupffer Cells, hepatic stellate cells, and sinusoidal endothelial cells triggering a variety of responses that initiate an homeostatic, wound healing response to repair tissue injury. However, the persistence of these signals can induce an exuberant response that can result in tissue inflammation and excessive scarring. A central

consequence of the release of DAMPs is the activation of a sterile inflammatory response via their interaction with immune cells that can result in a full inflammatory response in the absence of infection (8). DAMPs are recognized by immune cells via pattern-recognition receptors (PRR). Two key families of PRR have been growingly involved in NASH pathobiology include Toll-like receptors (TLRs) and the cytosolic complex termed the Inflammasome (9).

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NOTES

NASH:WHAT'S BILE GOT TO DO WITH IT?

Rohit Kohli, MBBS, MS, Cincinnati Children's Hospital Medical Center

The search for a better understanding of the consequences of obesity has led to a rise in the interest around of the role of bile acids as metabolic signal modulators. In hindsight, it probably makes intuitive sense that molecules triggered by the very act or thought of eating should be important in the control of satiety, energy balance and metabolism. We now understand that bile acids do much more than just form micelles!

Bile acids are synthesized in the liver from cholesterol by a complex series of reactions and then target molecular receptors and pathways responsible for lipogenesis and bile acids synthesis itself. One such target for bile acid signaling is the farnesoid X receptor (FXR). Direct hepatic FXR activation suppresses lipogenesis through SREBP1c (1) and the bile acid production enzymes Cyp8b1 and Cyp7a1 (2). A major treatment for obesity is of course bariatric surgery which also results in improved steatosis by decreasing hepatic lipogenesis (3). We and others have reported that patients that have undergone bariatric surgery have elevated serum bile acids (4). We further recently reported on the critical mechanistic role of FXR as a molecular effector of bariatric surgery efficacy using whole-body Fxr deficient mice (5). Activating FXR using 6-ethyl-chenodeoxycholic acid (obeticholic acid), has been shown to also protects against body weight gain and liver lipid accumulation in Zucker (fa/fa) rats (6), while more recently a large clinical trial reported a significant improvement in NASH when patients were treated with OCA but there were also disproportionate lipid abnormalities in patients on OCA compared to those on placebo (7). Clearly pure FXR agonism though efficacious may have its own perils. Short heterodimer partner (SHP) is an atypical orphan nuclear receptor that is directly influenced by FXR signaling and suppresses bile acid production (8). We have recently reported that it is the bile acid stimulated FXR/SHP signaling that is critical in resolution of NASH post-bariatric surgery and that these processes are independent of bile acids themselves (3). Thus, *NASH resolution requires an activated FXR-SHP signaling pathway but is independent of the bile acid increase*.

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WHAT DOSE OF EXERCISE REDUCES INSULIN RESISTANCE IN CHILDREN, AND APPLICATION TO NAFLD?

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Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in children, and can progress to nonalcoholic steatohepatitis (NASH). NAFLD affects 38% of obese children and adolescents.1 Aerobic exercise programs have been shown to reduce body fat, visceral fat, and insulin resistance in obese children.2 We randomized 222 7-11 year old overweight or obese children to a low dose (20 min/day) or a high dose (40 min/day) of vigorous after-school aerobic training 5 days/week over 3 months, or to a no-intervention control condition. The low dose was as effective in improving fitness and insulin resistance as the high dose, while the high dose group showed greater reductions in general and visceral adiposity.2

It is unclear whether exercise programs would be effective in reducing liver fat in obese children at risk for NAFLD, or in children with NAFLD or NASH. A few small NAFLD prevention trials have tested exercise training vs. a control condition in obese adolescents, with mixed results.3-5 We randomized 175 8-11 year old overweight or obese children to a 40 min/day vigorous aerobic training program for 8 months, vs a sedentary control condition. While the exercise program reduced adiposity (-4.7% vs -2.1%) and improved fitness (8.4% vs. 4.1%) relative to controls ($p = .04$), there was no differential impact of the exercise program on hepatic fat via MRI, liver stiffness via Fibroscan, alanine aminotransferase, or C-reactive protein. Because 87% of the sample was Black, and Black children are much less prone to NAFLD than White and Hispanic children, results may be different in a higher-risk demographic. Exercise alone has promise for pediatric NAFLD and NASH prevention and treatment, but may yield more benefit in combination with dietary changes (e.g. reducing sugar intake). NIH HL087923

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NOTES

INTERVENTIONS AND POLICIES TO PREVENT OBESITY AMONG VULNERABLE CHILDREN

Jennifer Woo Baidal MD Boston Children's Hospital

Childhood obesity, and its disparate impact on under-served populations, originates early in life. Among 2-5 year old children in the United States, Hispanic children have almost 5-fold and non-Hispanic black children have 3-fold higher obesity prevalence compared to non-Hispanic white counterparts. Recent evidence suggests that socio-economic disparities in childhood obesity may be widening.

Obesity interventions may have the greatest preventive effect if begun early in life. Yet, few effective interventions during early life exist and many target individual-level behaviors of parents and children. Interventions that operate at systems- levels to target multiple behaviors may hold promise for improving early life obesity prevention efforts. Policies that impact schools and supplemental nutrition programs may also narrow disparities in childhood obesity.

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NOTES

PREVENTION AND TREATMENT OF CHILDHOOD OBESITY: WHAT CAN WE LEARN AND APPLY TO THE PREVENTION OF NAFLD?

Sarah Barlow MD, Baylor College of Medicine

What can we learn? Healthy weight is a good thing in reducing NAFLD. Because obesity is a significant risk factor for NAFLD, we assume obesity prevention will prevent NAFLD. And weight reduction effectively treats NAFLD. Success in weight loss (or prevention of excess weight gain) is elusive; patients and providers both often feel that "nothing works." However, behavior-based treatment for childhood obesity is efficacious. As a result, the USPSTF recommends addressing childhood obesity through multi-component (nutrition, physical activity, and behavior modification) programs of moderate to high intensity.

What can we apply? Here is the challenge. Child/family participation in appropriate treatment is stymied by many things, among them structure and processes in the healthcare system. A fee for service reimbursement model pays for medical provider visits but often not for dietitians, therapists or health educators, who are likely to deliver programs more skillfully and at lower cost. Programs may not exist or, as reported by the Children's Hospital Association survey, may be underfunded or unreliably funded. Families often drop out, and one factor may be inconvenient time and location when programs are held at tertiary healthcare sites.

Changes in healthcare hold promise for an improved system. Medicare now recognizes obesity as a disease and covers treatment. The Affordable Care Act broadly requires payors to cover prevention strategies endorsed by the USPSTF. Medicaid is testing value-based reimbursement strategies. As a result, healthcare entities are organizing into Accountable Care Organizations, which expect incentives from outcomes, thereby directing investment into effective programs. Coordination between community programs and healthcare has been successful in the adult Diabetes Prevention Program, and is a model for weight management programs from children, with evaluation currently on-going.

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NOTES

GOALS OF THE NASH CRN AND OPPORTUNITIES FOR COLLABORATION

Joel Lavine MD, PhD, Professor and Vice-Chairman of Pediatrics, Columbia University

The Nonalcoholic Steatohepatitis Clinical Research Network <https://jhuccs1.us/nash/> was formed in 2002 as a collaborative multicenter network to focus on the etiology, contributing factors, natural history, complications and therapy of nonalcoholic steatohepatitis. There are 9 principal investigators who oversee a total of 21 centers, many of them exclusively devoted to pediatric studies. The clinical sites are managed by a Data Coordinating Center at the Bloomberg School at Johns Hopkins School of Public Health, and overseen by project officers and scientists at NIDDK (NIH). Besides the studies or clinical trials organized by the principal investigators or site investigators, there are many opportunities for ancillary studies proposed by investigators outside the NASH CRN, who may or may not include NASH CRN collaborators. These studies bring a variety of expertise and perspective for the full utilization of our resources. These resources include an extensive cross-sectional and longitudinal database on thousands of adults and children with biopsy proven NAFLD, along with a biorepository of materials including liver tissue, DNA, serum, plasma, urine and stool. Many collaborations and major studies are done in conjunction with industry, using a Collaborative Research and Development Agreement (CRADA) mechanism through announcements available in FedBizOpps.gov.

NOTES

NIDDK: SUPPORT MECHANISMS FOR FATTY LIVER DISEASE RESEARCH

Edward Doo, Program Director
Liver Diseases Research Branch
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health

The Liver Disease Research Branch of the NIDDK encourages investigative endeavors in fatty liver disease. The significance of fatty liver disease as a consequence of liver injury and inflammation as well as from metabolic and physiologic derangements was recognized as a separate chapter with delineated research priorities in the Trans-NIH Action Plan for Liver Disease Research released in 2004. Several research goals in fatty liver disease were identified with some of the long-term research priorities at the cusp of being addressed with advances in our understanding of the pathophysiologic mechanisms of fatty liver disease.

Several funding mechanisms through the NIDDK are available to basic, translational and clinical investigators. These include the standard Research Project Grant (R01) which supports narrow, focused, hypothesis driven proposals. Additionally, Program Project Grants (P01) and the Collaborative Interdisciplinary Team Science Grants (R24) are mechanisms that promote team science to address either an overarching scientific theme as in a Program Project proposal or a specific scientific challenge as in a Collaborative Interdisciplinary Team Science proposal.

At the NIDDK, clinical studies and trials are distinguished between those proposing to use 2 or less versus 3 or more clinical sites. For proposals that will engage no more than 2 or clinical performance sites, the standard R01 Research Project Grant is permissible. For multi-centered clinical studies or trial proposals that will engage 3 or more clinical sites, the NIDDK utilizes a staged funding mechanism approach involving a U34 Multi-Center Clinical Study Implementation Planning phase followed by a U01 Multi-Center Clinical Study Cooperative Agreement phase. A U34 grant permits investigators to complete the necessary administrative, regulatory approvals, manuals of operations, data collection forms, and other necessities prior to the initiation of study enrollment. Note that a U34 grant does not support the development of a protocol. If a U34 is successful in achieving performance milestones and obtains the approval of the NIDDK, an U01 application may be submitted for acquiring support to initiate the clinical study or trial. Investigators wishing to propose a multi-centered clinical trial or study are strongly encouraged to engage relevant NIDDK program staff well in advance in order to obtain necessary guidance.

The NIDDK also encourages investigators to explore the opportunities that exist with the Small Business grant program.

Informational web links:

NIH Action Plan for Liver Disease Research: http://archives.niddk.nih.gov/AboutNiddk/rdrb.aspx

NIDDK Program Projects (P01): http://grants.nih.gov/grants/guide/pa-files/PAR-13-266.html

Collaborative Interdisciplinary Team Science in NIDDK Research Areas (R24): http://grants.nih.gov/grants/guide/pa-files/PAR-13-305.html

NIDDK Multi-Center Clinical Study Implementation Planning Cooperative Agreements (U34):
http://grants.nih.gov/grants/guide/pa-files/PAR-13-268.html

NIDDK Multi-Center Clinical Study Cooperative Agreement (U01):
http://grants.nih.gov/grants/guide/pa-files/PAR-15-067.html

NIH Small Business Funding Opportunities:
R41/R42: http://grants.nih.gov/grants/guide/pa-files/PA-15-270.html
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Objectives - After attending this program you should be able to:

1. Bring together experts from diverse fields in order to generate synergy in pediatric nonalcoholic fatty liver disease research, to develop consensus regarding priorities in pediatric NAFLD research and to encourage young investigators and investigators from diverse backgrounds to study NAFLD in order to improve prevention and treatment of NAFLD.

Disclosure of Conflict of Interest

The table disclosure information is provided to learners and contains the relevant financial relationships that each individual in a position to control the content of CME disclosed to NASPGHAN. All of these relationships were treated as a conflict of interest, and have been resolved. (C7 SCS 6.1---6.2, 6.5)

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