Harold Hamm Diabetes Center

17th Annual Research Symposium

Answering the Call for Progress Against Diabetes

Friday, November 13, 2020

Virtual Conference

OU Health | Harold Hamm Diabetes Center

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Harold Hamm Diabetes Center Research Symposium 2020

Program Schedule

Friday, November 13, 2020

8:15 – 8:30 AM *Welcome*

Ann Louise Olson, Ph.D.
Professor of Biochemistry and Molecular Biology
Edith Kinney Gaylord Foundation Presidential Professor
Presidential Associates Presidential Professor
Member, Harold Hamm Diabetes Center
University of Oklahoma Health Sciences Center

Jed Friedman, Ph.D.
Director, Harold Hamm Diabetes Center
Associate Vice-Provost for Diabetes Programs
Chickasaw Nation Endowed Chair
Professor of Physiology, Biochemistry & Molecular Biology
Professor of Pediatrics, Division of Endocrinology and Metabolism
University of Oklahoma Health Sciences Center

ORAL PRESENTATIONS

SESSION 1
Moderator: David Fields, Ph.D.

8:30 – 8:45 AM *Role of maternal pyrroloquinoline Quinone (PQQ) in ameliorating diet-induced NAFLD in offspring of obese mice*

Karen Jonscher, Ph.D.
Associate Professor of Biochemistry & Molecular Biology
Member, Harold Hamm Diabetes Center
University of Oklahoma Health Sciences Center

8:45 – 9:00 AM *Deletion of Hepatic cannabinoid 1 receptor (CB1R) prevents fatty liver and improves glucose homeostasis via regulation of MTORC1*

Yoo Kim, Ph.D.
Assistant Professor of Nutritional Sciences
Oklahoma State University

9:00 – 9:30 AM *Gut-Liver Bile Acid Signaling Regulation of Hepatic Metabolism*
Tiangang Li, Ph.D.
Associate Professor of Physiology
Member, Harold Hamm Diabetes Center
University of Oklahoma Health Sciences Center

9:30 – 10:15 AM *Molecular Mediators of Fatty Liver*
Jay Horton, M.D.
Professor of Internal Medicine and Molecular Genetics
Dr. Robert C. Atkins and Veronica Atkins Chair in Obesity and Diabetes Research
Director of the Center for Human Nutrition
University of Texas Southwestern Medical Center at Dallas

10:15 – 10:30 AM *Break*

SESSION 2
Moderator: Kruti Shah, M.D.

10:30 – 10:45 AM *Fatty acid metabolism dysregulation and retinal dysfunction in diabetic retinopathy*
Martin-Paul Agbaga, Ph.D.
Assistant Professor of Cell Biology
Member, Harold Hamm Diabetes Center
University of Oklahoma Health Sciences Center

10:45 – 11:00 AM *Effect of athletic conditioning on skeletal muscle glucose transporter expression in dogs*
Michael Davis, DVM, Ph.D.
Professor of Physiological Sciences
John C. and Debbie Oxley Endowed Chair
Oklahoma State University

11:00 – 11:30 AM *In Vivo Lipid Programming of Adipocyte Stem-Like Cell Metabolism Early In Life*
Michael Rudolph, Ph.D.
Assistant Professor of Physiology
Harold Hamm Diabetes Center
University of Oklahoma Health Sciences Center

11:30 – 12:15 PM *New insights into muscle lipids and insulin resistance – is it all about location?*
Bryan Bergman, Ph.D.
Professor of Medicine
Division of Endocrinology, Diabetes, and Metabolism
University of Colorado Anschutz Medical Campus

12:30 – 2:30 PM *Student presentations and judging*

SESSION 3
Moderator: Jeanie Tryggestad, M.D.

2:30 – 2:45 PM *Evidence of increased cardiovascular disease risk in adolescents with nonalcoholic fatty liver disease*
Kevin Short, Ph.D., FACSM
Associate Professor
CHF Choctaw Nation Chair in Pediatric Endocrinology and Diabetes
Member, Harold Hamm Diabetes Center
University of Oklahoma Health Sciences Center

2:45 – 3:00 PM *NAD+ redox imbalance in the heart exacerbates diabetic cardiomyopathy*
Chi Fung Lee Ph.D.
Assistant Member
Cardiovascular Research Program
Oklahoma Medical Research Foundation

3:00 – 3:30 PM *Snail Transcription Factors and Immune Factor Tep2 Direct a Heart-To-Fat Metabolic Axis in Drosophila*
Hui-Ying Lim, Ph.D.
Assistant Professor of Physiology
Member, Harold Hamm Diabetes Center
University of Oklahoma Health Sciences Center

3:30 – 4:15 PM *Is Decreased Cardiorespiratory Fitness a Microvascular Complication of Diabetes?*

Jane Reusch, M.D., ASCI, AAP, FAHA
Professor, Division of Endocrinology, Metabolism and Diabetes;
Director of Diabetes Research and Personalized Medicine to Transform Care;
Assoc. Director, Center for Women's Health Research;
Co-Director, University of Colorado NIH Diabetes Research Center;
Departments of Medicine, Integrative Physiology, and Bioengineering
University of Colorado-Anschutz Medical Campus;
Staff Physician and Merit Investigator
Rocky Mountain Regional VAMC

4:15 – 5:00 PM *Awards Presentation & Meet the Speakers*

Ann Louise Olson, Ph.D.
Professor of Biochemistry and Molecular Biology
Edith Kinney Gaylord Foundation Presidential Professor
Presidential Associates Presidential Professor
Member, Harold Hamm Diabetes Center
University of Oklahoma Health Sciences Center

VISITING SPEAKERS BIOGRAPHICAL INFORMATION

Bryan C. Bergman, Ph.D.
Professor of Medicine
Division of Endocrinology, Diabetes, and Metabolism
University of Colorado Anschutz Medical Campus

Dr. Bergman is a Professor in the Division of Endocrinology, Diabetes, and Metabolism at the University of Colorado Anschutz Medical Campus. Dr. Bergman's research investigates the relationship between muscle lipids and insulin sensitivity, and he has been continuously funded by the NIH since 2005. His laboratory focuses on two main research themes. One theme seeks to understand the relationship between skeletal muscle subcellular lipid localization and insulin resistance in humans. Specifically, his lab is investigating how the intracellular location, molecular species, and isomers of diacylglycerol and sphingolipids promote insulin resistance in humans. The current study is investigating these changes after insulin sensitizing lifestyle interventions and is funded by R01DK111559. The second research emphasis aims to elucidate how intermuscular adipose tissue impacts skeletal muscle insulin sensitivity, muscle strength, and size in humans. This study combines muscle biopsy visits with elective surgeries to obtain intermuscular, subcutaneous, and visceral adipose tissue biopsies and is funded by R01DK118149. Dr. Bergman's laboratory also pursues mechanistic relationships between inter- and intra-muscular lipids and insulin sensitivity using primary muscle cell culture. This model is unique as the phenotype of donor is maintained in culture. They are using this model to determine mechanisms underlying the relationship between localized muscle lipids and insulin sensitivity, and how the secretome of intermuscular adipose tissue promotes insulin resistance. The overall goal of Dr. Bergman's research is to uncover novel therapeutic targets to increase muscle insulin sensitivity, a need not met by current therapies, to help prevent and treat pre-diabetes and type 2 diabetes.

Dr. Bergman is also the director of the Molecular and Cellular Analysis core for the Nutrition and Obesity Research Center, and his lab runs a "Lipidomics and Mass Spetrometry core" that is directed by Dr. Karin Zemski Berry. Further information on this core and related services can be found in the following link: http://cunorc.org/cores/molecular/lipidomic-analysis/

Jay D. Horton, M.D.
Professor of Internal Medicine and Molecular Genetics
Dr. Robert C. Atkins and Veronica Atkins Chair in Obesity and Diabetes Research
Director, Center for Human Nutrition
University of Texas Southwestern Medical Center at Dallas

Jay D. Horton obtained his B.S. and M.D. degrees from the University of Iowa in 1984 and 1988, respectively. He completed his internal medicine residency (1988-1991) and gastroenterology fellowship (1991-1994) at UT Southwestern Medical Center. During his gastroenterology fellowship he studied metabolic regulators of bile acid and cholesterol homeostasis in animals. Following the gastroenterology fellowship, he completed a Howard Hughes post-doctoral fellowship in the Department of Molecular Genetics at UT Southwestern Medical Center. The studies in this fellowship focused on the transcriptional regulation of cholesterol and fatty acid synthesis.

In clinical digestive diseases, Dr. Horton has an interest in conditions that lead to steatosis and obesity. Currently the laboratory is investigating molecular mediators of steatosis using various mouse models. Investigations from the laboratory have revealed how the primary transcriptional regulators of cholesterol metabolism (sterol regulatory element-binding proteins) are also key regulators of fatty acid synthesis in liver.

A major focus of the laboratory is to determine how these transcriptional regulators contribute to the development of steatosis in various disease processes such as diabetes, obesity, and beta-oxidation defects. A second area of investigation centers on determining the function of PCSK9, a protein that is involved in determining plasma LDL cholesterol levels through its ability to post-transcriptionally regulate the expression of the LDL receptor in liver.

Jane Elizabeth-Brown Reusch, M.D., ASCI, AAP, FAHA
Professor, Division of Endocrinology, Metabolism and Diabetes
Director of Diabetes Research and Personalized Medicine to Transform Care;
Associate Director, Center for Women's Health Research;
Co-Director, University of Colorado NIH Diabetes Research Center;
Departments of Medicine, Integrative Physiology, and Bioengineering
University of Colorado-Anschutz Medical Campus;
Staff Physician, Rocky Mountain Regional VAMC
Director, Diabetes Team and Mitochondrial Function Core,
Rocky Mountain Regional VAMC, Aurora, CO; CCTSI VA Liaison

Jane EB Reusch, M.D. is a Professor of Medicine, Bioengineering and Integrative Physiology, and Associate Director of the Center for Women's Health Research, Anschutz Medical Campus and staff physician and merit investigator at the Rocky Mountain Regional VAMC. She is an elected member of American Society for Clinical Investigation, American Association of Physicians and the American Diabetes Association 2018 President for Medicine and Science. She is currently working with the ADA, AHA and ACC on global strategies to decrease the cardiovascular burden of diabetes. She is dedicated to recruiting and mentoring the translational research workforce, especially in women's health and diabetes.

A physician-scientist, Dr. Reusch has made fundamental contributions to our understanding of cellular metabolism of diabetes and its complications. The focus of her basic science program is to identify the cellular and molecular mechanisms (i.e. mitochondrial dysfunction) that contribute to cardiac, vascular and skeletal muscle dysfunction in diabetes. Her shared clinical translational research program with Dr Judy Regensteiner examines and targets the biological variables in people with diabetes, particularly women, that lead to decreased functional exercise capacity and shortened lifespan.

JUDGES

POSTER PRESENTATIONS

David A. Fields, Ph.D.
CMRI Chickasaw Nation Chair in Diabetes Research
Associate Professor
Section of Diabetes and Endocrinology
Department of Pediatrics
Member, Harold Hamm Diabetes Center
University of Oklahoma Health Sciences Center

Tiangang Li, Ph.D.
Associate Professor
Department of Physiology
Member, Harold Hamm Diabetes Center
University of Oklahoma Health Sciences Center

Ann Louise Olson, Ph.D.
Professor
Department of Biochemistry and Molecular Biology
Edith Kinney Gaylord Foundation Presidential Professor
Member, Harold Hamm Diabetes Center
University of Oklahoma Health Sciences Center

Archana Unnikrishnan, Ph.D.
Assistant Professor
Department of Biochemistry and Molecular Biology
Member, Harold Hamm Diabetes Center/Chickasaw Nations Scholar
Oklahoma Center for Geroscience & Brain Aging.
University of Oklahoma Health Sciences Center

ORAL PRESENTATION MODERATORS

David A. Fields, Ph.D.
CMRI Chickasaw Nation Chair in Diabetes Research
Associate Professor
Section of Diabetes and Endocrinology
Department of Pediatrics
Member, Harold Hamm Diabetes Center
University of Oklahoma Health Sciences Center

Kruti Shah, M.D.
Clinical Instructor
Section of Diabetes & Endocrinology
Department of Pediatrics
Member, Harold Hamm Diabetes Center
University of Oklahoma Health Sciences Center

Jeanie Tryggestad, M.D.
Associate Professor
Section of Diabetes and Endocrinology
Department of Pediatrics
Member, Harold Hamm Diabetes Center
University of Oklahoma Health Sciences Center

NON-AWARD ELIGIBLE ABSTRACTS

FATTY ACID METABOLISM DYSREGULATION AND RETINAL DYSFUNCTION IN DIABETIC RETINOPATHY

Martin-Paul Agbaga1-4, Chris Schafer5, Jami Gurley2-3, Karan S. Multani2-3, Whitney Bohannan2-3, Richard S. Brush2-3

Department of Cell Biology1 and Ophthalmology2, Dean McGee Eye Institute and the University of Oklahoma Health Sciences Center3, Harold Hamm Diabetes Center4, Oklahoma Medical Research Foundation5

Diabetic retinopathy (DR) is one of the major causes of blindness in the world. Epidemiological studies suggest that hyperglycemia and/or dyslipidemia contribute to the progression of DR, however, the molecular mechanisms of hyperglycemia-induced alteration in retinal lipid metabolism that cause neuronal and microvascular damage are not well understood. Several fatty elongase (ELOVL1-7) and desaturases enzymes play essential roles in lipid metabolism. Ablation of ELOVL2 that makes anti-inflammatory 22:6n3 (DHA) leads to dysregulation of systemic lipid homeostasis, while deletion of ELOVL5 causes fatty liver. We seek to understand the impact on hyperglycemia on retinal photoreceptor and retinal microvascular lipid metabolism dysregulation that contributes to microvascular integrity dysfunction. We hypothesize that hyperglycemia-induced alterations in retinal lipid metabolism exacerbates photoreceptor and microvascular dysfunction in DR; and determined the impact of high glucose and hypoxia on retinal lipid metabolism dysregulation in photoreceptor cells (661W) and retinal microvascular endothelial cells (RMEC). Cells were exposed to low or high glucose, with or without CoCl2 to mimic hypoxic conditions followed by supplementation with or without polyunsaturated fatty acids (PUFA). Fatty acid analyses revealed accumulation of 22:5n3 and 24:5n3 in both 661W and RMECs treated with high glucose under hypoxic conditions. The cells treated with either low or high glucose under hypoxic conditions had significantly reduced 22:6n3 (docosahexaenoic acid, DHA), the most abundant retinal fatty acid that is also a precursor for neuroprotectin-D1. Further analyses confirmed that the decrease in 22:6n3 is due to the accumulation of the 22:5n3 and 24:5n3 that were not further elongated and desaturated through the Sprecher pathway that requires a $\Delta 6$ desaturation of the 24:5n3 to 24:6n3 and subsequent β-oxidation of the 24:6n3 in the peroxisome to make 22:6n3. We also showed increased levels of phosphatidylethanolamine plasmalogens in the cells grown under hypoxic conditions in either low or high glucose, which supports previous studies that reported that increase levels of plasmalogens protect human endothelial cells during hypoxia. Taken together, our data suggest that dysregulation of expression of lipid biosynthetic enzyme are affected in high glucose and hypoxic conditions, and that under these conditions, increased in plasmalogen levels is likely due to cellular mechanisms aimed at protecting the cells from further damage. We would take advantage of this in vitro system to understand the mechanism of how photoreceptor and endothelia cells lipid metabolism dysregulations contribute to vascular leakage in DR.

EFFECT OF ATHLETIC CONDITIONING ON SKELETAL MUSCLE GLUCOSE TRANSPORTER EXPRESSION IN DOGS

Michael S. Davis, Montana R. Fulton, and Ann L. Olson

Department of Physiological Sciences, College of Veterinary Medicine,
Oklahoma State University

Type 2 diabetes is strongly associated with a high-fat diet and obesity, but there exists a well-known "athlete's paradox", in which well-conditioned athletes have extremely high insulin sensitivity despite the presence of abundant fat stores in their muscle tissues. We have recently characterized the capacity for peripheral glucose clearance, including both insulin-stimulated and contraction-stimulated, in a unique model of the athlete's paradox: the racing Alaskan sled dog. Despite consumption of up to 6,000-7,000 fat calories per day, Alaskan sled dogs have remarkably high insulin sensitivity. Furthermore, we have recently reported that athletic conditioning results in a 2.5-3 fold increase in both insulin-dependent AND insulin-independent glucose clearance. Studies using giant sarcolemmal vesicles to measure both sarcolemmal transport of glucose as well as sarcolemmal abundance of glucose transports concurrently suggest that GLUT4 may not be the sole glucose transporter upregulated by athletic conditioning in these dogs. Therefore, we quantified the skeletal muscle expression of multiple glucose transporters as a function of athletic conditioning to test the hypothesis that skeletal muscle glucose uptake in well-conditioned athletes is mediated by multiple glucose transporters. Skeletal muscle microbiopsies were obtained from 12 elite racing Alaskan sled dogs prior to seasonal conditioning (after 4 months of rest) and after 7 months of progressive conditioning for endurance racing, including completion of a 1000-mile race. Biopsies were snap-frozen in liquid nitrogen vapor immediately following the biopsy procedure. Semi-quantitative western blot analysis was performed for GLUT1, GLUT3, GLUT4, and GLUT6, with each biopsy analyzed in duplicate and both pre-conditioning and post-conditioning biopsies for each dog analyzed on the same blot using fluorescent secondary antibodies. Each target was normalized for the presence of beta-actin in the homogenate, and the effect of conditioning was determined using a Z-test of the ratio of post-conditioning to preconditioning relative abundance of the target against a hypothesized ratio of 1 (no effect of conditioning). Athletic conditioning resulted in a 2.87 ± 2.12 fold increase in GLUT4 abundance ($p = 0.001$), which is in agreement with the 3.15 fold increase in insulin sensitivity previously reported in conditioned dogs. Similarly, athletic conditioning resulted in a 2.68 ± 1.27 fold increase in GLUT1 abundance ($p < 0.001$), which agrees well with the 2.5 fold increase in glucose-mediated glucose disposal previously reported. There was no effect of conditioning on the expression of GLUT6 (1.00 ± 0.22, $p = 0.53$). We were unable to detect a target in the homogenates using a primary antibody with affinity for canine GLUT3. These results support the hypothesis that multiple glucose transporters are upregulated by skeletal muscle conditioning of dogs, even in the face of very high dietary intake of fat.

ROLE OF MATERNAL PYRROLOQUINOLINE QUINONE (PQQ) IN AMELIORATING DIET-INDUCED NAFLD IN OFFSPRING OF OBESE MICE

Karen R. Jonscher, Kenneth L. Jones and Jacob E. Friedman

Harold Hamm Diabetes Center
The University of Oklahoma Health Sciences Center

Non-alcoholic fatty liver disease (NAFLD), a spectrum of pathologies ranging from simple steatosis to fibrosis and cirrhosis, is the most common cause of chronic liver disease, affecting over 80% of adults with obesity, one third of obese children ages 3-18 in North America and ~10% of the general pediatric population. Maternal obesity is a significant risk factor for pediatric NAFLD. However, a major limitation in this field is the lack of fundamental understanding as to how maternal diet and/or obesity sets liver physiology and development of the immune system, beginning early in life, on a course toward NAFLD. In Western diet (WD)-fed mice, we have shown that pre-natal and post-weaning supplementation with PQQ (a potent dietary antioxidant) significantly diminishes hepatic triglycerides and improves NAFLD pathophysiology in the offspring. Here, we describe a detailed lipidomic analysis of livers from adult offspring of obese dams, with and without postnatal PQQ supplementation. We found that chronic supplementation with PQQ dramatically reduced liver triglycerides and diglyerides without affecting body weight. When offspring were only exposed to maternal PQQ, we found little change in triglycerides as compared with non-supplemented controls. However, we found that sphingolipid abundances were increased and ceramides were decreased, suggesting PQQ exposure attenuates ceramide production. Furthermore, abundances of ceramides and sphingolipids were similar between offspring exposed only to maternal PQQ and offspring additionally supplemented post-weaning. These bioactive lipids promote inflammation and insulin resistance, therefore, ceramide lipid metabolism pathways, as well as inflammatory and insulin resistance pathways, were probed in adult mouse liver using single cell RNASeq. Our preliminary findings show that ceramide and sphingomyelin metabolism during gestation and lactation are persistently modulated by PQQ exposure, suggesting PQQ supplementation in early life may show therapeutic promise by targeting production of inflammatory ceramides.

DELETION OF HEPATIC CANNABINOID 1 RECEPTOR (CB1R) PREVENTS FATTY LIVER AND IMPROVES GLUCOSE HOMEOSTASIS VIA REGULATION OF MTORC1

Yoo Kim[1,2] and Josephine M. Egan[2]

[1]Department of Nutritional Sciences, Oklahoma State University,
[2]Laboratory of Clinical Investigation, National Institute on Aging, National Institutes of Health

Cannabinoid 1 receptors (CB1Rs) are G protein-coupled receptors that are present in peripheral organs such as liver, pancreas, adipose tissue and skeletal muscle where they are involved in fine-tuning many metabolic functions. It was previously reported that liver-specific genetic deletion of CB1R ($hCNR1^{-/-}$) mice fed high fat diets (HFD) had similar body weight to HFD-fed $hCNR1^{+/+}$ mice, but they retained insulin sensitivity comparable to normal chow-fed (NCD) $hCNR1^{+/+}$ mice. Therefore, this study was undertaken to uncover how hCB1Rs impact the insulin signaling pathway. Male $hCNR1^{-/-}$ and $hCNR1^{+/+}$ mice were fed with a high fat high sugar diet (HFSD: N = 8-12) for 15 weeks. In contrast with the previous study of HFD only, HFSD-fed $hCNR1^{-/-}$ mice had less body weight gain than HFSD-fed $hCNR1^{+/+}$ mice (25.1±2.7 vs 19.8±1.7g), less fat accumulation in the liver, 1.3-fold increase in glucose disposal and 1.7-fold increase in insulin sensitivity compared to HFSD-fed $hCNR1^{+/+}$ mice. Further study demonstrated that the lack of hepatic CB1R resulted in upregulated phosphorylation in liver of protein kinase B (AKT), causing activation of downstream target molecules, such as proline-rich AKT substrate 40 (PRAS40) in the mammalian target of rapamycin complex 1 (mTORC1). Similarly, primary hepatocytes isolated from $hCNR1^{-/-}$ mice had increased amounts of phosphorylated AKT and PRAS40 in comparison to hepatocytes from $hCNR1^{+/+}$ mice. The co-immunoprecipitation studies clearly revealed hepatic CB1R modulates insulin signaling by the association or dissociation of the components of mTORC1. These findings indicate that genetic deletion of hepatic CB1R contributes to improved glucose homeostasis. Therefore, modulation of CB1R activity in liver may be a useful therapeutic in obese and diabetic individuals.

SERUM MICRORNA-122 AND -192 ARE INCREASED IN ADOLESCENTS WITH NAFLD: POTENTIAL ROLE AS BIOMARKERS

Sirish Palle[1], Diana A. Hellman[2], Shaoning Jiang[2], Jeanie B. Tryggestad[2], Estefania Fematt [2], Kevin R. Short[2]

[1] Section of Gastroenterology, Hepatology, and Nutrition; and, [2] Section of Diabetes and Endocrinology, Department of Pediatrics, OUHSC

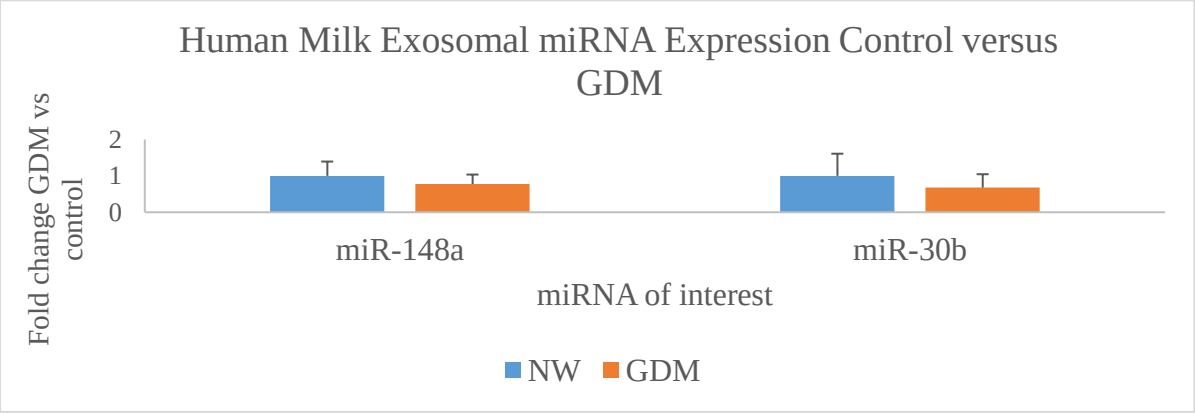
The best currently available blood biomarker for nonalcoholic fatty liver disease (NAFLD) is alanine aminotransferase (ALT). However, ALT is not a reliable marker for NAFLD severity. Several alternate blood measurements have been evaluated in adults, but very few have been tested in children. We tested the performance of serum microRNA-122 (miR-122) as a biomarker for NAFLD in adolescents as it was shown in animal models to inhibit hepatic lipogenesis; it is also exported from liver to circulation as the disease progresses. miR-122 was shown to be a biomarker for NAFLD in adults but the only study so far in children produced mixed results. We also measured miR-192, -130b, and -155 as they have roles in hepatic lipogenesis and are found in circulation. Participants were boys and girls, 12-20 y, with biopsy-confirmed NAFLD (n=23), and peers without NAFLD who were either obese (Ob, n=22), or normal weight (NW, n=24). RNA was extracted from fasting serum from all participants and from liver biopsies from the NAFLD group. The main finding was that serum miR-122 and -192 were 12- and 10-fold higher ($p< 0.01$), respectively, in NAFLD patients compared to either Ob and NW control groups. Within the NAFLD group, serum abundances of miR-122 and -192 were inversely correlated with their liver values ($r = -0.51$, $p = 0.002$ and $r = -0.40$, $p = 0.067$, respectively), and positively correlated with histological scores for steatosis ($r = 0.39$ and 0.28, respectively) and fibrosis ($r = 0.56$ and 0.54, respectively). mIR-122 and -192 content were also positively correlated with ALT ($r = 0.78$ for both) and with each other in both serum ($r = 0.92$) and liver ($r = 0.74$), suggesting some potential common control. Serum miR-130b, which regulates PGC-1 alpha, was 2.6-fold higher in serum from NAFLD patients versus both control groups, while serum miR-155, which regulates lipogenesis and inflammation, did not differ in NAFLD. Serum miR-130b and miR-155 values were not correlated with their corresponding values in liver biopsies. These initial analyses support the potential use of miR-122 and -192 as biomarkers for the presence and severity of NAFLD in adolescents. Further work to measure target transcripts of these miRNAs will clarify their roles in liver disease.

MATERNAL EXPOSURE TO GESTATIONAL DIABETES ALTERS HUMAN BREAST MILK EXOSOMAL MICRORNA EXPRESSION

Kruti Shah, David Fields, Ellen Demerath, Shelly Gulati, Steven Chernausek

Department of Pediatrics, Section of Pediatric Diabetes and Endocrinology
Harold Hamm Diabetes Center, University of Oklahoma College of Medicine
Division of Epidemiology and Community Health, University of Minnesota

microRNAs (miRNAs) are biologically active molecules that repress translation of mRNAs thereby influencing multiple physiological processes. Human milk (HM) is a rich source of miRNAs, which are predominately packaged in degradation-resistant exosomes, thus representing a potential mechanism affecting infant nutrition and metabolism. Children born to mothers with obesity and diabetes have increased risk of obesity and diabetes later in life. Alteration in the HM miRNA composition could be one potential mechanisms for the increased risk. The objective of this study was to determine the impact of gestational diabetes mellitus (GDM) on HM exosomal miRNAs. Previous studies have shown that miR-148a and miR-30b are highly abundant in HM and have the potential to influence metabolic pathways. Our recently published work also suggests that miR-148a is downregulated in Human Umbilical Vein Endothelial cells and placenta of infants exposed to GDM. RNA was isolated from human milk exosomes from 22 control (non GDM and normal weight) and 36 mothers with gestational diabetes mellitus (GDM-21/36-Obese/overweight) at 1-month of lactation. Reverse transcription was performed on equal volumes of total RNA and quantitative PCR was performed. Fold change expression of selected miRNAs (miR-148a and miR-30b) was calculated. miR-146b was used as a reference gene as it was highly abundant in breast milk and showed low variability between groups. Normality was calculated between the groups. Unpaired t tests were used for normally distributed data and Mann Whitney U test was used for non-normally distributed data to test differential expression of miRNAs between groups. Expression of miR-148a and miR-30b were significantly lower (23% and 33% respectively) in HM obtained from mothers with GDM as compared to control group (**Figure**). We have found that these miRNAs are substantially reduced in breastmilk from GDM mothers at 1-month post-partum. They have the potential to affect growth and function of lactating breast tissue as well as metabolic processes in the growing infant. Our recent work also suggests that miR-148a is downregulated in Human Umbilical Vein Endothelial cells and placenta of infants exposed to GDM. Genes targeted by these miRNAs are known to be involved in a set of pathways that are crucial in adipogenesis, insulin signaling and energy metabolism. Given the important roles of these miRNAs in variety of metabolic pathways and the intake of miRNAs by infants via breastfeeding, future mechanistic studies are required to better understand the role of HM exosomal miRNAs on infant growth and metabolic programming.



EVIDENCE OF INCREASED CARDIOVASCULAR DISEASE RISK IN ADOLESCENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

Kevin R. Short[1], Diana A. Hellman[1], Sirish Palle[2]

[1] Section of Diabetes and Endocrinology; and, [2] Section of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, OUHSC

Nonalcoholic fatty liver disease (NAFLD) in adults is associated with increased risk for cardiovascular disease, but less is known about those risks in pediatric NAFLD. We tested whether cardiovascular and metabolic function in adolescents with NAFLD were adversely affected beyond what could be attributed to obesity *per se*. Participants were boys and girls, 12-20 y, with biopsy-confirmed NAFLD (n=23), and controls without NAFLD who were either obese (Ob, n=29), or normal weight (NW, n=41). Measured variables were physical activity (PA, by accelerometry), body composition (DXA), aerobic fitness (VO_2peak), fasting blood chemistry, resting energy expenditure (REE), blood pressure (BP), carotid-femoral pulsewave velocity (PWV), and heart rate variability (HRV). The Ob and NAFLD groups had similar body mass index (98 ± 2 percentile) and body fat (44 ± 7 vs. 45 ± 7%), which were both higher than the NW group (BMI 54 ± 23 %ile; body fat 28 ± 7%; $p<0.01$). Daily PA was 18% lower ($p=0.025$) in the NAFLD than the NW group (with Ob intermediate). VO_2peak (1.93 ± 0.30 l/min adjusted for lean mass) and peak workload (132 ± 30 watts), however, did not differ among groups, indicating similarly low fitness. REE adjusted for lean mass did not differ between NAFLD and Ob groups, and was 14 and 7% higher ($p<0.03$), respectively, than the NW group. Glucose was normal and did not differ among groups, but compared to NW, insulin was 144% and 230% higher in the Ob and NAFLD groups, revealing high insulin resistance. The NAFLD group also had dyslipidemia, with higher triglycerides (88 to 168%) and free fatty acids (45%), and lower HDL-C (22 to 27%) than the Ob and NW groups, respectively, whereas the Ob group only had elevated triglycerides versus NW. The NAFLD group had 10-12% higher ($p<0.01$) PWV and systolic and diastolic BPs than either Ob or NW groups, while the control groups did not differ on those measures. Multiple indices of HRV were ~15% lower ($p<0.05$) in NAFLD than NW (with Ob intermediate). Although obesity is a major cardiometabolic disease risk factor, adolescents with NAFLD have greater arterial stiffening and dyslipidemia than obese peers with similar body composition and aerobic fitness. NAFLD was also associated with potential cardiac autonomic neuropathy. These early developing cardiometabolic disease risks could be potentially corrected with a lifestyle intervention emphasizing exercise and weight loss.

DIAGNOSIS OF MODY3 IN DE-IDENTIFIED DONOR PANCREATIC TISSUE LEADS TO VARIANT IDENTIFICATION IN LIVING RELATIVES

DAVID SPARLING[1], RACHANA HALIYUR[2], JILL LINDNER[2], LINDA WEBER[1], ANDREA RAMIREZ[2], MARCELA BRISSOVA[2], ALVIN C POWERS[2]

1: Section of Pediatric Diabetes and Endocrinology, Department of Pediatrics, College of Medicine, University of Oklahoma; 2: Division of Diabetes, Endocrinology, and Metabolism, Department of Medicine, Vanderbilt University Medical Center

As part of studies to understand human pancreatic islet pathophysiology in type 1 diabetes (T1D), we discovered normal β cell mass in a 33-year-old deceased organ donor with T1D for 17 years. Further analysis revealed the donor's diabetes resulted from a causative variant in hepatic nuclear factor 1-alpha (*HNF1A*), associated with Maturity-onset Diabetes of the Young-3 (MODY3) (J Clin Invest 129:246, 2019), which can be treated with sulfonylureas. Review of the donor's redacted medical chart suggested a family history of diabetes consistent with the known autosomal dominant pattern of inheritance of MODY3. With this clinically-actionable information, we desired to inform the donor's family. However, de-identified samples are not considered "human subject" research by Institutional Review Boards (IRB), so the family's identity was unknown with no defined pathway for communicating these findings. Working with a Human Tissue and Organ Research Resource and an organ procurement organization, we developed a new, IRB-approved communication path between those involved in tissue collection, scientific investigation, and the donor's family and physician. This allowed targeted genetic testing of potentially affected family members, which revealed five living relatives of the donor who carried the *HNF1A* variant: three adults diagnosed with diabetes before the age of 25 currently treated with insulin and two children (ages 6 months and 3 years) who did not have clinical diabetes. Since none of the identified individuals were known to have MODY3, they will likely benefit from appropriate clinical care and surveillance. This experience demonstrates the need for the scientific community to develop guidelines to address handling, reporting, and use of research findings from de-identified tissue collected for research. Defining ethical avenues for donor family-investigator communications will benefit for both organ donor families and scientific research.

SHORT PRESENTATIONS JUDGING SCHEDULE

Presentations will be via Zoom and in order as listed in the groups below

GROUP A

#	Time	Presenter	Title
1	12:30 – 12:45 pm	Raghuveer Chandrashekhar	EFFECT OF FOCAL MUSCLE VIBRATION ON BALANCE, MOBILITY, PAIN, AND SENSATION IN INDIVIDUALS WITH DIABETIC PERIPHERAL NEUROPATHY
2	12:45 – 1:00 pm	Tamas Csipo	LONGER REACTION TIME IS ASSOCIATED WITH NEUROVASCULAR DYSFUNCTION IN OBESE, OLDER ADULTS
3	1:00 – 1:15 pm	Josiah Rippetoe	IMPROVEMENT OF GAIT AFTER 4 WEEKS OF FOCAL MUSCLE VIBRATION THERAPY FOR INDIVIDUALS WITH DIABETIC PERIPHERAL NEUROPATHY
4	1:15 – 1:30 pm	Ru Wang	DERIVATION AND VALIDATION OF ESSENTIAL PREDICTORS AND RISK INDEX FOR EARLY DETECTION OF DIABETIC RETINOPATHY USING ELECTRONIC HEALTH RECORDS
5	1:30 – 1:45 pm	Duncan Mullins	A MATHEMATICAL MODEL OF THE GLOMERULR FILTRATION BARRIER DAMAGE IN DIABETIC KIDNEY DISEASE
6	1:45 – 2:00 pm	Beibei Liu	MECHANISM OF NEUROTROPHIN-MEDICATED NEUROPROTECTION IN DIABETIC RETINOPATHY
7	2:00 – 2:15 pm	David Sparling*	DIAGNOSIS OF MODY3 IN DE-IDENTIFIED DONOR PANCREATIC TISSUE LEADS TO VARIANT IDENTIFICATION IN LIVING RELATIVES

Judges: **non-award eligible presentation*

Tiangang Li, Ph.D.
Archana Unnikrishnan, Ph.D.

GROUP B

#	Time	Presenter	Title
8	12:30 – 12:45 pm	Maria Newhardt	INCREASING GLYCOLYSIS PROTECTS CARDIAC FUNCTION AGAINST HIGH FAT DIET- INDUCED CARDIOMYOPATHY
9	12:45 – 1:00 pm	Ankur Rughani	IMPACT OF MATERNAL DIABETES EXPOSURE ON MICRO RNA ABUNDANCE IN HUVEC AND CIRCULATIONS
10	1:00 – 1:15 pm	Ashok Mandala	THERAPEUTIC POTENTIAL OF MICROBIOTA-DEPENDENT INDOLES FOR PROTECTION AGAINST NAFLD
11	1:15 – 1:30 pm	Shiwali Goyal	A BIDIRECTIONAL MENDELIAN RANDOMIZATION STUDY TO EVALUATE THE CAUSAL ROLE OF REDUCED BLOOD VITAMIN D IN TYPE 2 DIABETES IN SOUTH ASIANS AND EUROPEANS
12	1:30 – 1:45 pm	Shiwali Goyal	TARGETED SEQUENCING OF GWAS-DERIVED CANDIDATE GENES OF T2DM IN ASIAN INDIAN ENDOGAMOUS ETHNIC GROUPS: FINDINGS FROM THE INDIGENIUS CONSORTIUM
13	1:45 – 2:00 pm	David Matye	TFEB REGULATION OF HEPATIC CYSTEINE AND COENZYME A SUPPORTS METABOLIC FLEXIBILITY
14	2:00 – 2:15 pm	Kruti Shah*	MATERNAL EXPOSURE TO GESTATIONAL DIABETES ALTERS HUMAN BREAST MILK EXOSOMAL MICRORNA EXPRESSION
15	2:15 – 2:30 pm	Sirish Palle*	SERUM MICRORNA-122 AND -192 ARE INCREASED IN ADOLESCENTS WITH NAFLD: POTENTIAL ROLE AS BIOMARKERS

Judges:

David Fields, Ph.D.

Ann Louise Olson, Ph.D.

**non-award eligible presentation*

SHORT PRESENTATIONS

All abstracts - listed alphabetically by author

1. **FATTY ACID METABOLISM DYSREGULATION AND RETINAL DYSFUNCTION IN DIABETIC RETINOPATHY**
   AGBAGA, MARTIN-PAUL; Chris Schafer, Jami Gurley, Karan S. Multani, Whitney Bohannan, Richard Brush

2. **EFFECT OF FOCAL MUSCLE VIBRATION ON BALANCE, MOBILITY, PAIN, AND SENSATION IN INDIVIDUALS WITH DIABETIC PERIPHERAL NEUROPATHY**
   CHANDRASHEKHAR, RAGHUVEER; Carol Dionne, Shirley James, Jenni Burzycki, Hongwu Wang

3. **LONGER REACTION TIME IS ASSOCIATED WITH NEUROVASCULAR DYSFUNCTION IN OBESE, OLDER ADULTS**
   CSIPO, TAMAS; Agnes Lipecz, Peter Mukli, Andriy Yabluchanskiy

4. **EFFECT OF ATHLETIC CONDITIONING ON SKELETAL MUSCLE GLUCOSE TRANSPORTER EXPRESSION IN DOGS**
   DAVIS, MICHAEL; Montana. Fulton, Ann Olson

5. **A BIDIRECTIONAL MENDELIAN RANDOMIZATION STUDY TO EVALUATE THE CAUSAL ROLE OF REDUCED BLOOD VITAMIN D IN TYPE 2 DIABETES IN SOUTH ASIANS AND EUROPEANS**
   GOYAL, SHIWALI; Cynthia Bejar, Shoaib Afzal, Massimo Mangino, Ang Zhou, Peter Van der Harst, Bao Yanchun, Vipin Gupta, Melissa Smart, Gagandeep Walia, Niek Verweij, Christine Power, Dorairaj Prahbakaran, Jai Rup Singh, Narinder Mehra, Gurpreet Wander, Sarju Ralhan, Sanjay Kinra, Meena Kumari, Martin De Borst, Elina Hyppönen, Tim Spector, Børge Nordestgaard, Piers Blackett, Dharambir K. Sanghera

6. **TARGETED SEQUENCING OF GWAS-DERIVED CANDIDATE GENES OF T2DM IN ASIAN INDIAN ENDOGAMOUS ETHNIC GROUPS: FINDINGS FROM THE INDIGENIUS CONSORTIUM**
   GOYAL, SHIWALI; Vettriselvi Venkatesan, Cynthia Bejar, Juan Lopez-Alvarenga, Rector Arya, Teena Koshy, Umarani Ravichandran, Surendra Sharma, Sailesh Lodha, Amaresh Reddy Ponnala, Krishna Kumar Sharma Sr., Mahaboob Vali Shaik, Roy Resendez, Deepika Ramu, Priyanka Venugopal, Parthasarathy R, Noelta S, Juliet Ezeilo,

Srinivas Mummidi, Chidambaram Natesan, John Blangero, Krishna M. Medicherla, Sadagopan Thanikachalam Sr., Thyagarajan Sadras Panchatcharam, Dileep Kumar K, Rajeev Gupta, Solomon Franklin Paul, Ravindranath Duggirala, Dharambir Sanghera

7. **ROLE OF MATERNAL PYRROLOQUINOLINE QUINONE (PQQ) IN AMELIORATING DIET-INDUCED NAFLD IN OFFSPRING OF OBESE MICE**
   JONSCHER, KAREN; Kenneth Jones, Jacob Friedman

8. **DELETION OF HEPATIC CANNABINOID 1 RECEPTOR (CB1R) PREVENTS FATTY LIVER AND IMPROVES GLUCOSE HOMEOSTASIS VIA REGULATION OF MTORC1**
   KIM, YOO; Josephine Egan

9. **NAD+ REDOX IMBALANCE IN THE HEART EXACERBATES DIABETIC CARDIOMYOPATHY**
   LEE, CHI FUNG

10. **MECHANISM OF NEUROTROPHIN-MEDICATED NEUROPROTECTION IN DIABETIC RETINOPATHY**
    LIU, BEIBEI; Meili Zhu, Yun-Zheng Le

11. **THERAPEUTIC POTENTIAL OF MICROBIOTA-DEPENDENT INDOLES FOR PROTECTION AGAINST NAFLD**
    MANDALA, ASHOK; Rachel Janssen, Jacob Friedman, Karen Jonscher

12. **TFEB REGULATION OF HEPATIC CYSTEINE AND COENZYME A SUPPORTS METABOLIC FLEXIBILITY**
    MATYE, DAVID; Cheng Chen, Tiangang Li

13. **A MATHEMATICAL MODEL OF THE GLOMERULR FILTRATION BARRIER DAMAGE IN DIABETIC KIDNEY DISEASE**
    MULLINS, DUNCAN; Ashlee Ford Versypt

14. **INCREASING GLYCOLYSIS PROTECTS CARDIAC FUNCTION AGAINST HIGH FAT DIET- INDUCED CARDIOMYOPATHY**
    NEWHARDT, MARIA; Albert Batushansky, Satoshi Matsuzaki, Michael Kinter, Kenneth Humphries

15. **SERUM MICRORNA-122 AND -192 ARE INCREASED IN ADOLESCENTS WITH NAFLD: POTENTIAL ROLE AS BIOMARKERS**
PALLE, SIRISH; Diana Hellman, Shaoning Jiang, Jeanie Tryggestad, Estefania Fematt, Kevin Short

16. **IMPROVEMENT OF GAIT AFTER 4 WEEKS OF FOCAL MUSCLE VIBRATION THERAPY FOR INDIVIDUALS WITH DIABETIC PERIPHERAL NEUROPATHY**
RIPPETOE, JOSIAH; Bethany Block, Matthew Beckner, Shirley James, Carol Dionne, Hongwu Wang

17. **PULMONARY GLUCOSE DYSREGULATION LEADS TO GREATER INFLUENZA REPLICATION AND MORTALITY**
ROCHOWSKI M, Campolo A, Allen S, Lin Liu, Lacombe VA

18. **IMPACT OF MATERNAL DIABETES EXPOSURE ON MICRO RNA ABUNDANCE IN HUVEC AND CIRCULATIONS**
RUGHANI, ANKUR

19. **MATERNAL EXPOSURE TO GESTATIONAL DIABETES ALTERS HUMAN BREAST MILK EXOSOMAL MICRORNA EXPRESSION**
SHAH, KRUTI; David Fields, Ellen Demerath, Shelly Gulati, Steven Chernausek

20. **EVIDENCE OF INCREASED CARDIOVASCULAR DISEASE RISK IN ADOLESCENTS WITH NONALCOHOLIC FATTY LIVER DISEASE**
SHORT, KEVIN; Diana Hellman, Sirish Palle

21. **DIAGNOSIS OF MODY3 IN DE-IDENTIFIED DONOR PANCREATIC TISSUE LEADS TO VARIANT IDENTIFICATION IN LIVING RELATIVES**
SPARLING, DAVID; Rachana Haliyur, Jill Lindner, Linda Weber, Andrea Ramirez, Marcela Brissova, Alvin Powers

22. **DERIVATION AND VALIDATION OF ESSENTIAL PREDICTORS AND RISK INDEX FOR EARLY DETECTION OF DIABETIC RETINOPATHY USING ELECTRONIC HEALTH RECORDS**
WANG, RU; Zhuqi Miao, Tieming Liu, Mei Liu

AWARD ELIGIBLE ABSTRACTS

EFFECT OF FOCAL MUSCLE VIBRATION ON BALANCE, MOBILITY, PAIN, AND SENSATION IN INDIVIDUALS WITH DIABETIC PERIPHERAL NEUROPATHY

Raghuveer Chandrashekhar[1], Carol Dionne[1], Shirley James[1], Jenni Burzycki[1], Hongwu Wang[1,2]

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The most common complication of type 2 diabetes mellitus (T2DM), diabetic peripheral neuropathy (DPN) affects 50-70% of all with T2DM. Individuals with DPN commonly experience sensation loss and pain, which cause impairments in balance and mobility, thus negatively impacting their activities of daily living, independence and quality of life. Unfortunately, most pharmacological and non-pharmacological interventions are ineffective, but, early evidence has shown that vibration therapy may improve the symptoms of DPN.

This pilot study examined the effects of a four-week home-based wearable focal muscle vibration (FMV) intervention on balance, mobility, pain, and sensation in individuals with DPN. Of the 24 participants enrolled, 23 completed both baseline and post-intervention visits. They were randomized into three intervention groups receiving three intensities of FMV. A modified Myovolt™ wearable device was used to apply FMV to the tibialis anterior, the distal quadriceps, and the belly of the gastrocnemius/soleus muscle (on both the legs). Each muscle was vibrated 10 minutes (total 30 minutes vibration for each leg), with an intersession interval of one minute, three days a week, for four weeks. The primary outcomes were: berg balance scale (BBS), brief pain inventory-DPN (BPI-DPN), standard and cognitive timed Up-and-Go (TUG), and Semmes Weinstein monofilament test (SWMT). All participants also completed a log of the device usage and a device feedback survey with a semi-structured interview during their second visit.

Statistically significant improvements were observed in TUG ($p=0.04$), TUG cognitive ($p=0.003$), average pain ($p=0.007$), and pain interference with walking ability ($p=0.03$). There was no statistically significant difference between the three intervention groups. Based on the log from the 21 participants who logged their usage of the device, it is evident that the FMV intervention had 100% compliance. The feedback for the FMV device was mostly positive, but, a common grievance with the device was the discomfort and inconvenience of the straps provided to attach and secure the device. The promising findings warrant further studies with a control group and larger sample size and more accurate outcome measures to establish the effectiveness and efficacy of FMV.

LONGER REACTION TIME IS ASSOCIATED WITH NEUROVASCULAR DYSFUNCTION IN OBESE, OLDER ADULTS

Tamas Csipo, Agnes Lipecz, Peter Mukli, Andriy Yabluchanskiy

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Currently, over 35% of individuals aged 65 and older are obese, and if the current trend continues, nearly half of the elderly population in the U.S. will be obese by 2030. Several epidemiological studies, including the Framingham Heart Study and the Baltimore Longitudinal Study on Aging, suggest that aging and obesity exert synergistic negative effects on cognition. There is also increasing evidence that both aging and obesity causes structural and functional impairment in the cerebral microcirculation, which plays a crucial role in the pathogenesis of vascular cognitive impairment (VCI).

The cells of the central nervous system are not capable of storing large reserves of energy sources; therefore, they are critically dependent on the moment-to-moment adjustment of cerebral blood flow. Neurovascular coupling (NVC) is the process that provides the additional blood flow to activated brain regions, and one of the mechanisms of cerebrovascular dysfunction is the impairment of NVC.

In this study, we included individuals of 65 to 80 years of age, who participated in the Oklahoma Longitudinal Study on Aging. We performed multi-domain cognitive function assessments, and measured NVC responses in older adults with normal (BMI 18-25) or obese body mass index (BMI >30). Cognitive function was assessed via the Cambridge Neuropsychological Test Automated Battery (CANTAB). NVC was measured in the brain cortex via functional near-infrared spectroscopy (fNIRS) during a finger-tapping task, and with dynamic retinal vessel analysis (DVA) during flicker light stimulation.

Cognitive evaluations showed significantly longer reaction time in obese older adults during the reaction time (RTI) task (374±36.7 ms vs. 271.3±19.7 ms in normal BMI group, $p=0.017$) DVA detected a significant ($p=0.01$) decrease in flicker light-evoked retinal arteriolar hyperemia (expressed as arteriolar dilation [%] * length of stimulation [s]) in obese older adults (median [IQR]: 37.8 [4.63 to 48.3] %*s) vs. the normal weight group (86.4 [54.5 to 117.5] %*s). fNIRS detected a more widespread NVC response over the left primary motor cortex during a right finger tapping task, which may indicate less efficient cortical activation in obese individuals.

Our results suggest that obesity impairs NVC in older adults, evidenced by the decreased flicker light-induced retinal hyperemia. This retinal NVC impairment was associated with a less efficient activation of the motor areas of the brain while subjects were performing a simple motor task. This inefficiency may explain the lower performance of obese older adults during reaction time assessments.

A BIDIRECTIONAL MENDELIAN RANDOMIZATION STUDY TO EVALUATE THE CAUSAL ROLE OF REDUCED BLOOD VITAMIN D IN TYPE 2 DIABETES IN SOUTH ASIANS AND EUROPEANS

Shiwali Goyal[1], Cynthia A. Bejar[1], Shoaib Afzal[3], Massimo Mangino[4], Ang Zhou[5], Peter Van der Harst[6], Bao Yanchun[7], Vipin Gupta[8], Melissa C. Smart[7], Gagandeep K. Walia[9], Niek Verweij[10], Christine Power[12], Dorairaj Prahbakaran[9], Jai Rup Singh[13], Narinder K. Mehra[14], Gurpreet S. Wander[15], Sarju Ralhan[15], Sanjay Kinra[16], Meena Kumari[7], Martin H. De Borst[11], Elina Hyppönen[5], Tim D. Spector[4], Børge G. Nordestgaard[3], Piers R. Blackett[2], Dharambir K. Sanghera[1]

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Multiple observational studies have reported an inverse relationship between 25-hydroxyvitamin D concentrations (25(OH)D) and type 2 diabetes (T2D). However, the results of short- and long-term interventional trials concerning the relationship between 25(OH)D and T2D risk have been inconsistent. To evaluate the causal role of reduced blood 25(OH)D in T2D, here we have performed a bidirectional Mendelian randomization study using 57,693 individuals (4698 T2D cases and 52995 controls) from European and Asian Indian ancestries. We used six known SNPs including 3 T2D SNPs (*IGF2BP2* rs1470579, *TCF7L2* rs7903146, and *KCNQ1* rs2237896) and 3 vitamin D pathway SNPs (*GC* rs2282679, *CYP2R1* rs12794714, and *DHCR7* rs12785878) as a genetic instrument to evaluate causality and direction of the association between T2D and circulating 25(OH)D concentration.

Results of the combined meta-analysis of eight participating studies showed that a composite score of three T2D SNPs would significantly increase T2D risk by 0.05% (95%CI 0.03%, 0.07%; p=1.9x10E-21) which however had no significant association with 25(OH)D status (Beta -0.0013 ± SE 0.0006; p=0.52). Likewise, the genetically instrumented composite score of 25(OH)D raising alleles significantly increased 25(OH)D concentrations (2.1 nmol/L± SE 0.1nmol/L]) (p=9.8x10E-86) but was not associated with protection from T2D (OR 1.0 95%CI 0.99, 1.00; p=0.29). However, using 25(OH)D synthesis SNP (*DHCR7*; rs12785878) as an individual genetic instrument, a per allele reduction of 25(OH)D concentration (-4.2 nmol/L ± SE 0.3 nmol/L) was predicted to increase T2D risk by 5% [95% CI 0.04%, 15%; p= 0.006]. This effect, however, was not seen in other 25(OH)D SNPs (*GC* rs2282679, *CYP2R1* rs12794714) when used as an individual instrument. Our new data on this bidirectional Mendelian randomization study suggests that genetically instrumented T2D risk does not cause changes in 25(OH)D levels, or *vice versa*. However, we cannot totally exclude variants of 25(OH)D synthesis gene (DHCR7) for influencing the risk of T2D. **FUNDING:** This work was supported by NIH grants -R01DK082766, R01DK118427 funded by the National Institute of Health (NIDDK) and NOT-HG-11-009 funded by NHGRI, and a VPR Bridge Grant from University of Oklahoma Health Sciences Center. The authors thank all the participants of AIDHS/SDS and are grateful for their contribution to this study.

TARGETED SEQUENCING OF GWAS-DERIVED CANDIDATE GENES OF T2DM IN ASIAN INDIAN ENDOGAMOUS ETHNIC GROUPS: FINDINGS FROM THE INDIGENIUS CONSORTIUM

Shiwali Goyal[1], Vettriselvi Venkatesan[2], Cynthia A. Bejar[1], Juan C. Lopez-Alvarenga[3], Rector Arya[3], Teena Koshy[2], Umarani Ravichandran[2], Surendra Sharma[4], Sailesh Lodha[4], Amaresh Reddy Ponnala[5], Krishna Kumar Sharma Sr.[5], Mahaboob Vali Shaik[5], Roy G. Resendez[3], Deepika Ramu[2], Priyanka Venugopal[2], Parthasarathy R[2], Noelta S[2], Juliet A. Ezeilo[3], Srinivas Mummidi[3], Chidambaram Natesan[2], John Blangero[3], Krishna M. Medicherla[4], Sadagopan Thanikachalam Sr.[2], Thyagarajan Sadras Panchatcharam[2], Dileep Kumar K[5], Rajeev Gupta[4], Solomon Franklin Paul[2], Ravindranath Duggirala[3], Dharambir Sanghera[1]

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South Asians (SA), people for Indian subcontinent comprise one quarter of the global population and have 6 times higher risk of developing Type II Diabetes Mellitus (T2DM) than Europeans. However, underlying causes of this disparity are currently unknown and are difficult to be explained by conventional risk factors of T2DM. Here, we aimed to evaluate genetic determinants of T2DM using family-based cohorts from four distinct Endogamous Ethnic Groups (EEGs) representing two Northern (Punjab [Sikhs] and Rajasthan [Agarwals]) and two Southern (Tamil Nadu [Chettiars] and Andhra Pradesh [Reddys]) states of India, and to examine whether genetic variants found through targeted sequencing of the previously established 8 South Asian T2DM risk loci (including the one from the Sikh population) are relevant to other EEGs, all are part of the INDIGENIUS consortium, supported by an Indo-U.S. Collaborative Research Partnership on T2DM.

Targeted sequencing of 8 SA-specific GWAS loci (HMG20A, AP3S2, ST6GAL1, GRB14, VPS26A, HNF4A, SGCG and TMEM163, containing 48 genes and intergenic regions) was performed on 32 multiplex families of Sikh EEG and validation studies were performed on additional ~3150 individuals of Punjabi ancestry; all individuals were part of the Asian Indian Diabetic Heart Study/Sikh Diabetes Study (AIDHS/SDS). Our data revealed a large number of common and rare variants associated with T2DM and other cardio-metabolic traits. A new association signal represented by a common variant (rs2166480; MAF 0.35) in *CCNT2-AS1* gene was observed to be robustly associated with decreased risk of T2DM (Beta -0.29; p=1.2E-08) in meta-analysis. In addition, multiple significant rare variants were population-specific (rs996956640 *ST6GAL1* and 13:24149429 *SGCG*) and not observed in Exome Aggregation Consortium (ExAC) or 1000Genomes; some of these novel variants were private and only restricted in few pedigrees. Currently, we are replicating these variants in our other EEGs. Our present pedigree-based design provides additional insight into mechanisms underlying T2DM and show the potential for the discovery of new genetic loci of T2DM. Identification of population-specific genetic signatures would help characterize non-obese/metabolically obese phenotype of T2DM in South Asians. **FUNDING:** National Institute of Diabetes and Digestive and Kidney Diseases (R21DK105913), Indian Council of Medical Research (55/6/2/Indo-US/2014-NCD-II). AIDHS/SDS was also supported by National Institute of Health grants KO1 TW006087, funded by the Fogarty International Center and R01DK082766, funded by National Institute of Diabetes and Digestive and Kidney Diseases.

MECHANISM OF NEUROTROPHIN-MEDICATED NEUROPROTECTION IN DIABETIC RETINOPATHY

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To study Müller cell (MC)-mediated neuroprotection in diabetic retinopathy (DR), we previously demonstrated that disrupting vascular endothelial growth factor (VEGF) receptor-2 in MCs caused accelerated loss of retinal MCs, neurons, and major neuroprotectant, brain-derived neurotrophic factor (BDNF) in diabetes (*Diabetes*, 64: 3554). To determine the mechanism(s) of VEGF-/BDNF-mediated MC viability, we asked the question whether VEGF supports MC directly by improving the survival of MCs, indirectly by upregulating the production/secretion of BDNF, or both, we measured the levels of secreted BDNF with ELISA and the number of MCs with live cell assay in cultures of rat MC line (rMC1). While VEGF stimulated MC viability and BDNF secretion in a dose-dependent manner under diabetes-like condition (high glucose, HG), BDNF produced by each MC was comparable. This result suggests that VEGF stimulates BDNF production mainly through the increase of MC viability. Targeting the main retinal BDNF receptor, tropomyosin receptor kinase B (TRK-B), with siRNA caused a significant reduction of activated AKT and ERK and MC viability. In summary, VEGF-stimulated MC viability results in additional BDNF production, which in turn, elevates MC viability through ATK survival and ERK proliferation pathways. As a substantial portion of patients treated with anti-VEGF drugs for 5 years appeared to have very thin retinas (presumably severe retinal cell/neuron loss), which bears striking resemblance to that in our diabetic MC-specific VEGFR2 KO mice, it is likely that blocking VEGF signaling in MC may cause unwanted retinal neuronal degeneration in DR patients subjected to long-term anti-VEGF treatment due to blocking VEGF signaling-mediated MC survival directly and reducing BDNF level-mediated cell loss indirectly. Therefore, supporting MC viability with BDNF may be a feasible strategy for neuroprotection during anti-VEGF treatment for DR and hypoxic retinal diseases.

THERAPEUTIC POTENTIAL OF MICROBIOTA-DEPENDENT INDOLES FOR PROTECTION AGAINST NAFLD

Ashok Mandala, Rachel C. Janssen, Jacob E. Friedman and Karen R. Jonscher

Harold Hamm Diabetes Center, The University of Oklahoma Health Sciences Center

Nonalcoholic fatty liver disease (NAFLD) is a progressive liver disease affecting 40% of obese youth and up to 10% of the general pediatric population worldwide. NAFLD can progress to Non-Alcoholic Steatohepatitis (NASH), a more severe form of the disease associated with inflammation and fibrosis as macrophages move into the liver and crosstalk with hepatic stellate cells to promote fibrosis. In the past decade, a wealth of preclinical and human studies demonstrated that maternal over-nutrition alters developmental programming in offspring, inducing inflammation as well as various microbial species and their metabolites associated with NAFLD. The microbiota, acting via secreted factors related to indoles, regulate inflammatory processes, but their cellular targets in the pathogenesis of NAFLD is unclear. Indoles act via the aryl hydrocarbon receptor (AHR) which promotes epithelial barrier protection and protects against infection and damage caused by hyper-inflammatory responses. The question arises as to how indoles orchestrate repair and immune responses so as to provide protection against NAFLD directly in the liver, immune cells, or the stellate cell itself. To elucidate their function as anti-inflammatory factors in the pathogenesis of NASH, we tested whether pretreatment with indole and I3A prevented lipopolysaccharide (LPS)-induced inflammation and ceramide accumulation in RAW264.7 macrophage cells and free fatty acid (FFA)-induced inflammation in HepG2 human hepatoma cells. In LPS stimulated macrophages and FFA-treated hepatocytes, we found that pre-treatment with indole and I3A significantly reduced the gene expression of inflammatory *Il1b, Tnfα, Nlrp3*, and *Mcp1*, as well as genes involved in de-novo ceramide synthesis such as *Sptlc2* and *Degs1.* Moreover, in culture-activated mouse primary hepatic stellate cells (mHSC) cells, indole and I3A treatment reduced the mRNA expression of genes involved in HSC activation, such as *Acta2*, *Col1a1*, *Tgfb1*, as well as fibroblast growth factor-inducible 14 (Fn14; *Tnfrsf12a*) and its ligand *Tnfsf12* (TWEAK), a factor secreted from macrophages that regulates cellular processes such as proliferation, differentiation, migration and cell survival. Further, treatment of human hepatic stellate cells (LX2) with indole and I3A decreased TGFβ- and Tweak-induced cellular proliferation. Together, these findings suggest that supplementation of microbiota-derived agonists of AHR protects against inflammation in macrophages, hepatocytes and prevents HSC activation *in-vitro*. Hence, activation of AHR signaling by indoles have the potential as therapeutics to protect against inflammation and associated liver fibrosis.

TFEB REGULATION OF HEPATIC CYSTEINE AND COENZYME A SUPPORTS METABOLIC FLEXIBILITY

David Matye, Cheng Chen, Tiangang Li

Harold Hamm Diabetes Center, Department of Physiology, University of Oklahoma Health Sciences Center

Background: Hepatic fat accumulation is a hallmark of fatty liver disease and type-2 diabetes and promotes insulin resistance and hyperglycemia. Transcription factor EB (TFEB) has recently been identified as a master inducer of lysosomal biogenesis and autophagy. TFEB attenuates hepatic steatosis and inflammation and is a promising therapeutic target for fatty liver disease. Activation of hepatic TFEB enhances mitochondrial fatty acid oxidation through mechanisms that are incompletely understood. Coenzyme A (CoA) is a central metabolic cofactor synthesized from cysteine and pantothenate. Critically, CoA is required for oxidation of fatty acids and is found in high levels in mitochondria. Hepatic CoA deficiency exacerbates hepatic steatosis and inflammation in experimental models of fatty liver disease. **Aim:** This study aims to investigate the role and mechanisms of TFEB regulation of hepatic cysteine and CoA metabolism to support fatty acid oxidation. **Method:** We used a global metabolomic approach to identify TFEB regulated metabolic pathways in liver specific TFEB overexpressing mice fed either chow or Western diet (WD). Protein and sulfur amino acid adjusted diet feeding in combination with metabolomics were used to determine the contribution of cysteine availability to CoA synthesis and fatty acid oxidation. Adenovirus-mediated liver specific knockdown of the CoA biosynthetic enzyme pantothenate kinase (PanK1) in mice was used to demonstrate the importance of hepatic CoA deficiency in promoting steatosis. **Results:** Global metabolomic analysis revealed that hepatic TFEB activation in mice selectively increased cellular cysteine and CoA concentration and decreased hepatic fat accumulation. Mechanistically, TFEB stimulated the hepatic methionine cycle and transsulfuration pathway resulting in increased conversion of methionine to cysteine to support cellular CoA synthesis. Gene expression analysis revealed that TFEB promotes cysteine synthesis from methionine by induction of methionine adenosyltransferase, which converts methionine to S-adenosylmethionine. Mice fed a protein restricted diet had hepatic cysteine and CoA deficiency and acylcarnitine accumulation. Furthermore, fatty livers showed hepatic cysteine and CoA deficiency, which correlated with an accumulation of acylcarnitine. Reduction in hepatic CoA synthesis by knockdown of liver PanK1 sensitized mice to Western diet-induced hepatic steatosis, which was attenuated upon hepatic TFEB overexpression in mice. **Conclusion:** We demonstrated that hepatic cysteine and CoA deficiency significantly promotes hepatic steatosis by limiting fatty acid oxidation capacity. We identified a novel pathway whereby TFEB induces the methionine cycle and transsulfuration pathway to increase cellular cysteine availability which supports hepatic CoA synthesis and fatty acid oxidation, resulting in attenuated fat accumulation in fatty liver disease.

A MATHEMATICAL MODEL OF THE GLOMERULR FILTRATION BARRIER DAMAGE IN DIABETIC KIDNEY DISEASE

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The glomerulus has been determined to be the central structure damaged within the kidney in diabetic kidney disease. Due to the difficulty in acquiring experimental data, particularly regarding the progression of diabetic kidney disease within the glomerulus, mathematical modeling has risen in popularity in recent years. One of the hallmarks for diabetic kidney disease is the development of albuminuria. This albuminuria develops, in part, due to the loss of functionality within the glomerular filtration barrier. This work develops a mathematical model for tracking the damage within the glomerular filtration barrier through the progression of diabetic kidney disease, focusing on the thickening of the glomerular basement membrane, the rarefaction of the glycocalyx, and the changes to endothelial fenestration density. Additionally, this work develops a framework for calculating the concentration of three key chemicals within the progression of diabetic kidney disease: glucose, transforming growth factor beta (TGF- β), and vascular endothelial growth factor (VEGF). Finally, this work aims to create a method for tracking the chemical dependent damage within diabetic kidney disease, as these are integral chemicals whose dysregulation results in some of the most crucial and severe damage within diabetic kidney disease.

INCREASING GLYCOLYSIS PROTECTS CARDIAC FUNCTION AGAINST HIGH FAT DIET- INDUCED CARDIOMYOPATHY

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The healthy heart has a dynamic capacity to respond and adapt to changes in both nutrient availability and energy demands. This metabolic flexibility is critical for the maintenance of proper tissue function and its disruption has deleterious effects on the heart. For example, a signature characteristic of diabetic cardiomyopathy is metabolic inflexibility whereby the heart increases reliance on fatty acids to meet energetic demands. The goal of this study is to determine if increasing glycolysis in the diabetic heart can mitigate cardiac dysfunction. Wild type (WT) and transgenic mice with cardiac-specific increased glucose utilization ($Glyco^{Hi}$) were fed a low fat (LFD) or a high fat diet (HFD) for 16 weeks to induce the metabolic inflexibility seen in type 2 diabetes. Metabolic profiles were determined by measuring mitochondrial respiration and targeted quantitative proteomics analysis. Echocardiography was used to assess cardiac function. Heart mitochondria from $Glyco^{Hi}$ mice on LFD exhibited increased rates of glucose-substrate supported respiration compared to WT/LFD. Mitochondria of both groups on HFD exhibited increased fatty acid-supported respiration. However, $Glyco^{Hi}$ mitochondria showed a decrease in fatty acid reliance compared to WT. Quantitative proteomics data further supported that $Glyco^{Hi}$ hearts have resistance to HFD induced metabolic inflexibility. Increasing glycolysis also had beneficial effects on cardiac function. Echocardiography analysis revealed a decrease of diastolic function in WT/HFD but not in $Glyco^{Hi}$/HFD. Together these results strongly support that increasing glycolysis in diabetic hearts is cardio-protective.

IMPROVEMENT OF GAIT AFTER 4 WEEKS OF FOCAL MUSCLE VIBRATION THERAPY FOR INDIVIDUALS WITH DIABETIC PERIPHERAL NEUROPATHY

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Approximately 30 percent of individuals diagnosed with type II diabetes will develop the debilitating complication of diabetic peripheral neuropathy (DPN), which causes balance, posture, and gait impairments. Current interventions for gait impairments in individuals with DPN have limited effectiveness. Focal muscle vibration (FMV) has demonstrated improved gait performance in other conditions, but has not been assessed in patients with DPN. The purpose of this study was to investigate FMV as an intervention to improve gait performance in individuals with DPN.

The investigators used a randomized parallel groups clinical trial design. The investigators recruited 23 individuals with type II diabetes and DPN from the Oklahoma City metropolitan area from October 2018 to August 2020. This study included a four week at home FMV intervention using two MyoVolt™ FMV devices. The participants were randomized to three groups depending upon the mode of vibration: sinusoidal, pulsing, and continuous. Participants applied FMV to the bilateral quadriceps, gastrocnemius, and tibialis anterior, 10 minutes per muscle, three times per week over a four-week period. 3-D motion capture was utilized to acquire spatiotemporal, kinematic, and kinetic gait parameters of the participants at baseline and following at-home FMV therapy.

There were no significant differences on the demographic data among the three vibration mode groups ($p>0.05$). Gait speed, left and right step duration, stance duration, left initial single limb support duration, bilateral double limb support duration, and peak left and right knee flexor moments were significantly improved post-intervention ($p<0.05$). Between group analysis demonstrated that changes on maximum left dorsiflexion was significantly different among the mode of vibration ($p<0.05$).

Spatiotemporal parameters significantly improved and changes in kinematic and kinetic parameters were observed but were not significant after four weeks of at home FMV therapy. These results warrant an expanded study of FMV therapy for gait performance improvement in gait performance in the long-term by individuals with DPN.

PULMONARY GLUCOSE DYSREGULATION LEADS TO GREATER INFLUENZA REPLICATION AND MORTALITY

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Diabetes is characterized by sustained hyperglycemia due to either lack of insulin production (Type 1) or lack of insulin action (Type 2). Hyperglycemia is an independent risk factor for the development of severe respiratory infections, including influenza infections. However, the regulation of glucose metabolism in the lung (a major organ to utilize glucose) during diabetes or infection has received little attention. We hypothesize that hyperglycemia predisposes diabetic patients to an excess of glucose in the airway, which may lead to increased pulmonary viral replication. To test this hypothesis, primary cultured human bronchial epithelial cells (HBECs) infected with influenza A were incubated in different glucose concentrations (1mg/mL, 2mg/mL, 4mg/mL, or 6mg/mL) or with the glycolytic inhibitor 2-deoxyglucose. Viral loads were determined by immunofluorescence staining and qrtPCR for the viral membrane protein hemagglutinin. In addition, both streptozotocin-induced type 1 diabetic (T1Dx) mice and high fat diet induced type 2 diabetes (T2Dx) mouse model were intranasally infected with influenza (A/PR/8/34, 250 PFU). Subsets of T1Dx and T2Dx mice were treated with insulin or metformin, respectively, in order to restore euglycemia. Viral titer was measured via qRT-PCR of whole-lung homogenates and glucose concentration was measured in bronchoalveolar lavage fluid (BALF) via glucose oxidase assay. *In vitro*, HBECs incubated in 2 and 4 mg/ml [glucose] had a significantly higher percentage of infected cells than those incubated in 1 mg/ml [glucose] ($p=0.0043$ and 0.0001, respectively). Conversely, HBECs treated with the glycolytic inhibitor 2-deoxyglucose demonstrated reduced viral replication. Similarly, both diabetic and infected mice demonstrated significantly increased concentrations of glucose in BALF. Viral titer was significantly greater in lung homogenates of T2Dx mice ($p=0.03$ vs. their respective controls, n=3/group), with a statistical trend in T1Dx mice ($p=0.052$, n=4/group), which was rescued by metformin or insulin treatment, respectively. Finally, diabetic mice demonstrated significantly greater mortality than their control counterparts following H1N1 challenge. These novel findings suggest that: 1) influenza infection alone or hyperglycemia increased BALF [glucose], 2) increased pulmonary glucose concentration (both *in vitro* and *in vivo*) increased H1N1 viral replication, 3) influenza is dependent on host-cell glycolysis. Since hyperglycemia alone is an independent risk factor for viral infection, better understanding of the mechanisms altering glucose metabolism during viral infection may lead to the discovery of novel therapeutic targets for diabetic patients infected with influenza.

IMPACT OF MATERNAL DIABETES EXPOSURE ON MICRO RNA ABUNDANCE IN HUVEC AND CIRCULATIONS

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Exposure to diabetes in utero "programs" offspring toward future cardiometabolic disease. MicroRNA (miRNA) may be an epigenetic mechanism by which these changes occur. The present study used a nonbiased sequencing approach to examine the impact of diabetes exposure in utero on miRNA abundance in HUVEC and cord blood serum from six infants born to mothers with diabetes and six infants born to mothers with normal glycemia matched for infant sex, ethnicity, and gestational age. HUVEC and serum total RNA samples were submitted to LC Sciences (Houston, TX) for sequencing analysis. Approximately 1 ug of total RNA was used to prepare the small RNA library according to the TruSeq Small RNA Sample Prep Kits protocol (Illumina, San Diego, USA). Single-end sequencing of 50bp was performed on an Illumina Hiseq 2500 at LC Sciences (Hangzhou, China) following the vendor's recommended protocol. Raw reads were subjected to an in-house program, ACGT101-miR (LC Sciences, Houston, Texas, USA) to remove adapter dimers, common RNA families (rRNA, tRNA, snRNA, snoRNA) and repeats. Unique sequences with lengths of 18-26 nucleotides were mapped to species-specific precursors in miRBase 22.0 by BLAST search to identify known and novel 3p- and 5p- derived miRNAs. To predict the genes targeted by the most abundant miRNAs, two computational target prediction algorithms, TargetScan and Miranda 3.3a, were used to identify miRNA binding sites. The data predicted by both algorithms were combined and the overlaps were calculated.

The gene ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways of these most abundant miRNAs and their mRNA targets were also annotated. Thirty-one miRNAs were more abundant including miR-210, miR-130b-3p, miR-491-5p and six miRNAs were less abundant including miR-146b-5p, mIR-192-3p, and miR-30e-5p ($p<0.05$) in HUVEC from infants born to mothers with diabetes compared to matched controls. In the serum, four miRNAs were more abundant in the infants born to mother with diabetes (mIR-15a-5p, miR-26a-5p, miR-22-3p, and miR-126-3p) and none was downregulated. Using these results as a screen, analysis with RT-PCR revealed a 25% decrease (p 0.03) in miR-146b from the HUVEC of DM-exposed infants (N = 23) as compared to controls (N = 39), validating the miRNA sequencing technique. GO target enrichment analysis suggested the targets of the most abundant miRNAs were involved in transport, protein binding, mitochondria, DNA transcription, and cell cycle. The KEGG analysis found the most significantly enriched pathways were PI3K-Akt, AGE-RAGE signaling in diabetic complications, apoptosis, FoxO signaling, MAPK signaling, and cell senescence. MiRNA-146b, for instance, targets the inflammatory proteins IRAK1 (interleukin-1 receptor-associated kinase 1) and TRAF6 (TNF receptor-associated factor 6), both of which modulate the NF-kB inflammatory pathway and contribute to the progression of cardiovascular disease. Using this unbiased approach, we have identified miRNAs that are differentially expressed with diabetes exposure in utero, and these miRNAs target mRNAs that are involved in insulin signaling and energy metabolism pathways. Results from RT-PCR validate the use of miRNA sequencing as a screen to explore miRNA expression.

DERIVATION AND VALIDATION OF ESSENTIAL PREDICTORS AND RISK INDEX FOR EARLY DETECTION OF DIABETIC RETINOPATHY USING ELECTRONIC HEALTH RECORDS

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Diabetic retinopathy (DR) is a retinal complication of diabetes and is a leading cause of vision-loss among working-aged adults globally. DR is asymptomatic at early stage and the recommended comprehensive eye exams have low patient compliance. Therefore, it is very urgent for medical researchers to develop a tool that can detect DR as early as possible. In this study, we aim to identify crucial risk factors of DR, and then develop and validate a risk score system. We performed a retrospective case/control cohort study using data extracted from a large electronic health records (EHR) database. Bivariate analysis was implemented to test the relationship of 3 demographic variables, 2 diabetic complications (neuropathy and retinopathy), and 20 blood test results to DR incidence. Then, an ensemble feature selection approach was applied to find key variables. Subsequently, a logistic regression with only essential variables included was built to derive a risk score system. At last, the proposed prediction model and risk score were externally validated on a separate cohort. 4,312 cases and 43,120 controls were included in the study population. Twelve variables were chosen from the feature selection method.

The prediction model obtained an AUC of 0.83 and 0.76 in internal and external validation, respectively. And the risk score index had an AUC of 0.78 for the derivation cohort and an AUC of 0.72 for the validation cohort. Based on the results, the developed models demonstrated promising accuracy in predicting DR without losing generality. These simple models have the potential to facilitate early DR detection.

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