Alberta Diabetes INSTITUTE

2024 RESEARCH DAY

0800-1635 | 1-040 LKS (Oborowsky Degner Seminar Hall) & LKS Foyer

THURSDAY OCTOBER 10

KEYNOTE SPEAKER

Christine Doucette, PhD

Associate Professor, Department of Physiology & Pathophysiology, University of Manitoba

Co-Sponsored by:

Alberta Diabetes FOUNDATION

UNIVERSITY OF ALBERTA

Alberta Diabetes INSTITUTE

2024 ADI RESEARCH DAY

Thursday, October 10 | 0800-1635 h (MT)
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Program

Alberta Diabetes INSTITUTE

Leading the World in the Prevention, Treatment and Cure of Diabetes

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Note from the Director

Welcome to the 2024 Alberta Diabetes Institute Research Day. This annual event, hosted by the ADI since 2005, provides ADI Trainees - from first year undergraduate summer students to seasoned postdoctoral fellows - the opportunity to showcase their research efforts. This year, we are excited to host our event fully in-person! With the help of our dedicated ADI Trainee Working Group, ADI Members, Trainees, and Administration, we have organized an exciting day of oral and poster presentations that will provide an enriching experience for everyone attending.

While our Research in Progress events provide snapshots of the diverse approaches to understand diabetes used by different groups within the ADI, our Research Day provides a unique opportunity to see the diverse strengths, prompting new ideas and catalyzing new intra-institute collaborations.

We are delighted to welcome Dr. Christine Doucette, Associate Professor from the University of Manitoba, as this year's keynote speaker and judge. Dr. Doucette is well known to many of us in the ADI, having trained at UofT and as an associate editor of the Canadian Journal of Diabetes. She has now been running her own lab since 2012 exploring the molecular and metabolic factors that contribute to childhood-onset T2D. Working with Indigenous community partners, her research seeks to understand how post-colonial environmental and genetic factors interact to influence pancreatic function and metabolic health.

We are honoured that Dr. Doucette accepted our ADI Trainee Working Group members' invitation and we look forward to welcoming her to Alberta, and to the ADI.

Our research day is intended to provide a forum to showcase the research efforts of our **ADI Trainees**. With respect to this, there are two **oral presentation** sessions (junior/senior trainees) and two poster **presentation sessions** (junior/senior trainees). During Research Day, our trainees have the opportunity for direct interaction with Dr. Doucette over lunch.

The ongoing support and contributions from generous donors, the Alberta Diabetes Foundation, DRIFCan, and other generous partners, is deeply appreciated for their vital and sustained contributions to the work of the ADI.

I am indebted to our ADI Trainee Working Group (supported by Dr. Vincent Rogers) for their help in organizing and running this year's ADI Research Day. I would also like to thank all of our volunteers, judges, session chairs, and A/V support.

We hope today will provide an opportunity to interact with and learn from your peers by listening and asking questions, further inspiring your curiosity, and encouraging all of us to pursue excellence in our scientific endeavors.

Dr. Peter Senior
Director, Alberta Diabetes Institute
Dr. Charles A. Allard Chair in Diabetes Research

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Keynote Speaker

Dr. Christine Doucette, PhD

The ADI is excited to announce this year's keynote speaker, Dr. Christine Doucette. Dr. Doucette is an Associate Professor in the Department of Physiology & Pathophysiology at the University of Manitoba and is also a Research Scientist at the Children's Hospital Research Institute of Manitoba. Dr. Doucette is an active member of the "DREAM" (Diabetes Research Envisioned and Accomplished in Manitoba) theme, which is a multidisciplinary, translational team of basic scientists, clinicians and community partners dedicated to the prevention and improved treatment of T2D in children.

Dr. Doucette began her academic career in Toronto, receiving her Bachelor of Science (2000) and PhD (2007) from the University of Toronto, under the supervision of Dr. Greg Vanlerberghe. Her PhD work was focused on defining the role of mitochondrial complexes (alternative oxidase) in the control of plant pathogen responses. After successful completion of her PhD in 2007, Dr. Doucette changed scientific focus and pursued a Postdoctoral Fellowship in the diabetes field, under the mentorship of Dr. Michael Wheeler, also at the University of Toronto. Here, she focused on understanding the role of uncoupling proteins, reactive oxygen species production and their roles in regulating insulin secretion. In 2012, she was recruited by the University of Manitoba as an Assistant Professor and principal investigator where she started a research program that is now focused on defining the molecular and metabolic factors that contribute to childhood-onset T2D. Since joining the University of Manitoba and DREAM theme, Dr. Doucette's research has been informed by Indigenous community partners and as a result, her research now largely focuses on understanding how the post-colonial environmental factors and genetic factors interact to influence pancreatic function and overall metabolic health. Dr. Doucette also has research interests in the developmental origins of diabetes and circadian clock development.

On October 10th, from 8:30-9:30 am, Dr. Doucette will be delivering her keynote speech in the Oborowsky Degner Seminar Hall. We would also like to thank Dr. Doucette for hosting the trainee lunch Q&A and joining us for the entire day filled with exceptional research.

Welcome Dr. Doucette!

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Morning & Afternoon Schedule

MORNING SESSION

WELCOME

08:00	Welcome to 2024 Research Day	Refreshments in the LKS Foyer
08:15	Opening Remarks	Dr. Peter Senior, ADI Director
08:25	Introduction to Keynote Speaker	Honyi Ong – ADI Trainee Working Group President

KEYNOTE SPEAKER

08:30 - 09:30	Dr. Christine Doucette Associate Professor, Department of Physiology & Pathophysiology, University of Manitoba	Keynote Speech

POSTER PRESENTATION - JUNIOR

09:43	Luisa Pessoa-Soares Tsai Lab	MSc Student	**Page 1**	MATERNAL DYSBIOSIS AFFECTS BREAST MILK PROTEOME, MODULATING TYPE 1 DIABETES INCIDENCE IN OFFSPRING
09:51	Boshra Mandour Richard Lab	MSc Student	**Page 2**	DIETARY INTAKE AND IMMUNE FUNCTION IN ADULTS WITH OBESITY: PRELIMINARY DATA FROM THE NUTRITION AND IMMUNITY (NUTRIMM) STUDY
09:59	Paris A. T. Jones Davenport Lab	MSc Student	**Page 3**	IMPACT OF POSTPARTUM PHYSICAL ACTIVITY ON CARDIO-METABOLIC HEALTH: A SYSTEMATIC REVIEW AND META-ANALYSIS
10:07	Sufyan Malik Lopaschuk Lab	MSc Student	**Page 4**	INHIBITION OF MYOCARDIAL FATTY ACID OXIDATION IMPROVES CARDIAC FUNCTION AND LESSENS THE SEVERITY OF DIABETIC CARDIOMYOPATHY
10:15	Camilla Fonseca Rezende Haqq Lab	MSc Student	**Page 5**	3DO BODY COMPOSITION ASSESSMENT AND ITS ASSOCIATION TO CHILDHOOD CARDIOMETABOLIC RISK
10:23	Archee Panwar Lopaschuk Lab	MSc Student	**Page 6**	STIMULATING MYOCARDIAL GLUCOSE OXIDATION IN DIABETIC CARDIOMYOPATHY
10:31	Matthieu Zolondek Dyck Lab	MSc Student	**Page 7**	CARDIAC SPECIFIC RESTORATION OF ROMO1 BLUNTS HEART FAILURE BY PROTECTING MITOCHONDRIAL STRUCTURE AND FUNCTION
10:39	Yuanjun (Dennis) Cai Haqq Lab	Undergraduate Student	**Page 8**	MYOSTEATOSIS: HIDDEN FACTOR IN OBESITY LEADING TO INSULIN RESISTANCE

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Morning & Afternoon Schedule

10:47	Pulkit Kumar Pepper Lab	MSc Student	**Page 9**	EVALUATING THE EFFICACY OF LIPROXSTATIN-1 IN DELAYING DIABETES ONSET IN NOD MICE
10:55	Eliora Begna Ferdaoussi Lab	Undergraduate Student	**Page 10**	THE ROLE OF FERROPTOSIS IN GLUCOCORTICOID-INDUCED DIABETES
11:03	Mya Schmidt Dyck Lab	MSc Student	**Page 11**	KETONES: ESSENTIAL MODULATORS OF THE INFLAMMATORY RESPONSE?
11:11	Kiersten Rajotte Rayat Lab	Undergraduate Student	**Page 12**	C3G IMPROVES BETA CELL RESILIENCE UNDER STRESS

ORAL PRESENTATION - SENIOR

11:15	Alice Carr Senior Lab	Post-Doctoral Fellow	**Page 13**	SEQUENTIAL ISLET TRANSPLANTS FOR TYPE 1 DIABETES DO NOT CUMULATIVELY INCREASE HEPATIC PORTAL VENOUS PRESSURE
11:30	Theodore dos Santos MacDonald Lab	PhD Student	**Page 14**	PATCH-SEQ REVEALS ALPHA CELL ELECTRICAL DYSFUNCTION LINKED TO ALTERATIONS IN IDENTITY, PARACRINE SIGNALING, METABOLISM, IMMUNE RESPONSE, AND MTOR ACTIVITY IN T1D
11:45	Jasmine Maghera Macdonald Lab	PhD Student	**Page 15**	UNVEILING GAPS IN HESCβ-CELL FUNCTION: COMBINING SNIGLE-CELL ELECTROPHYSIOLOGY AND SCRNA-SEQ
12:00	Purushothaman Kuppan Korbutt and Pepper Lab	Post-Doctoral Fellow	**Page 16**	NANOFIBROUS BIOABSORBABLE FUNCTIONALIZED SCAFFOLDS SUPPORT THE SUBCUTANEOUS ISLET ENGRAFTMENT AND FUNCTION IN MICE
12:15	Yasser Abuetabh Dyck Lab	Post-Doctoral Fellow	**Page 17**	SEMAGLUTIDE REDUCES CARDIOMYOCYTE SIZE AND CARDIAC MASS IN LEAN AND OBESE MICE

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Morning & Afternoon Schedule

TRAINEE LUNCH WITH THE SPEAKER

12:30 – 13:30	Oborowsky Degner Seminar Hall By invitation: ADI Trainee Research Day Presenters/ADI Research Day Trainee Volunteers	Guest Dr. Christine Doucette / ADI Trainees LUNCH PROVIDED

AFTERNOON SESSION

POSTER PRESENTATION - SENIOR

13:35	Julien Wourms Yue Lab	MSc Student	**Page 18**	DIRECT PROTEIN KINASE A ACTIVATION, BUT NOT GLUCAGON *PER SE*, IN THE NUCLEUS OF THE SOLITARY TRACT DECREASES HEPATIC TRIGLYCERIDE SECRETION IN A MODEL OF TYPE 2 DIABETES
13:43	Lynn Dong Ussher Lab	PhD Student	**Page 19**	BAICALEIN AMELIORATES DIABETIC CARDIOMYOPATHY THROUGH INHIBITING ALOX15
13:51	Shawn Duckett MacDonald Lab	MSc Student	**Page 20**	CHARACTERIZING THE ROLE OF IDENTITY FACTORS ON α-CELL FUNCTION IN DIABETES
13:59	Kateryna Polishevska Pepper Lab	PhD Student	**Page 21**	NEUTROPHIL-TARGETING ANTI-LY6G ANTIBODY PRESERVE MOUSE PANCREATIC ISLET GRAFT FUNCTION IN THE SUBCUTANEOUS SPACE
14:07	Alice Missagia Springer Haqq Lab	PhD Student	**Page 22**	SYNERGISTIC EFFECTS OF METFORMIN AND FIBER SUPPLEMENTATION ON INSULIN RESISTANCE IN ADOLESCENTS WITH SEVERE OBESITY
14:15	Amanda Schukarucha Gomes MacDonald Lab	PhD Student	**Page 23**	HETEROGENOUS GLYCINE-EVOKED CURRENTS IN HUMAN β CELLS
14:23	Ezra Ketema Lopaschuk Lab	PhD Student	**Page 24**	SIRT2 DELETION SUPPRESSES GLYCOLYSIS THROUGH HYPERACETYLATION OF GLYCOLYTIC ENZYMES
14:31	Janyne Johnson Light Lab	PhD Student	**Page 25**	REGULATION OF PANCREATIC ALPHA CELL GLUCAGON-LIKE PEPTIDE-1
14:39	Jamie Boisvenue Senior Lab	PhD Student	**Page 26**	VISUALIZING MEDICAL TRAUMA BY AGE AT DIAGNOSIS IN PEOPLE LIVING WITH TYPE 1 DIABETES USING EPISTEMIC NETWORK ANALYSIS

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14:47	Jordan Chan Ussher Lab	PhD Student	**Page 27**	HIGH FRUCTOSE MEDIATED PREDIABETES DOES NOT INDUCE LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN MALE MICE
14:55	Summer Helmi Pepper Lab	Post-Doctoral Fellow	**Page 28**	STATIC SUSPENSION VERSUS DYNAMIC SUSPENSION CULTURE SYSTEMS FOR NEONATAL PORCINE ISLET (NPI) DIFFERENTIATION
15:03	Seyed Amirhossein Tabatabaei Dakhili Ussher Lab	Post-Doctoral Fellow	**Page 29**	CHEMICAL DEVELOPMENT OF A NEW CLASS OF SUCCINYL COA:3-KETOACID COA TRANSFERASE (SCOT) INHIBITORS WITH REDUCED BRAIN PERMEABILITY THAT PROMOTE GLUCOSE-LOWERING IN OBESITY

ORAL PRESENTATION – JUNIOR

15:15	Arghyadip Bose Korbutt and Pepper Lab	PhD Student	**Page 30**	MESENCHYMAL STROMAL CELLS IMPROVE VASCULARIZATION IN A PRE-VASCULARIZED SUBCUTANEOUS APPROACH FOR ISLET TRANSPLANTATION
15:30	Zofia Czarnecka Shapiro Lab	MSc Student	**Page 31**	CHARACTERIZATION OF OFF-TARGET CELL POPULATIONS IN HUMAN INDUCED PLURIPOTENT STEM CELL (HIPSC) DERIVED ISLETS IN IMMUNODEFICIENT MICE
15:45	Ivan J. Ma Korbutt Lab	MSc Student	**Page 32**	IMPACT OF 24-HOUR STATIC COLD STORAGE OF NEONATAL PIG PANCREAS ON ISLET RECOVERY AND FUNCTIONALITY
16:00	Ren Wang Field Lab	PhD Student	**Page 33**	FEEDING LONG-CHAIN POLYUNSATURATED FATTY ACIDS ALTERED SPLENOCYTE MEMBRANE FATTY ACID COMPOSITION IN A DOSE-DEPENDENT MANNER AND MODULATED CYTOKINE PRODUCTION IN YOUNG WISTAR RATS
16:15	Maria Elena Wong Richard Lab	MSc Student	**Page 34**	THE EFFECT OF SEX AND BUTTERMILK-DERIVED LIPID-SOLUBLE FORM OF CHOLINE ON IMMUNE DYSFUNCTION IN THE CONTEXT OF OBESITY: PRELIMINARY FINDINGS

CLOSING REMARKS

16:25-16:35	Dr. Peter Senior, ADI Director	Awards announced on Friday, October 17

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Awards

Prize winners will be notified by email on October 17th and announced via ADI Update and social media.

ORAL PRESENTATION SESSION (Junior Trainees)

- 1 Best Award & 1 Honourable Mention

ORAL PRESENTATION SESSION (Senior Trainees)

- 1 Best Award & 1 Honourable Mention

POSTER SESSION (Junior Trainees)

- 1 Best Award & 1 Honourable Mention

POSTER SESSION (Senior Trainees)

- 1 Best Award & 1 Honourable Mention

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KETEMA Ezra Lopaschuk Lab	24	SIRT2 DELETION SUPPRESSES GLYCOLYSIS THROUGH HYPERACETYLATION OF GLYCOLYTIC ENZYMES
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RAJOTTE Kiersten Rayat Lab	12	C3G IMPROVES BETA CELL RESILIENCE UNDER STRESS
REZENDE Camilla Fonseca Haqq Lab	5	3DO BODY COMPOSITION ASSESSMENT AND ITS ASSOCIATION TO CHILDHOOD CARDIOMETABOLIC RISK
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WANG Ren Field Lab	33	FEEDING LONG-CHAIN POLYUNSATURATED FATTY ACIDS ALTERED SPLENOCYTE MEMBRANE FATTY ACID COMPOSITION IN A DOSE-DEPENDENT MANNER AND MODULATED CYTOKINE PRODUCTION IN YOUNG WISTAR RATS
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ABSTRACTS

Morning Session

Poster Presentation

JUNIOR

UNIVERSITY OF ALBERTA

Abstracts

MATERNAL DYSBIOSIS AFFECTS BREAST MILK PROTEOME, MODULATING TYPE 1 DIABETES INCIDENCE IN OFFSPRING

Luisa Pessoa-Soares[1*#], Erin Strachan[1#], Tingting Ju[2,3], Alejandro Schcolnik-Cabrera[1], Henry Wang[4], Masoud Akbari[1], Carol Huang[5], Olivier Julien[4], Benjamin P. Willing[2], Xavier Clemente-Casares[1], Sue Tsai[1**]

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[2] Dept. of Agricultural, Food & Nutritional Science, University of Alberta, Edmonton, AB, Canada
[3] Dept. of Animal Sciences, Purdue University, West Lafayette, IN, USA
[4] Dept. of Biochemistry, University of Alberta, Edmonton, AB, Canada
[5] Depts. of Endocrinology, Medical Science, Pediatrics, University of Calgary, Calgary, AB, Canada
[#] Both authors contributed equally to this work.
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Introduction: The gastrointestinal microbiome plays a crucial role in overall health by influencing immune defense and intestinal homeostasis. This immune-microbiota interaction is particularly critical during early life, where maternal microbiome impacts neonatal gastrointestinal tract by promoting long-term immune tolerance. This process is dependent on maternal factors and when it fails to occur at appropriate times, there is an increased susceptibility to immune-mediated pathologies in offspring. Whether maternal dysbiosis can perpetuate the same in offspring and affect maternal factors, potentially contributing to the development of autoimmune diseases such as type I diabetes (T1D), remains largely unknown.

Methods: Using a nonobese diabetic (NOD) mouse deficient in immunoglobulin A (IgA) as a dysbiotic model, we examined if and how maternal dysbiosis influenced maternal factors and T1D onset.

Results: Our findings revealed that offspring from dysbiotic IgA-deficient mothers exhibit lower diabetes incidence, and less insulitis compared to those from IgA-sufficient dams. The proteome of breast milk from dysbiotic dams shows significant enrichment in immune-related and metabolic protein levels. In these mice, there is an increase in breast milk immunoglobulin G (IgG) levels, which can modulate gut microbiome in the pups and be internalized through the neonatal Fc receptor (FcRn). The higher milk IgG levels in dysbiotic dams do not contribute to increased microbe coating in pups, but is internalized in higher amounts, possibly influencing immune education. We are currently investigating the immunological mechanisms behind this protection through IgG supplementation and FcRn blockade. Additionally, we explore the breast milk antibody repertoire and its connection to specific microbiome changes.

Conclusion: Collectively, our study indicates that maternal dysbiosis driven by IgA-deficiency contributes to changes in breast milk proteome, which in turn can affect immune development in offspring, leading to diabetes protection.

Abstracts

DIETARY INTAKE AND IMMUNE FUNCTION IN ADULTS WITH OBESITY: PRELIMINARY DATA FROM THE NUTRITION AND IMMUNITY (NUTRIMM) STUDY

Boshra Mandour[1,2], Jenneffer Rayane Braga Tibaes[1], Maria Ines Barreto Silva[1,3], Laurie Mereu[4], Paulina Blanco[1], Alexander Makarowski[1], Paul Veugelers[2], Caroline Richard[1]

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Introduction: Obesity, hyperglycemia, inflammation, and poor diet negatively impact immune function, increasing the risk of infection. However, it is unclear how diet affects immune function over and above its effect on obesity, hyperglycemia, and inflammation. The objective of this study is to investigate how diet is associated with immune function in the NutrIMM study.

Methods: This cross-sectional analysis of the NutrIMM study at baseline assessed participants that were recruited to one of four groups: 1) lean-normoglycemic (lean-NG; n=31), 2) obese-NG (n=24), 3) obese-glucose intolerant (GI; n=31) and 4) obese-type 2 diabetes (T2D; n=27). Antigen presenting cell (APC) function was assessed by IL-1β secretion after lipopolysaccharide (LPS) stimulation of peripheral blood mononuclear cells. Habitual diet and Healthy Eating Index (HEI)-2015 scores were obtained using the Diet History Questionnaire III (DHQIII) and analyzed using one-way ANOVA and Waller-Duncan post hoc test. Nutrient intakes were adjusted per 1,000 kcal, and participants who reported a daily calorie intake of <600 kcal or >5000 kcal were excluded. Partial Pearson correlation was used for group-adjusted correlation analysis. Significance is defined as $p \leq 0.05$.

Results: IL-1β production increased from lean-NG to T2D where all groups with obesity produced significantly more IL-1β compared to the lean-NG group. Total HEI-2015 score decreased significantly in the obese-NG and T2D groups compared to the lean-NG group for which HEI scores for Whole Grain, Fatty Acid (FA), Seafood and Plant Protein were highest in lean-NG. Compared to other groups, lean-NG had lowest intakes of saturated FA and white potato starchy vegetable and highest intakes of iron and phytic acid. The T2D group had the highest intake of aspartame and zinc, and the lowest intake of alcohol compared to other groups. Folate, magnesium, total fibre, and HEI score for Total Fruits were negatively correlated with IL-1β while white potato starchy vegetable and total starchy vegetable intake was positively correlated with IL-1β.

Conclusion: Our data suggests that the observed lower diet quality and higher pro-inflammatory IL-1β production by APC in individuals living with obesity appears to be modulated by key nutrients and foods known to affect immunometabolism (e.g. folate, magnesium, fibre, fruits, starchy foods). Therefore, improving overall diet quality may be important to counteract obesity-related immune dysfunction in this population.

Abstracts

IMPACT OF POSTPARTUM PHYSICAL ACTIVITY ON CARDIO-METABOLIC HEALTH: A SYSTEMATIC REVIEW AND META-ANALYSIS

Paris A. T. Jones[1] , Amy Moolyk[1], Stephanie-May Ruchat[2] , Muhummad Usman Ali[3], Karen Fleming[4], Sarah Meyer[1], Talia Sjwed[1], Jenna B. Wowdzia[1], Lauren Maier[1], Michelle F. Mottola[5], Allison Sivak[6], Margie H. Davenport[1]

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[4] Department of Family & Community Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada.
[5] R. Samuel McLaughlin Foundation- Exercise and Pregnancy Laboratory, School of Kinesiology, Faculty of Health Sciences, Department of Anatomy and Cell Biology, Schulich School of Medicine and Dentistry, Children's Health Research Institute, The University of Western Ontario, London, Ontario, Canada.
[6] Geoffrey & Robyn Sperber Health Sciences Library, University of Alberta, Edmonton, Alberta, Canada.

Introduction: To examine the relationship between postpartum physical activity, and maternal postnatal cardiometabolic health, breastfeeding, injury, and infant growth and development.

Methods: Systematic review with random-effects meta-analysis and meta-regression. Study eligibility criteria: Online databases were searched up until January 12, 2024. Studies of all designs in all languages were eligible (except case studies and reviews) if they contained information on the population (postpartum individuals), intervention (frequency, intensity, duration, volume, or type of exercise), comparator (no or low volumes of physical activity), and outcomes: hypertension, diabetes, cardiometabolic risk factors (systolic blood pressure [SBP], diastolic blood pressure [DBP], total cholesterol, high density lipoproteins [HDL-c], low density lipoproteins [LDL-c], and triglycerides, HbA1C, glucose and insulin concentration), breastfeeding (breastmilk quality and volume), infant growth (length and weight) and development, and postpartum injury.

Results: 46 unique studies (n=8766 participants) from 20 countries were included. Moderate certainty of evidence showed exercise+co-interventions reduced the odds of developing diabetes by 28% (7 RCTs, n=2496; OR 0.72 95% CI 0.54, 0.98, I^2 12%), reduced SBP (10 RCTs, n=2753; MD -2.15 95% CI -3.89, -0.40, I^2 73%), and DBP (9 RCTs, n=2575; MD -1.38 95% CI -2.60, - 0.15, I^2 66%) compared to controls.

Conclusion: Physical activity improves cardiometabolic health without adversely impacting breastmilk supply or quality, infant growth or maternal injury.

Abstracts

INHIBITION OF MYOCARDIAL FATTY ACID OXIDATION IMPROVES CARDIAC FUNCTION AND LESSENS THE SEVERITY OF DIABETIC CARDIOMYOPATHY

Sufyan Malik, Archee Panwar, Qiuyu Sun, Cory S. Wagg, Magnus Stenlund, Muhtasim Adib, John Ussher, Gary D. Lopaschuk

Introduction: Diabetic cardiomyopathy (DbCM) is a complication of diabetes that leads to adverse structural and functional changes in the heart, including myocardial hypertrophy, fibrosis, and diastolic dysfunction, all of which compromise the heart's ability to efficiently pump blood throughout the body. These changes are attributable to the disrupted metabolic profile of the diabetic heart, which is characterized by accelerated fatty acid oxidation and reduced glucose oxidation rates. This study involved assessing the therapeutic potential of optimizing cardiac energy metabolism in DbCM, specifically by inhibiting fatty acid oxidation in T2D mice. We hypothesized that inhibiting fatty acid oxidation would confer cardioprotection by enhancing glucose oxidation and lessen the severity of DbCM.

Methods: For 9 weeks, 12 to 14-week-old C57BL/6J female mice were fed either a regular chow diet (control), a 60% high fat diet (DbCM), or a 60% high fat diet mixed with an inhibitor of malonyl-CoA decarboxylase (MCDi, CBM-3001106), which inhibits fatty acid oxidation (DbCM + MCDi). After 4 weeks of the feeding protocol, mice in either of the DbCM groups were provided a single low-dose injection of streptozotocin (75 mg/kg i.p.) to induce experimental T2D, while mice in the control group were injected with equivalent volumes of vehicle. Ultrasound echocardiography was performed at the end of the protocol to assess cardiac function, after which the mice were euthanized and had their hearts perfused in the working mode to assess cardiac energy metabolism. Separate cohorts of mice from all groups were used for the histological assessment of cardiac fibrosis following the feeding protocol.

Results: Mice in the DbCM + MCDi group displayed improved glucose homeostasis compared to the DbCM group, accompanied by a reduced rate of weight gain. No significant differences in blood pressure and exercise capacity were observed between groups. While mice in the DbCM group displayed significant diastolic dysfunction and hypertrophy, as indicated by decreases in e'/a' ratios and increases in E/e' ratios and left ventricular mass compared to control mice, these effects were all reversed in DbCM + MCDi mice. As expected, hearts from DbCM mice had significantly impaired insulin-stimulated glucose oxidation and glycolysis rates, along with higher fatty acid oxidation rates overall. The effect of acute treatment with MCDi was also assessed in isolated working hearts from DbCM + MCDi mice, where it was observed to stimulate glucose oxidation and glycolysis rates while inhibiting fatty acid oxidation rates.

Conclusion: Our findings indicate that fatty acid oxidation is markedly increased in DbCM, and that inhibition of fatty acid oxidation via MCD inhibition not only stimulates myocardial glucose utilization, but also reduces the severity of DbCM by alleviating myocardial hypertrophy and diastolic dysfunction. As such, strategies aimed at inhibiting myocardial fatty acid oxidation may represent a promising therapeutic approach for the treatment of DbCM.

Abstracts

3DO BODY COMPOSITION ASSESSMENT AND ITS ASSOCIATION TO CHILDHOOD CARDIOMETABOLIC RISK

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Introduction: Childhood obesity is a worldwide health issue due to its cardiometabolic risks, making early screening vital for effective intervention[(1)]. The World Health Organization recommends the use of body mass index (BMI) to identify childhood obesity, but its precision is debatable since it does not differentiate body compartments, such as fat mass (FM) and muscle mass (MM)[(2)], tissues well known for their roles on the development of cardiometabolic diseases[(3,4)]. For this reason, an alternative and more precise screening tool for body composition (BC) is needed[(2)]. BC refers to the different body compartments, specifically fat mass (FM), muscle mass (MM), and bone mineral content (BMC)[(5,6)]. There are several methods to evaluate BC, such as magnetic resonance imaging and computerized tomography, dual-energy x-ray absorptiometry (DXA), air-displacement plethysmography (ADP), and bioelectrical impedance analysis (BIA), but their availability and accessibility are limited, or have significant error sources[(7–11)]. The use of a multi-compartment, model where the strengths of each method are used in combination to generate more accurate measures, is considered the gold-standard method for BC assessment; however, it is not a viable approach in clinical settings([12)]. Three-dimensional optical (3DO) body scanners have emerged as a new BC tool due to its quick and convenient use in clinical settings(13). It has proven to be valid and precise in adults[(14–16)] and to better predict metabolic disease risk than BMI alone(17). However, few studies have evaluated the use of 3DO in pediatric populations and the relationship of their estimates with cardiometabolic risk[(18,19)]. This study aims to assess the performance of 3DO (validity and precision) in estimating BC in adolescents with and without obesity and analyze its association with cardiometabolic risk.

Methods: This study will recruit 94 adolescents aged 10-18 years, with a balanced representation of males/females and obesity status (≥95 percentile or ≥85 percentile with obesity-related comorbidities). Exclusion criteria will include: participants using medications known to influence BC for the past 90 days, chronic diseases with an impact on BC, acute infections, recent hospitalization, metal implants, pacemaker or amputations, and pregnancy/breast-feeding. Assessments will be conducted at the Clinical Research Unit at the University of Alberta. Two different 3DO scanners will be employed, a platform device (Styku®) and a smartphone application (Me360®). The validity of the 3DO estimates will be examined against a 4 compartment model, using body weight from a calibrated scale, BMC from DXA, body volume from ADP, and total body water from BIA. Precision will be evaluated by test re-test measurement. Cardiometabolic measures will be collected, including fasting glucose, fasting insulin, and HbA1c, and insulin indices will be calculated (homeostatic model assessment for IR and quantitative insulin sensitivity check index). The 3DO estimates validity and precision will be calculated using the intraclass correlation coefficient (ICC)[(20)] , root mean square error, and coefficient of variation (CV%)[(21)]. Multivariate regression models will explore associations between BC estimates both by 3DO and multi-compartment modeling with cardiometabolic risk factors.

Expected results and conclusion: We hypothesize that 3DO body scanners will prove to be valid and precise for BC assessment of adolescents with and without obesity. Providing easily applicable and cost-effective BC methods into clinical practice will guide more precise management and monitoring of cardiometabolic diseases in adolescence, such as insulin resistance and diabetes, and avoid the development of life-long chronic diseases in adulthood.

Abstracts

STIMULATING MYOCARDIAL GLUCOSE OXIDATION IN DIABETIC CARDIOMYOPATHY

Archee Panwar, Sufyan Malik, Qiuyu Sun, Cory S. Wagg, Gary D. Lopaschuk

Introduction: Diabetic cardiomyopathy (DbCM) is a form of heart failure in which individuals with diabetes develop structural and functional changes in the heart. These changes often include hypertrophy, fibrosis, and diastolic dysfunction, which can compromise heart function. In DbCM, the heart switches from glucose oxidation to fatty acid oxidation, resulting in a disrupted energy metabolic profile of the heart. We therefore pharmacologically stimulated cardiac glucose oxidation in a mouse model of DbCM to assess whether optimizing cardiac energetics can exert functional benefits.

Methods: 13-week-old C57BL/6J female mice were given a 60% high fat diet for 9 wk as well as a streptozotocin (STZ, 75mg/kg dose) injection during wk 5 to induce DbCM. Control and DbCM mice were randomized to receive either vehicle or the PDKi MMR-0053 (40mg/kg/day) via the drinking water. Echocardiography was performed to assess cardiac function prior to performing isolated working heart perfusions to quantify metabolic rates of different energy substrates. Hearts were perfused with 5 mM glucose and 0.8 mM palmitate, with 100uU/ml insulin being added to the perfusate after 30 min for all mice. For mice given the PDKi, 50µM PDKi was added for the last 20 min of the perfusion to study the metabolic response.

Results: DbCM mice experienced accelerated weight gain and glucose intolerance. Of importance, DbCM hearts show significantly impaired insulin-stimulated glucose oxidation rates compared to that of control hearts (308 ± 53 vs 800 ± 125 nmol $\cdot$ g dry $wt^{-1} \cdot min^{-1}$). Acute PDKi addition to the perfusate significantly increased glucose oxidation rates in treated DbCM hearts (683 ± 95 vs. 323 ± 59 nmol $\cdot$ g dry $wt^{-1} \cdot min^{-1}$). DbCM hearts showed cardiac dysfunction compared to control hearts, with significantly decreased %EF and increased isovolumetric relaxation times. PDKi treatment significantly increased the e'/a' ratio and decreased the e/e'ratio in control hearts, thereby enhancing diastolic function. DbCM mice treated with the PDKi showed similar diastolic function compared to vehicle-treated DbCM mice.

Conclusion: In DbCM mice, insulin-stimulated cardiac glucose oxidation is significantly impaired. PDKi treatment stimulates myocardial glucose oxidation and enhances diastolic function in control mice, but does not induce notable functional changes in DbCM mice.

Abstracts

CARDIAC SPECIFIC RESTORATION OF ROMO1 BLUNTS HEART FAILURE BY PROTECTING MITOCHONDRIAL STRUCTURE AND FUNCTION

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Introduction: People with diabetes are 2- to 4-times more likely to develop heart failure (HF) than age-matched people living without diabetes. HF occurs when the heart is damaged to a point where it becomes unable to supply adequate blood flow to the rest of the body. Despite reductions in mortality in all patients due to advancements in medical and surgical therapies, the current one-year mortality rate after diagnosis of HF remains disturbingly high at 24-33%. As a result, HF remains a major contributor to increased morbidity and mortality in diabetic patients, emphasizing the importance of developing new strategies to treat this debilitating disease. Recently, we have identified a protein named ROMO1 that is involved in regulating mitochondrial structure/function and may thus play a role in the pathogenesis of HF. Indeed, in failing hearts of both humans and mice, ROMO1 protein expression is significantly decreased, leading us to propose that the loss of ROMO1 contributes to poor mitochondrial function and cardiac function in HF. Based on this we hypothesize that restoration of ROMO1 expression in HF will prevent damage to mitochondrial structure, function, and integrity, thereby improving cardiac function.

Methods: We sought to explore the effect of ROMO1 overexpression on cardiac and mitochondrial function in HF. To do this, we subjected male mice (n = 24) to sham control surgeries or transverse aortic constriction (TAC) surgery to induce HF. In addition, mice were injected with a cardiac-specific ROMO1 expressing adenoviral associated gene (AAV9-αMHC- ROMO1) or control (AAV9-αMHC-Null) expressing viruses. Using transthoracic echocardiography, we observed a significant decrease in cardiac function 2.5 weeks post-surgery following TAC that was significantly blunted by ROMO1 restoration. Scanning electron microscopy of mitochondria from ROMO1-expressing hearts revealed a restoration of mitochondrial structure and size compared to AAV-control TAC mouse hearts. In addition, cardiac mitochondrial respiratory capacity from these hearts was evaluated using High-Resolution Respirometry (Oroboros Instruments).

Results: Hearts from AAV-control TAC mice demonstrated a significant reduction in electron transport capacity (ETc), and relative oxygen flux through complex I and complex II of the respiratory system. Hearts from AAV-ROMO1 TAC mice resulted in a significant recovery in all three measures, demonstrating total normalization of mitochondrial function. Importantly, ETc was found to be significantly correlated with ejection fraction, demonstrating the intimate relationship between ROMO1- mediated cardiac mitochondrial function and heart function.

Conclusion: Our study explored the role of ROMO1 in the pathology of HF and identified ROMO1 as a regulator of cardiac mitochondrial structure and function. Restoration of ROMO1 prevented a decrease in ejection fraction and loss of mitochondrial oxidative capacity that occurred in HF. Taken together, these results suggest that ROMO1 plays an essential role in regulating mitochondrial function, and that ROMO1 may be targeted to blunt HF progression in the presence or absence of diabetes.

Abstracts

MYOSTEATOSIS: HIDDEN FACTOR IN OBESITY LEADING TO INSULIN RESISTANCE

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Introduction: Myosteatosis, an excessive infiltration of adipose tissue into muscle, is a hidden health condition in obesity, commonly disregarded and underdiagnosed. It is associated with poor health outcomes, such as insulin resistance and type 2 diabetes. This study explored in- depth the pathophysiology and clinical outcomes of myosteatosis and its relationship with obesity.

Methods: A literature search was performed on MEDLINE using keywords related to myosteatosis, muscle quality, and obesity. We identified 475 papers, of which 178 were further analyzed in this narrative review.

Results: Obesity leads to adipocyte dysfunction and secretion of pro-inflammatory cytokines, generating a state of low-grade chronic inflammation. Adipose inflammation creates mitochondrial dysfunction by impacting autophagy, resulting in mitochondrial oxidative stress, and reducing lipid oxidation and energy production. As a result, there is a decrease in muscle function and glucose uptake by the muscle. Additionally, obesity is also associated with mobility limitation and sedentary behavior. The combination of adipocyte and mitochondrial dysfunctions, with inflammation and reduced muscle glucose uptake results in metabolic dysfunction manifesting as insulin resistance, dyslipidemia, and fatty infiltration into organs such as muscle. Excessive fat infiltration into muscle tissue and cells leads to myosteatosis, a condition associated with poor health outcomes. Intra and intermuscular fat are pro inflammatory compared to subcutaneous fat; their excess result in decreased muscle cell function and insulin sensitivity, creating a vicious cycle of inflammation and metabolic derangements. Clinically, myosteatosis increases the risk of functional disability, insulin resistance, type 2 diabetes, metabolic syndrome, and mortality.

Conclusion: Muscles are a key organ in glucose metabolism and, thus, heavily implicated in glucose tolerance and insulin resistance. Myosteatosis has the potential to predict morbidity and mortality in individuals with obesity and clinical populations. The evaluation of myosteatosis is an additional tool for clinicians to consider when making clinical decisions. However, body composition assessment in clinical practice is still limited, and standard evaluations of muscle quantity do not capture key alterations in muscle quality. Emergent techniques such as ultrasound and bioelectrical impedance analysis generate proxy measures of fatty infiltration and could be further explored for myosteatosis assessment and prognostic use for insulin resistance and diabetes risk. Interventions that can prevent and reduce myosteatosis are likely to have a positive impact on insulin sensitivity and improve glucose control and potentially risk for diabetes.

Abstracts

EVALUATING THE EFFICACY OF LIPROXSTATIN-1 IN DELAYING DIABETES ONSET IN NOD MICE

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Introduction: The prevalence of Type 1 diabetes (T1D) necessitates ongoing research into therapeutic interventions that can delay or mitigate disease onset. Liproxstatin-1 (Lip-1), known for its potent anti-ferroptosis properties, has been theorized to offer protective benefits against oxidative stress-related beta-cell death. This study aims to evaluate the potential of Lip-1, administered via food from an early age, to modulate disease progression and insulin sensitivity in female Non-Obese Diabetic (NOD) mice.

Methods: A total of 40 female NOD mice at 4 weeks of age were allocated into two groups: 1) the control group (n=20), which was fed a standard diet, and 2) the treatment (Lip) group (n=20), that received a diet with 50 mg/kg of Lip; both diets contained 15% kcal of fat. The weight of these mice was monitored weekly, and their non-fasting blood glucose levels were measured twice weekly to track the onset of diabetes. Prior to the diabetes onset at 13 weeks, IPGTTs and ITTs were conducted to assay for glucose clearance and insulin clearance, and pancreases were collected from control (n=3) and Lip (n=3) to look for insulitis by histological assessment. Upon the development of diabetes (>18mM, for two consecutive readings), pancreatic tissues were collected for histological analysis for insulitis (H&E and the presence of T cells measured as CD3 and CD8 + cells) and the integrity of the islets (insulin and glucagon) and cell death.

Results: Interim results showed no differences between the groups in terms of IPGTT, ITT and insulitis at 13 weeks. Furthermore, hyperglycemia onset between the treatment and control groups was comparable. Immunohistochemical analysis is underway to assess insulitis severity, islet integrity, and cell death.

Conclusion: To date, 50mg/kg of Lip-1 supplemented diet does not significantly delay the onset of diabetes in NOD mice under the conditions tested. Despite this, given the role of oxidative stress in autoimmune diabetes, Lip-1's anti-ferroptotic properties may still confer therapeutic benefits by increased dosage in the diet, combining Lip-1 with other interventions or in conjunction with other anti-inflammatory agents. Future research is focused on examining the dose-response relationship and potential synergistic effects of Lip-1 with cell death inhibitors to more comprehensively evaluate its utility as a preventive strategy against T1D.

Abstracts

THE ROLE OF FERROPTOSIS IN GLUCOCORTICOID-INDUCED DIABETES

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Introduction: Glucocorticoids, such as dexamethasone, are widely employed in medical practice due to their versatile pharmacological profile. However, prolonged usage of these drugs has been linked to the development of glucocorticoid-induced diabetes, which manifests symptoms akin to type 2 diabetes. Interestingly, there is a link between glucocorticoids and their ability to sensitize cells to ferroptosis; a novel iron-dependent programmed cell death mechanism. Our research aims to elucidate the role of ferroptosis in the development of glucocorticoid-induced diabetes.

Methods: Mice were given vehicle or dexamethasone at 0.42 mg/kg/day in the drinking water for a total of 3 weeks in the presence or absence of ferroptosis inhibitor Liproxstatin-1 added to the diet at 50 mg/kg. Glucose- and insulin-tolerance tests were assessed at 2 and 2.5 weeks, respectively. Liver was collected at the end of the treatment and gene expression of key markers of hepatic glucose homeostasis and ferroptosis were assessed by qPCR.

Results: Dexamethasone induces insulin resistance and reduces body weight without deteriorating glucose tolerance. Remarkably, despite the lack of improvement in insulin resistance, liproxstatin-1 improves glucose tolerance in dexamethasone-treated mice. Our data shows that the genes Tsukushi (*Tsk*) and α-SMA (*Acta2*) are upregulated in response to dexamethasone, indicating hepatic failure and fibrosis, respectively. We also observed a disruption in the expression of ferroptotic genes involved in iron homeostasis regulation, without affecting other ferroptotic gene pathways like *Gpx4* or *Slc7a11*. Specifically, dexamethasone leads to an increase in the expression of Lipocalin-2 (*Lcn2*) and a decrease in the expression of Ferritin heavy chain 1 (Fth1).

Conclusion: Our data suggests that the hepatic iron homeostasis arm of the ferroptosis pathway is activated in response to prolonged usage of glucocorticoids. Furthermore, we observed that ferroptosis inhibition improves glucose tolerance in mice treated with glucocorticoids without improving insulin resistance, highlighting a distinct organ effect of ferroptosis inhibitor. Future research on the effect of ferroptosis on key organs regulating glucose homeostasis will provide more insight into the potential of targeting ferroptosis as a promising therapeutic approach for preventing or treating diabetes in patients undergoing glucocorticoid therapy.

Abstracts

KETONES: ESSENTIAL MODULATORS OF THE INFLAMMATORY RESPONSE?

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Introduction: Chronic low-grade inflammation is a pernicious and multifactorial component of type 2 diabetes (T2D). It arises from sources such as excess adiposity-induced cytokine release, leaky gut-driven endotoxemia, systemic oxidative stress, ectopic lipid deposition, and immune cell infiltration into metabolic organs—all of which converge to impair insulin signaling and β-cell function. Interestingly, β-hydroxybutyrate (βHB), the primary ketone body produced by the liver, not only serves as an alternative energy source for cells but also exhibits potent anti-inflammatory effects. βHB exerts its anti-inflammatory action through several pathways, including inhibition of the NLRP3 inflammasome and mediating epigenetic modifications. Given these newfound properties of βHB, as well as our recent finding that βHB supplementation robustly improves systemic inflammation in a mouse model of sepsis, we set out to determine if normal levels of βHB in the circulation are a requirement for proper orchestration of the inflammatory response.

Methods: To investigate the effects of reduced circulating ketone levels, we generated a line of mice with the potential to have the rate-limiting ketogenic enzyme, 3-hydroxy-3 methylglutaryl-CoA synthase 2 (HMGCS2), knocked out in an inducible manner. This was accomplished via the flox-Cre system, with Cre recombinase delivered through an adeno-associated virus under the control of the albumin promoter, achieving hepatocyte-specific deletion of HMGCS2. To induce a systemic inflammatory response, we injected 8-week-old C57BL/6 male wildtype (WT) and knockout (KO) mice with 10 mg/kg of lipopolysaccharides (LPS) and collected plasma and tissues after 24 hours.

Results: To our surprise, we found no significant differences in temperature, bodyweight reduction, or behaviour scores between WT and KO mice, nor any differences in transcript levels of inflammatory cytokines such as *Il-1b*, *Il-6*, or *Tnf-a* in the heart, liver, kidneys, or brain. Furthermore, we did not find any significant differences in plasma biomarkers of liver and kidney damage, such as alanine aminotransferase, aspartate aminotransferase, or blood urea nitrogen.

Conclusion: Overall, our results indicate that βHB is not essential for proper coordination of the inflammatory response, at least during LPS-induced inflammation. However, this does not diminish the potential therapeutic value of βHB. In fact, βHB supplementation remains a highly promising avenue of treatment for inflammatory disorders, and further research into the efficacy of ketone therapy in contexts like T2D is warranted.

Abstracts

C3G IMPROVES BETA CELL RESILIENCE UNDER STRESS

Kiersten Rajotte, Jeongbeen Kim, Reaghan Rajotte, Jeongsoo Kim, Fiza Rajput, Brett Wickware, Daxter Cornand, Illia Levin, Gina R. Rayat

Introduction: Previous research has demonstrated the beneficial effects of Cyanidin-3-O-glucoside (C3G), from Chinese bayberry, on pancreatic islets isolated from various species, including mice, newborn pigs, and humans. Building on these findings, the current study investigates the protective role of C3G in beta cell lines under various cellular stresses.

Methods: We utilized MIN6 and Beta-Tc-Tet cell lines, subjecting them to ER stress by thapsigargin, high glucose (to mimic diabetic conditions), sodium chloride (to create a hyperosmotic environment), and Triton X-100 (a detergent to induce cell lysis) in addition to oxidative stress (H2O2 and immunosuppressive drugs (Rapamycin). These conditions simulate the challenges encountered during islet transplantation.

Results: We hypothesized that C3G would mitigate the detrimental effects of these stressors, thereby enhancing cell viability. To test this, we conducted a viability assay, where cells were treated with C3G at concentrations of 0.5 µM and 1 µM. Viability and recovery were compared to untreated controls. Further validation was achieved through six-well experiments, assessing cell morphology, as well as eight-well chamber assays for immunofluorescence staining to identify molecules of interest.

Conclusion: Our findings indicate that C3G significantly improves beta cell resilience under stress, potentially reducing the number of viable islets required for successful transplantation. These results warrant further exploration of C3G as a therapeutic agent to enhance islet transplantation outcomes in diabetes treatment.

Keywords: cyanidin 3-O-glucoside (C3G), beta-Tc-tet, cell viability, islet transplantation

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Abstracts

SEQUENTIAL ISLET TRANSPLANTS FOR TYPE 1 DIABETES DO NOT CUMULATIVELY INCREASE HEPATIC PORTAL VENOUS PRESSURE

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Introduction: The future of islet transplantation (ITx) is rapidly advancing, with stem-cell based therapies demonstrating short term insulin independence when delivered into the hepatic portal vein. It is likely that multiple infusions will be needed to maintain insulin independence long term. We examined the effects of sequential ITx on portal pressures and how features of the transplanted preparation influence acute changes in portal pressure.

Methods: We include data from adults undergoing intraportal ITx at the University of Alberta Hospital between May 1999 to April 2023. We assessed, by pairwise comparison, acute changes in portal pressure at each ITx infusion and used linear mixed-effects models to: 1) compare sequential pre-infusion portal pressure with reference to pre-first ITx infusion and 2) assess the relationship between change in portal pressure and the transplant preparation parameters: packed cell volume (PCV), purity and islet equivalents per kilogram (IEQ/kg) as well as Standard Liver Volume (SLV). We include 299 adults (44% M) who received up to 5 (median 2 (IQR 2-3)) ITx infusions and a median total 16,791 IEQ/kg (IQR12,146, 21,686).

Results: Median purity across all infusions was 55% (IQR 45, 70) with a median PCV of 3ml (IQR 2.5, 4). The total time to final ITx was a median 320 days (47, 1,537). Portal pressure acutely increased similarly after each infusion by a median 2.0 mmHg [IQR 1.0-4.0] and was not sustained. PCV exhibited the strongest relationship with changes in portal venous pressure, with a 1 mmHg increase in portal pressure per 1 ml of PCV (Slope: 1.09 [95% CI 0.93,1.26]; p<0.001). In addition, purer preparations and larger liver volumes were associated with smaller increases in portal pressure. A combined model of these factors explained 29.4% of the differences in portal venous pressure changes observed between individuals.

Conclusion: A significant interaction between PCV and purity indicated that the effect of PCV on portal venous pressure was moderated at higher purities of the islet cell preparation. Insights from deceased-donor intraportal ITx can inform safe implementation of future stem-cell based therapies in people living with diabetes.

Abstracts

PATCH-SEQ REVEALS ALPHA CELL ELECTRICAL DYSFUNCTION LINKED TO ALTERATIONS IN IDENTITY, PARACRINE SIGNALING, METABOLISM, IMMUNE RESPONSE, AND MTOR ACTIVITY IN T1D

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Introduction: Pancreatic alpha (α) cells and their role in glucose regulation are gaining renewed interest especially given their potential role in metabolic disorders like diabetes. Considerable efforts have defined the cellular changes that occur in non-beta cells in type 2 diabetes. However, similar research in α cells in type 1 diabetes (T1D) has proven difficult, in part since islets from donors with T1D for research are scarce, and transcriptomic findings alone fail to capture cellular behavior. Thus, we combined single-cell functional and transcriptomic approaches, aiming to identify mechanisms behind α cell dysfunction and dysregulated glucagon secretion in T1D.

Methods: We compared α cells from human donors with T1D (n=596, 9 donors) to matched control donors without diabetes (n=248, 18 donors) using whole-cell patch-clamp electrophysiology followed by single-cell RNA-sequencing of the same cell (patch-seq). We linked identified transcriptomic variations to observed behavioral discrepancies and contrasted them in ND vs T1D by employing differential expression analyses (DEA), gene-set enrichment analyses (GSEA), Spearman's rank correlations, and machine learning (ML) modeling.

Results: Compared to ND, T1D α cells at 5 mM glucose show electrical behavior supportive of hyper-excitability and elevated glucagon secretion, inclusive of elevated exocytosis ($p<0.0001$, df=829), and Ca2+ ($p<0.0001$, df=734) and Na+ ($p<0.0001$, df=813) currents. ML modeling of electrical data corroborated these findings ($p<0.0001$, df= 842), suggesting an overall loss of canonical electrical function. Transcriptionally, GSEA revealed significant (FDR<0.05) enrichments of pathways involved in antigen presentation (MHC-I and proteasome components), paracrine signaling (SSTR2, FFAR1, GIPR), and metabolism (carbohydrate, pyruvate, and the citric acid cycle). Notably, markers of α cell identity had increased fold change (FC) expression in T1D, including ISL1 ($p<0.0001$, FC=3.4), NEUROD1 ($p<0.0001$, FC=3.6), FEV ($p<0.0001$, FC=2.6), and LOXL4 ($p<0.0001$, FC=7.5). Further, we discovered a potential suppression of mechanistic/mammalian target of rapamycin (mTOR) signaling, with downregulations of MTOR ($p=0.016$, FC=-1.62), RHEB ($p=0.003$, FC=-1.6), LAMTOR3 ($p=0.037$, FC=-1.5), LAMTOR5 ($p<0.0001$, FC=-1.5), RRAGC($p=0.011$, FC=-2), RRAGD ($p<0.0001$, FC=-2.2), and upregulation of mTOR inhibitor DEPTOR ($p=0.0006$, FC=2.5). Significant (p<0.05) correlations between expression and electrical behavior recaptured these markers; thus, indicating their potential role in α cell dysfunction in T1D.

Conclusion: Patch-seq identifies multiple mechanisms that may contribute to α cell secretory dysfunction in T1D, from broad alterations in behavior, to specific impairments in identity and signaling. We are currently validating our patch-seq findings at the protein level by imaging biopsy samples from the donors in this study and performing functional tests by modulating mTOR activity.

Abstracts

UNVEILING GAPS IN HESCβ-CELL FUNCTION: COMBINING SNIGLE-CELL ELECTROPHYSIOLOGY AND SCRNA-SEQ

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Introduction: T1D can be treated with islet transplantation, but limited donors necessitate new cell sources. hESCβs are an alternative; however, insufficient glucose-regulated excitability, sensing, and insulin release prevent hESCβs from being an alternative for cell-replacement therapy today.

Methods: We combine single-cell electrophysiology and scRNA-sequencing to compare younger hESCβs (stage-6 D23-33), older *in-vitro* aged hESCβs (stage-6 D47-57), and human primary β-cells (β-hPCs). Followed up by oxygen consumption measurement at the cluster/islet level and transmission electron microscopy.

Results: Younger hESCβs (96 cells, 8 preps) and older hESCβs (73 cells, 7 preps) displayed altered electrophysiological properties compared with β-hPCs (47 cells, 11 ND donors). Both younger and older hESCβs are significantly larger in cell-size, and show significantly more exocytosis (35.07, $p<0.0001$ and 17.12, $p=0.0148$) compared to β-hPCs. This is paralleled by larger voltage-activated Na+ and Ca2+ currents. scRNA-seq indicates that hESCβs have similar levels of *KCNJ11*, *NKX2.2*, and *FOXA2*. However, some genes, including *INS*, *IAPP*, and *NEUROD1*, increase in expression only after *in-vitro* culturing. Despite this, many key β-cell genes, including *MAFA* and *CHGB*, are still lowly expressed, and pathways related to protein synthesis, and mitochondrial function and efficiency are enriched in β-hPCs. These differences could explain why both older (5 preps) and younger (6 preps) hESCβs have a lower glucose stimulated oxygen consumption index (1.139 pmol/min·µg, $p = 0.0068$ and 1.058 pmol/min·µg, $p = 0.0003$) compared with primary human islets (1.058 pmol/min·µg). Finally, despite mitochondrial density being non-significant between young hESCβs (3 preps) and β-hPCs (3 ND donors), the mitochondrial population size is smaller in hESCβs than β-hPCs ($p < 0.0001$) indicating mitochondrial dysfunction visible by TEM.

Conclusion: Our study offers insights into hESCβs' functional maturity and likeness to β-hPCs. Machinery for exocytosis and excitability is functional by stage 6 of differentiation, but *in-vitro* aging of hESCβs increases key genes related to β-hPCs maturity and identity. Despite these increases in genes, further refinement to differentiation protocols are still needed to achieve proper metabolic, glucose sensing, and insulin release in hESCβs.

Abstracts

NANOFIBROUS BIOABSORBABLE FUNCTIONALIZED SCAFFOLDS SUPPORT THE SUBCUTANEOUS ISLET ENGRAFTMENT AND FUNCTION IN MICE

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Introduction: The subcutaneous (SQ) space is an appealing transplant site for human, xenogeneic, and stem cell-derived islets due to its minimally invasive nature, ability to accommodate large transplant volumes, retrievability and the potential for monitoring graft function. Pre-conditioning the SQ space before islet infusion is a prerequisite due to the tissue's innate hypervascularity, but chronic foreign body reaction as a result of permanent devices and scaffolds remains a challenge. Hence, we hypothesize that the use of nanofibrous bioabsorbable functionalized scaffolds will overcome these challenges and create a highly vascularized niche to support islet engraftment and function.

Methods: Electrospun poly (lactic-co-glycolic acid) (PLGA) and gelatin (PLGA+G) scaffolds were fabricated and functionalized with vascular endothelial growth factor (VEGF; V) and laminin (L) peptide mimics, wrapped around a nylon catheter and implanted into the ventral SQ space of B6 Rag mice (n=4, 2M/2F). Catheter only (DL), PLGA, PLGA+G and kidney capsule (KC) were used as control. Histological assessment using H&E, lectin, CD31 and SMA staining was performed 4 weeks post-implant to evaluate vascularization; functional assessment was performed by transplanting 3000 neonatal porcine islet (NPI), 550 mouse islets, or 1500 human islets into streptozotocin-induced diabetic mice within the SQ scaffolds 4 weeks post-implant, or under KC. Non-fasting blood glucose, intraperitoneal glucose tolerance tests, and serum insulin were measured to evaluate graft efficacy.

Results: Scanning electron micrographs confirmed the fibrous architecture of the PLGA+G+V+L scaffold. Fluorescent micrographs validated the successful tagging of VEGF and laminin peptides within the scaffold. The PLGA+G+V+L group showed improved vascularization with higher lectin + and CD31 + cells (*$p<0.05$) 4 weeks post-implantation as compared to controls. Additionally, the intraluminal presence of lectin + and SMA + cells within the peri-scaffold matrix confirmed the formation of mature and patent blood vessels. Recipients of PLGA+G+V+L scaffolds with NPI resulted in achieving superior euglycemia rates (*$p<0.05$), reduced time to euglycemia (*$p<0.05$) and greater stimulated serum porcine insulin secretion (*$p<0.05$), compared to controls. Syngeneic mouse islet transplants into PLGA+G+V+L showed comparable function with DL and KC groups. In contrast, recipients of PLGA+G+V+L scaffolds transplanted with human islets exhibited partial graft function compared to the KC groups.

Conclusion: Our study demonstrates that functionalized PLGA+G+V+L scaffold facilitates superior vascularization, faster engraftment and function of NPIs in the SQ space. Furthermore, the PLGA+G+V+L scaffold supports comparable function of syngeneic mouse islet grafts and partial human islet grafts function compared to the KC. Our prevascularized SQ scaffold transplantation modality site may provide a clinically relevant and alternative site for beta cell replacement therapies.

Abstracts

SEMAGLUTIDE REDUCES CARDIOMYOCYTE SIZE AND CARDIAC MASS IN LEAN AND OBESE MICE

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Introduction: The significant reduction in body weight (BW) induced by glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as semaglutide, has led to recent clinical trials demonstrating benefit in certain forms of cardiovascular disease (CVD). While these findings are promising for CV patients, one side-effect of GLP-1RAs use is the loss of skeletal muscle (lean BW) mass. While it is likely that the metabolic benefits from weight loss may outweigh modest sarcopenia, this loss of lean BW could potentially lead to exercise intolerance that may reduce the quality of life in individuals at risk for or with heart failure. Given this, intense research efforts are ongoing to try to understand how GLP-1RAs induce loss of skeletal muscle mass. However, little attention has been given to the potential that other types of muscle, such as cardiac muscle, may also be lost in response to GLP-1RAs.

Methods: To address this, we induced obesity by feeding male mice a high fat, high sucrose diet for 10 weeks. This protocol caused an average BW gain of 18.6 ± 1.2g, and was intentionally chosen to not induce type 2 diabetes, cardiac hypertrophy or any cardiac dysfunction to mimic the population of individuals using GLP1-RAs for weight loss/management, in the absence of CVD and/or the metabolic syndrome. Following this, mice were switched to a regular chow diet to simulate the reduced caloric intake employed in the STEP1 clinical trial. Mice were then administered 120 µg/kg/day semaglutide for 21 days.

Results: As expected, mice treated with semaglutide lost ~30% of their BW and ~65% of their fat mass compared to vehicle-treated mice. No changes in systolic or diastolic function were observed in these 2 groups as assessed by echocardiography. However, semaglutide induced a significant reduction in echocardiographic assessed LV mass (16.51 %, decrease, $p<0.0001$), overall heart weight (12.84% decrease, $p<0.0006$), and histologic assessed cardiomyocyte area (30.37% decrease, $p<0.0001$. Additionally, this reduced cardiac mass occurred in the absence of any changes in transcript levels of gene products that are known to regulate fibrosis or atrophy. Lastly, although lean mice treated with semaglutide displayed no overt changes in BW, semaglutide treatment did cause an 8.2% loss in skeletal muscle mass over 3 weeks. This loss in lean BW is also consistent with the loss of lean mass observed in previous reports using obese mice treated with semaglutide. Consistent with semaglutide treatment of obese mice, semaglutide-treated lean mice showed no changes in systolic function but did show a decrease in LV mass and overall heart weight, as well as a decrease in cardiomyocyte area, in the absence of changes in fibrosis or atrophy gene transcripts. Together these data indicate that the reduction in cardiac size induced by semaglutide occurs independent of weight loss.

Conclusion: Overall, these data show that semaglutide has a direct effect on the cardiomyocyte and induces a reduction in cardiac mass and suggest that like skeletal muscle, the same effect may be observed in hearts of individuals taking semaglutide. This potential to alter cardiac structure in settings that may be impacted by reduced cardiac mass is important given the growing use, and guideline-endorsement, of GLP-1RAs in patients with and without CVD. Therefore, to confirm this in patients administered GLP-1RAs, we suggest that cardiac structure and function be carefully evaluated in previous and ongoing clinical studies.

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ABSTRACTS

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Abstracts

DIRECT PROTEIN KINASE A ACTIVATION, BUT NOT GLUCAGON *PER SE*, IN THE NUCLEUS OF THE SOLITARY TRACT DECREASES HEPATIC TRIGLYCERIDE SECRETION IN A MODEL OF TYPE 2 DIABETES

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Introduction: Glucagon has extensive roles in lipid metabolism via direct actions on peripheral organs, including the liver and adipose tissue. Glucagon also modulates lipid metabolism via its actions in the brain. Glucagon in the nucleus of the solitary tract (NTS), an important brain region involved in whole-body metabolism, decreases hepatic triglyceride-rich very low-density lipoprotein (VLDL-TG) secretion in healthy rats. This lipid-lowering effect of NTS glucagon requires the activation of protein kinase A (PKA) within the NTS. Here, we aimed to assess if the effects of NTS glucagon lower the hypersecretion of hepatic VLDL-TG in diabetic rats, which exhibit elevated VLDL-TG secretion.

Methods: Male Sprague-Dawley rats underwent stereotaxic NTS bilateral cannulation and vascular catheterizations to enable simultaneous NTS infusions, blood sampling, and IV injections. Experimental type 2 diabetes (T2D) was induced using combination injections of nicotinamide and streptozotocin coupled with high-fat diet-feeding for 7 days as previously described and verified with daily monitoring of blood glucose levels. Hepatic VLDL-TG secretion was measured in 10h-fasted rats after intravenous injection of poloxamer, a lipoprotein lipase inhibitor, with concurrent NTS infusions of vehicle, glucagon, or PKA activator (Sp-cAMPS).

Results: In T2D rats, NTS glucagon failed to lower VLDL-TG secretion compared to NTS vehicle control. However, direct activation of PKA selectively in the NTS with an infusion of Sp-cAMPS lowered VLDL-TG secretion in hypertriglyceridemic T2D rats. This occurred independent of differences in plasma glucose, insulin, and glucagon, but was associated with lowered plasma levels of free fatty acids.

Conclusion: We provide evidence that although direct glucagon action within the NTS may be impaired in metabolic disease states such as T2D, activation of its downstream signalling targets within the NTS remains intact and is involved in the regulation of lipid metabolism. Understanding the mechanisms of glucagon action in the NTS may help in the development of therapeutics to treat aberrant blood lipid levels present in metabolic disease states. Our future work will assess the role of the hepatic vagus nerve in the transmission of NTS glucagon-PKA signalling to the liver to regulate VLDL-TG secretion. Additionally, IHC and RNAScope techniques will be utilized to further characterize glucagon receptor localization in the NTS.

Abstracts

BAICALEIN AMELIORATES DIABETIC CARDIOMYOPATHY THROUGH INHIBITING ALOX15

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Introduction: The pathogenesis and clinical features of diabetic cardiomyopathy have been well-studied in the past decade, but effective approaches to prevent and treat this disease are limited. Oxidative stress is a common observation in diabetic hearts. ALOX15-mediated lipid peroxidation could increase oxidative stress and drive cardiomyocytes to death. Deletion of ALOX15 could reduce cardiac inflammation, oxidative stress and improve cardiac function in diabetic mice. Baicalein as a natural antioxidant and an inhibitor of ALOX15 has been proven to have cardioprotective effect, but its therapeutical effect on diabetic cardiomyopathy remains to be explored. Therefore, the aim of this study was to investigate whether baicalein can combat diabetic cardiomyopathy through inhibition of ALOX15.

Methods: 10-week-old male C57BL/6J mice were fed either 60% high fat diet or chow diet (D12492i) for 16 weeks and was given a single dose of STZ (75mg/kg) to induce T2D. Mice maintained on standard chow were used as lean controls. After 8 weeks of high fat diet feeding, mice were grouped into T2D-vc group and baicalein-treated group. Mice in baicalein-treated group were given 200 mg/kg/d baicalein by oral gavage, while mice in T2D-vc group were given placebo. Ultrasound echocardiography and EchoMRI were sued for cardiac function assessment and body composition analysis, respectively. At study completion, mice were euthanized and hearts were extracted for further studies.

Results: There's no change of body weight and body composition between T2D-vc group and baicalein-treated group. However, the cardiac function assessment results showed an increased level of E/A ratio and a decreased level of E/e' ratio in baicalein-treated group compared with those of T2D-vc group. The pre-treatment and post-treatment analysis of cardiac function showed improved diastolic function after 4 weeks treatment of baicalein. Baicalein significantly decreased ALOX15 expression in diabetic hearts. Meanwhile, to investigate the anti-oxidative stress of baicalein in cardiomyocytes, H9c2 cells were used for ROS, lipid peroxidation, 12-HETE and 15-HETE level measurements. Briefly, cells were treated with 0.2 mM palmitate acid with or without baicalein for 24 hours. Results showed a decrease of ROS level and lipid peroxidation in H9c2 cells when treated with baicalein. 12-HETE and 15-HETE which are products of ALOX15 also decreased in H9c2 cells when treated with baicalein.

Conclusion: The results of our *in vivo* study suggested that baicalein could improve cardiac function in T2D mice through inhibiting ALOX15. Our *in vitro* study suggested the anti-oxidative stress effect of baicalein on cardiomyocytes. However, the sample size is small for this study, and further studies are needed to elucidate the potential therapeutical effect of baicalein on diabetic cardiomyopathy.

Abstracts

CHARACTERIZING THE ROLE OF IDENTITY FACTORS ON α-CELL FUNCTION IN DIABETES

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Introduction: Type 1 diabetes (T1D) and type 2 diabetes (T2D) are associated with altered glucagon secretion from pancreatic α cells, however exact cellular mechanisms underlying this are limited. Transcription factor (TF) expression that are key for lineage and identity (*ARX, NEUROD1, ISL1, NKX2-2*, etc.) differ in subpopulations of α-cells from donors with diabetes when compared to those without diabetes, and correlates to the impairment of ion channel function and glucagon granule exocytosis. Thus, a loss of α cell identity may contribute to inappropriate glucagon secretion in diabetes.

Methods: In this study, we explore whether genetic loss of α cell identity factors results in impaired α cell electrical phenotype in α cells from human organ donors and from C57/bl6 mice by whole-cell patch clamp following knockdown of key TFs to measure: ***1)*** exocytosis by recording capacitance of the cell (readout for the change in cell size); ***2)*** calcium channel activity; and ***3)*** sodium channel activity. Finally, I will measure: ***4)*** glucose-dependent (1, 2.8, 10, 16.7 mM) action potential firing in the perforated patch configuration. Calcium channel isoform specific inhibitors will be used to measure distinct contributions from P/Q-type calcium channels (α cell phenotype) and L-type calcium channels (β -cell type phenotype). Since voltage dependent sodium channel inactivation in α cells shifts to a β-cell-like phenotype in diabetes, the effect of TFs knockdown on sodium channel inactivation will be measured.

Results: Current results show that ARX knock down using siRNA in dispersed murine islets trends towards decreased average exocytosis from single α cells. Total change in capacitance measured during ten depolarization steps from -70 to 0 mV averaged 42.97 pA/pF in ARX knock down α cells compared to 31.22 pA/pF in siRNA scramble control α cells ($p = 0.5161$, $n = 9$ and 14 cells from 4 mice). Average voltage dependent sodium channel half current inactivation voltages (V50) fitted using a Boltzmann curve, shifted from -56.24 mV in siRNA scramble cells compared to -52.14 mV in ARX knockdown α cells ($n = 8$ and 5 cells from 4 mice) suggesting that the sodium channel inactivation curves shifts left in ARX knockdown murine α cells.

Conclusion: Dysfunction of α cells is essential for the development of diabetes and decreases the safety of current blood sugar management options such as insulin. This work aims to better understand α cell physiology in diabetes. Current preliminary data suggest knockdown of essential α cell maturation factor ARX changes functional parameters such as decreased exocytosis and decreased voltage dependent sodium channel inactivation in murine α cells, trending towards a β cell-like phenotype. However, ongoing experiments will further clarify the roles that identity factors play in α-cell electrical phenotypes.

Abstracts

NEUTROPHIL-TARGETING ANTI-LY6G ANTIBODY PRESERVE MOUSE PANCREATIC ISLET GRAFT FUNCTION IN THE SUBCUTANEOUS SPACE

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Introduction: Pancreatic islet transplantation represents a proven strategy to restore physiologic glycemic homeostasis in patients with T1D who suffer from impaired hypoglycemia awareness. However, limiting factors prevent islet transplantation from replacing insulin therapy, including donor shortage, lifelong immunosuppression, and procedural risks. The prevascularization of the subcutaneous (SC) space preconditions this transplant site into a sustainable microenvironment for islet survival. However, immune modulation is still required. Previous studies have identified that neutrophil recruitment mediates islet transplant rejection. Therefore, we hypothesize that using a neutrophil-targeting anti-Ly6G antibody (Ab) for prevascularized SC islet transplantation will increase engraftment efficacy by minimizing inflammation associated with early graft failure.

Methods: To validate the efficacy of anti-Ly6G antibody therapy to improve islet engraftment and function within a prevascularized SC space, 500 BALB/c syngeneic islets were transplanted into streptozotocin-induced (180 mg/kg, i.p) diabetic mice. Anti-Ly6G Ab (40 mg/mouse) was administrated i.p. at days -3 to +1 peritransplant. Islet transplant groups included: 1) renal subcapsular (internal control) n=4, 2) anti-Ly6G SC n=7, and 3) IgG2a SC (isotype control) n=6, 4) SC n=5 (internal control). Blood was collected for flow cytometry analysis (CD11b+ Ly6G+) to confirm neutrophil depletion. 50 days post-transplant, the metabolic capacity of the graft was assessed by intraperitoneal glucose tolerance test (IPGTT). A recovery graft explantation was performed to assess the return to hyperglycemia to ensure graft-dependent euglycemia. Harvested grafts were histologically assessed for innate immune infiltrate.

Results: Flow cytometry confirmed the impact of the anti-Ly6G Ab, revealing a notable reduction in the number of circulating neutrophils mean 5.19 SD 1.473 (day +1) compared to baseline levels mean 42.65 SD 6.764. Transplant efficacy data demonstrates that anti-Ly6G Ab treatment effectively facilitates early islet engraftment.

Conclusion: The present study demonstrates that anti-Ly6G Ab therapy is a promising modality to augment *in vivo* islet functional potency within the SC space. This transplantation approach holds the potential to decrease post-transplant inflammatory responses, thereby improving islet survival and expediting graft function.

Abstracts

SYNERGISTIC EFFECTS OF METFORMIN AND FIBER SUPPLEMENTATION ON INSULIN RESISTANCE IN ADOLESCENTS WITH SEVERE OBESITY

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Background: Adolescents with obesity are at an increased risk of developing insulin resistance (IR) and type 2 diabetes mellitus (T2DM), leading to long-term, irreversible health complications in adulthood. Traditional treatments, such as diet and exercise, have demonstrated limited success in managing these conditions. (1–4) Metformin and dietary fiber have each shown promise in enhancing insulin function and promoting weight loss, partially through their impact on the gut microbiome. (5-7). However, just a few studies have studied the combination of both, especially in pediatrics. This study aims to investigate the metabolic effects of metformin and dietary fiber, alone and in combination, on reducing IR and improving glucose tolerance in this high-risk population. Investigating the combined effects of metformin and dietary fiber is crucial, as their potential synergistic impact on the gut microbiome and insulin sensitivity may provide a more effective approach to reducing IR and improving glucose tolerance than either intervention alone.

Methods: This is a preliminary baseline analysis of a double-blind, randomized controlled trial with a three-arm parallel design. We are recruiting adolescents (12-18 years) with obesity (BMI > 95th percentile for age/sex), IR (Homeostatic Model Assessment for Insulin Resistance [HOMA-IR] > 3.16), and family history of T2DM. Participants receive either MET (1700 mg/day), fiber (35 g/day), or a combination of both over 12 months. Data collection occurs at baseline, 1, 3, 6, 9, and 12 months. Participants undergo an oral glucose tolerance test (OGTT), and HOMA-IR and the quantitative insulin sensitivity check index (QUICKI) are calculated. Additionally, lipid profile and C-reactive protein (CRP) are measured. Anthropometrics are collected by trained researchers and body composition is assessed through air displacement plethysmography (fat mass and fat-free mass). Continuous variables were described with medians and interquartile range (IQR). Spearman correlations were performed between body composition and anthropometric data with glucose/insulin indices and inflammation.

Results: To date, we enrolled 23 participants (52% males) with ages 15.21 (IQR: 13.41-16.28) years old and, BMI z-score of 3.28 (IQR: 2.85-4.14). Most patients (95.6%, n=22) were in mid-late pubertal stage. The median HOMA-IR was 6.42 (IQR: 4.58-8.52), QUICKI 0.29 (IQR: 0.28-0.31), and glycated hemoglobin 5.4% (IQR: 5.3%-5.5%). No participants had a QUICKI above the reference range (>0.36) or glycated hemoglobin above the reference threshold (>6.0%). Fasting glucose median was 90.09 mg/dL (IQR: 86.48-93.96), and insulin 27.93 µU/mL (IQR: 20.59-36.87). Four participants (17.4%) presented with high low-density lipoprotein (LDL <2.84 mmol/L) and almost half (47.8%, n=11) with inflammation (CRP>3.0 mg/L). CRP was positively correlated with waist circumference (r=0.46, p=0.03), BMI (r=0.44, p=0.04), percent fat (r=0.55, p=0.01), and fat mass (r=0.44, p=0.03). We did not find correlations between QUICKI and HOMA-IR with body composition and anthropometric measures, or CRP.

Conclusion: Preliminary results from this ongoing study indicate that adolescents with severe obesity and insulin resistance have metabolic and inflammatory alterations. Measures of adiposity were associated with inflammation, including body fat, waist circumference, and BMI, with body composition presenting the strongest correlation. More robust analyses with additional health markers will be performed when the study is completed. These findings emphasize the importance of alternative treatments to improve insulin sensitivity and inflammation in adolescents with obesity and IR.

Abstracts

HETEROGENOUS GLYCINE-EVOKED CURRENTS IN HUMAN β CELLS

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Introduction: Pancreatic β cells are transcriptionally and functionally heterogeneous, but their ion channel heterogeneity has not yet been greatly explored. Glycine receptors (GlyRs) are ligand-gated chloride channels present in human β cells, with impaired activity in type 2 diabetes (T2D). Previous work demonstrated that β cell calcium responses to GlyR activation are heterogeneous, either increasing, decreasing, or having no effect on β cell calcium responses. The reason behind this heterogeneity and its significance for β cell function is unknown, but could be related to variation in GlyR activity. To uncover GlyR current heterogeneity and molecules involved with GlyR signaling, we analyzed gene transcription correlates of β cell glycine-evoked currents with the Patch-Seq technique.

Methods: Glycine-mediated currents were measured in human β cells using whole-cell patch- clamp, by applying 300 µM glycine ± 10 µM strychnine (a GlyR antagonist). Immediately after the electrophysiological recording, the cells were collected and stored at -80°C, until the single- cell sequencing of their whole transcriptome was performed using a modified SmartSeq-3 protocol. Libraries were sequenced with the NextSeq 500 Sequencing System (Illumina). Spearman Rank Correlations were performed between current amplitude and expression level for genes detected in at least 50% of cells.

Results: We find that there is a wide variance of glycine-evoked current amplitudes between β cells. These currents are significantly correlated or anticorrelated to the expression of 99 different transcripts. Among them are several genes known to influence β cell function, including enzymes (Carboxypeptidase E - CPE, Stearoyl-CoA desaturase - SCD, ATPase inhibitory factor 1 - *ATPIF1*), membrane receptors (Calcium sensing receptor - *CASR*, Renin receptor - *ATP6AP2*, Adhesion GPCR-G1/GPCR56 - *ADGRG1*), RNA binding proteins (Heterogeneous nuclear ribonucleoprotein K - *HNRNPK*, Cold inducible binding protein - *CIRBP*, Polypyrimidine tract- binding protein 1 - *PTBP1*), the TASK-1 ion channel (*KCNK3*), and the Eukaryotic translation initiation factor 4E binding protein 1 translation inhibitor - *EIF4EBP1*.

Conclusion: Heterogenous responses of β cells to glycine could be partly explained by variation in GlyR activity. We define a previously unknown set of genes that are potentially related to GlyR function and could be involved in GlyR downregulation in T2D.

Abstracts

SIRT2 DELETION SUPPRESSES GLYCOLYSIS THROUGH HYPERACETYLATION OF GLYCOLYTIC ENZYMES

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Introduction: Myocardial glycolysis increases in hypertrophic and failing hearts. Hyperacetylation of metabolic enzymes, including glycolytic enzymes, also occurs in the diabetes and failing heart. Variable effects of acetylation on the activities of glycolytic enzymes have been reported. However, the overall impact of acetylation on the glycolytic flux and the extent to which hyperacetylation contributes to altered glycolytic rates remain poorly understood. Additionally, the acetyltransferases and sirtuins regulating the acetylation status of cardiac glycolytic enzymes is unclear. The aim of this study was to determine whether changes in the acetylation of glycolytic enzymes and the activity of the cytosolic deacetylase SIRT2 regulates cardiac glycolysis.

Methods: Glycolysis rates were directly measured in rat heart-derived H9c2 cardiomyocytes perfused with 5 mM [5-^{3}H]glucose, 0.8 mM palmitate, and 4% bovine serum albumin. Before these metabolic measurements, H9c2 cells were treated with either a SIRT2 inhibitor (10 µM AGK2) or a vehicle for 24 hours. In separate experiments, SIRT2 was also knocked down in H9c2 cells using siRNA, followed by glycolysis rate determinations. The impact of SIRT2 inhibition or SIRT2 knockdown on overall or glycolytic enzyme acetylation was also assessed.

Results: SIRT2 inhibition markedly decreased glycolysis rates in H9c2 cells compared to vehicle-treated cells (524±108 vs 2631±372 nmol·g dry wt^{-1}·min^{-1}, $p<0.05$). Similarly, SIRT2 knockdown resulted in a significant reduction in glycolysis rates compared to scrambled siRNA-treated H9c2 cells (745±31 vs 1659±168 nmol·g dry wt^{-1}·min^{-1}, $p<0.05$). The decrease in SIRT2 was accompanied by an increase in the acetylation status of the glycolytic enzymes including glyceraldehyde phosphate dehydrogenase (GPDH), phosphoglycerate mutase (PGAM2). Moreover, a trend towards increased phosphofructokinase (PFK) acetylation was also observed in SIRT2 knockdown H9c2 cells compared to scrambled siRNA-treated cells.

Conclusion: SIRT2 inhibition or deletion in H9c2 cells significantly decreases glycolysis rates. SIRT2 deletion was also associated with an increased acetylation of glycolytic enzymes. SIRT2 may therefore contribute to the increased glycolysis seen in heart failure.

Abstracts

REGULATION OF PANCREATIC ALPHA CELL GLUCAGON-LIKE PEPTIDE-1

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Introduction: Glucagon-Like Peptide-1 (GLP-1) is released from intestinal endocrine cells in response to dietary glucose. GLP-1 enhances insulin production and secretion from pancreatic beta cells, and GLP-1R signalling supports beta cell health during metabolic stress. In certain conditions, GLP-1 is produced by pancreatic alpha cells. Alpha cell GLP-1 acts on neighbouring beta cells to improve their function and survival. We aim to identify the molecular mechanism that promotes GLP-1 production in the pancreas so that we may explore this pathway in future drug discovery.

Methods: Alpha-TC1/9 cells were cultured in control conditions and proinflammatory conditions (interleukin-6 [IL-6], stromal-derived factor-1 [SDF-1]) for 72 hours to monitor changes in proglucagon processing. Since prohormone convertase 1/3 (PC1/3) is required for GLP-1 processing, we focused on changes in its gene expression and enzymatic function. Gene expression was evaluated with qPCR, PC1/3 function was assessed with a fluorogenic substrate (pERTKR-AMC), and GLP-1 content was measured by hormone ELISA. Similar assays were conducted in primary human alpha cells from the Alberta Clinical Islet Distribution program and uAlberta IsletCore. Finally, the arrangement of hormone granules in alpha-TC1/9 cells and dispersed human islets was assessed by brightfield and confocal microscopy.

Results: 72hrs incubation with IL-6 or SDF-1 alters the proglucagon processing environment to enhance GLP-1 production. This is reflected by significant increases in *PCSK1* (the PC1/3 gene) expression, PC1/3 enzymatic activity, and GLP-1 production. Since IL-6 and SDF-1 share common intracellular signalling pathways, we focused on Akt1 signalling downstream of both cytokines as a potential modulator of PCSK1 transcription. Exposure to the small molecule Akt1 activator SC-79 increases PC1/3 function and GLP-1 production in alpha-TC1/9 cells. SC-79 also enhances GLP-1 production in human islets *in vitro*. A subpopulation of human alpha cells maintained in both vehicle conditions and SC-79 had significant levels of mature GLP-1 in their secretory granules. Furthermore, these secretory granules were completely distinct from glucagon-containing vesicles with no evidence of hormone colocalization.

Conclusion: The proinflammatory cytokines IL-6 and SDF-1 are strong potentiators of *PCSK1* and PC1/3 expression in alpha cells, and cytokine-mediated GLP-1 production depends on Akt1 signalling. While we have not yet resolved the details of proglucagon processing, hormone granule organization suggests that GLP-1 and glucagon are differentially sorted in alpha cells and may belong to different secretory pathways.

Keywords: alpha cell, GLP-1, proglucagon, hormone processing

Abstracts

VISUALIZING MEDICAL TRAUMA BY AGE AT DIAGNOSIS IN PEOPLE LIVING WITH TYPE 1 DIABETES USING EPISTEMIC NETWORK ANALYSIS

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Introduction: Medical trauma plays an important role in how people living with type 1 diabetes (T1D) experience and interact with healthcare services. The age at which an individual is diagnosed with T1D impacts patient perceptions of care. The aim of this study was to assess how age at diagnosis and previous medical trauma impact how people living with T1D perceive and seek future care.

Methods: We conducted a secondary analysis using semi-structured interviews with 41 individuals recruited in the Reshape T1D study who are living with T1D. Participants were included if they were living with T1D for three or more years, ≥ 18 years of age, and Alberta residents. Individuals were stratified by age at diagnosis (childhood < 18 years & adulthood ≥ 18 years). Using the principles of quantitative ethnography, interview data was modelled using epistemic network analysis (ENA), a visualization technique for assessing how qualitative codes co-occur together across participant interview data.

Results: More individuals were diagnosed in childhood (n=28) compared to adulthood (n=13). ENA revealed that there are statistically significant differences in participant discourse regarding the manifestation of codes for medical trauma between childhood and adulthood T1D diagnosis mean networks (U=60.0, p=0.0004, r=0.6703). Both groups faced challenges in healthcare access, powerlessness, and feeling unheard. The childhood diagnosis group attributed medical trauma with avoidance behaviours in recounting healthcare experiences related to initial diagnosis and the stress of going through hospitalization. The adulthood diagnosis group attributes experiences of medical trauma to misdiagnoses during early adult-onset T1D and the frustrations associated with feeling unheard in the initial stages of T1D.

Conclusion: We present a novel approach for analyzing qualitative semi-structured patient interview data. Using ENA, we demonstrate that the age at T1D diagnosis significantly impacts the co- occurrence of codes related to medical trauma in clinical settings. By mapping the relationships between codes, we illustrate how medical trauma varies with age at diagnosis in individuals with T1D, highlighting the important insights on the role of medical trauma in informing ongoing clinical quality improvement and health services provision in Alberta.

Abstracts

HIGH FRUCTOSE MEDIATED PREDIABETES DOES NOT INDUCE LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN MALE MICE

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Introduction: Several dietary models of obesity/type 2 diabetes (T2D) are available though they have inconsistent actions to induce cardiac dysfunction. Of importance, the increase dietary consumption of added sugars, such as fructose, has been linked to the development of insulin resistance and T2D; however, it remains elusive whether this contributes to cardiac dysfunction in mice. Therefore, the aim of our study was to understand whether high-fructose diets can induce diastolic dysfunction and diabetic cardiomyopathy (DbCM) which is often observed with the high-fat diet (HFD; 60% kcal from lard; Research Diets D12492) and low-dose streptozotocin (STZ; 75 mg/kg) model of T2D.

Methods: 10-week-old male C57BL/6J mice were fed either a high-fructose diet (HFruc; 60% kcal from fructose; Research Diets D23091504), a high fat (40% kcal from palm oil), high fructose (20% kcal from fructose) diet (40/20; Research Diets D091100310) or subjected to HFD/STZ-mediated T2D for 16 weeks. Mice maintained on standard chow were used as lean controls. In vivo cardiac function and body composition analysis was assessed using ultrasound echocardiography and EchoMRI, respectively, prior to and following diet administration. At study completion, mice were euthanized and had their hearts extracted and snap frozen in liquid nitrogen for molecular studies. A separate cohort of mice had their hearts fixed in paraformaldehyde at euthanasia for histological assessment.

Results: Mice maintained on the 40/20 diet or subjected to the HFD/STZ model of T2D had increased body weight, adiposity and worsened glucose tolerance compared to both lean and HFruc-fed counterparts. With regards to cardiac function, we observed no significant differences in systolic function (i.e. left ventricular ejection fraction and left ventricular fractional shortening) between all 4 treatment groups. Importantly, however, both the 40/20 and HFruc diets failed to induce diastolic dysfunction, as indicated by a normal e'/a'; (1.51 ± 0.04 and 1.52 ± 0.09 vs. 1.18 ± 0.02) and E/e'; ratio (26.79 ± 1.45 and 26.27 ± 1.28 vs. 29.30 ± 1.52) versus HFD/STZ mice. These overt differences in diastolic function could not be fully explained by perturbations in cardiac energetics. Indeed, myocardial glucose oxidation was similarly impaired in both the 40/20 and HFD/STZ mice as determined by an increase in cardiac pyruvate dehydrogenase (PDH) phosphorylation and PDH kinase expression. Furthermore, 40/20 and HFD/STZ animals had increased cardiac expression of key enzymatic regulators of lipolysis and fatty acid oxidation.

Conclusion: As both the 40/20 and HFruc diets failed to induce diastolic dysfunction, our findings suggest that high-fructose-based diets may not be appropriate models for DbCM in mice. In our future studies, it will be imperative to also elucidate the molecular differences between the fructose-fed and HFD/STZ models to better understand which contributing mechanisms are imperative towards the development of diastolic dysfunction in DbCM.

Abstracts

STATIC SUSPENSION VERSUS DYNAMIC SUSPENSION CULTURE SYSTEMS FOR NEONATAL PORCINE ISLET (NPI) DIFFERENTIATION

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Introduction: Cell replacement therapy is an advancing field for the treatment of type 1 diabetes mellitus. While whole pancreas transplantation and islet transplantation have shown promise, they are limited by donor scarcity. Induced pluripotent stem cell-generated pancreatic islets face challenges of off-target effects and delayed beta cell maturation. Neonatal porcine islets (NPIs) emerge as a promising xenotransplantation alternative, offering controlled transplantation quantities, safe terminal differentiation, and full functionality post-transplantation.

Methods: This study compared conventional static suspension culture with vertical wheel bioreactors for culturing day 3 NPIs. We assessed aggregate size, viability, beta cell differentiation, and function in both culture systems. The vertical wheel bioreactor was evaluated for its potential to optimize NPI production and enhance beta cell characteristics.

Results: Preliminary results indicate that vertical wheel bioreactor cultures yielded smaller, more viable aggregates compared to static systems. These findings suggest that dynamic suspension culture may offer advantages in NPI production.

Conclusion: Ongoing research aims to further elucidate the effects of vertical wheel bioreactors on beta cell differentiation, survival, and function. The ultimate goal is to develop a well-controlled manufacturing process for NPIs. This research contributes to the ongoing efforts to optimize isolation, functionality, and transplantation outcomes of NPIs, potentially advancing cell replacement therapy for type 1 diabetes.

Abstracts

CHEMICAL DEVELOPMENT OF A NEW CLASS OF SUCCINYL COA:3-KETOACID COA TRANSFERASE (SCOT) INHIBITORS WITH REDUCED BRAIN PERMEABILITY THAT PROMOTE GLUCOSE-LOWERING IN OBESITY

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Introduction: Despite significant advances in treatment options for type 2 diabetes (T2D), achieving optimal blood sugar control in patients with T2D remains challenging, necessitating the development of new effective drugs with a novel mechanism of action. Previous research has demonstrated that attenuating ketone oxidation can enhance glycemia in obese mice. Pharmacological inhibition of ketone metabolism can be achieved with the administration of diphenylbutylpiperidines (DPBPs) class such as pimozide. Canonically act as antagonists of the dopamine 2 receptor (DRD2), these drugs were later identified through molecular modeling studies as inhibitors of succinyl CoA:3-ketoacid CoA transferase (SCOT), the rate-limiting enzyme of ketone oxidation. Although DPBPs have potential therapeutic benefits in reducing hyperglycemia in obese mice, their clinical utility is compromised by central nervous system (CNS) side effects and their ability to cross the blood-brain barrier (BBB), potentially limiting cerebral access to ketones, a vital energy substrate for the brain. Here, we propose a new chemical entity based on the structure of the DPBPs, but with characteristics that prevent it from crossing the BBB, mitigating potential systemic SCOT inhibition concerns.

Methods: Following computer modeling, a new compound, PASI-51, was synthesized and evaluated. The compound was tested for its binding affinity to SCOT, activity against DRD2, and permeability across the BBB using various in vitro assays. Its efficacy was further assessed in obese mice to evaluate glucose homeostasis and brain ketone metabolism.

Results: PASI-51 inhibited SCOT activity in cell-free assays, while decreasing ketone oxidation in the working heart. Moreover, PASI-51 treatment improved glycemia in obese mice without altering brain ketone metabolism or antagonizing the D2R.

Conclusion: Our research demonstrates that selective inhibition of SCOT in peripheral tissues sustains the glucose-lowering properties of DPBPs and eliminates CNS side effects, suggesting that peripherally acting SCOT inhibitors may be an effective therapeutic option for T2D treatment.

Alberta Diabetes INSTITUTE

ABSTRACTS

Afternoon Session

Oral Presentation

JUNIOR

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UNIVERSITY OF ALBERTA

Abstracts

MESENCHYMAL STROMAL CELLS IMPROVE VASCULARIZATION IN A PRE-VASCULARIZED SUBCUTANEOUS APPROACH FOR ISLET TRANSPLANTATION

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Introduction: Intraportal islet transplantation established proof-of-concept that cellular therapies can provide insulin independence. Endeavours evaluating extrahepatic implantation sites are being explored, including the subcutaneous (SC) space, due to the minimally invasive implantation procedure, its capacity to accommodate large tissue volumes and its accessibility for graft monitoring and retrieval. However, the innate hypovascularity of the site severely impacts engraftment, survival and function and hence, pre-vascularization strategies are being evaluated. Mesenchymal stromal cells (MSCs) have shown to facilitate vascular regeneration. We hypothesize that MSCs have the potential to increase vascularization upon delivery in the SC space.

Methods: MSCs were generated from the acinar component of the human pancreas; morphology, flow cytometry and trilineage differentiation were used to confirm successful MSC generation. Electrospun poly lactic-co-glycolic acid and gelatin (PLGA + G) scaffolds were wrapped around 1.8 cm nylon catheters and seeded with 5 $\times 10^6$ human MSCs in 3% rat-tail collagen before being implanted into the ventral subcutaneous space of B6 Rag mice (n=6); PLGA + G without MSC scaffolds (n=6) were used as control, both balanced for sex. After 2 weeks, all animals were intravenously injected with lectin and grafts were histologically assessed for neovascularization. In a separate cohort, 3000 neonatal porcine islets (NPIs) were transplanted into the preconditioned SC space of streptozotocin-induced diabetic B6 Rag mice and kidney capsule (KC) transplants were used as control (n=8 per group; balanced for sex). Blood glucose was monitored weekly, and intraperitoneal glucose tolerance tests were performed every 4 weeks from the 4th week post-transplant.

Results: Adherent cells isolated from the acinar component of human pancreas consistent with MSC morphology (fibroblast-like; spindle-shaped), >98% of the cells were $CD105^+$, $CD73^+$, $CD90^+$ and were capable of trilineage differentiation into osteocytes, chondrocytes and adipocytes. MSC coating of the scaffold was confirmed with H&E and anti-human mitochondria staining. Lectin was used to quantify the number of vessels in the implant site between control (PLGA + G) and PLGA + G + MSC implanted animals. PLGA + G +MSC implanted animals showed increased vessel number / mm^2 ($p = 0.0108$), increased vessel area / mm^2 ($p = 0.0024$) and increased vessel size ($p = 0.0001$) in the implant site compared to control. Additionally, PLGA + G + MSC implanted animals had significantly more $lectin^+$ ($p = 0.0381$), $CD31^+$ ($p = 0.0001$) and smooth muscle $actin^+$ ($p = 0.0382$) cells. Interim data shows that diabetes reversal was significantly faster in the PLGA + G + MSC group at 15 weeks, compared to 25 weeks for PLGA ($p = 0.0341$) and 17 weeks for KC.

Conclusion: These data demonstrate that MSCs enhance the vascularization of the implant site, which correlates with improved islet survival, engraftment and function. The data obtained from this study will enable the development of a clinically relevant islet transplantation approach by creating a richly vascularized region within the SC space that enhances islet survival and function. Our multidimensional approach is anticipated to be a viable treatment option for patients with T1D in the near future. Ideally, data collected from the study will be used to generate the necessary pilot data to apply for regulatory, ethics and Health Canada approval for testing of our approach in a Phase I/II clinical trial in Edmonton.

Abstracts

CHARACTERIZATION OF OFF-TARGET CELL POPULATIONS IN HUMAN INDUCED PLURIPOTENT STEM CELL (HIPSC) DERIVED ISLETS IN IMMUNODEFICIENT MICE

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Introduction: Type 1 Diabetes (T1D) is characterized by the destruction of insulin-producing pancreatic ß-cells. Islet cell transplantation for T1D is limited by donor cell supply and has prompted exploration into induced pluripotent stem cells (iPSCs). iPSCs are differentiated into islet-like cells through six stages. Off-target cell populations remain a challenge and may form tumors and cysts in vivo. More efficient early differentiation in the pancreatic progenitor stage will generate fewer off-target cells upon maturation to stage 6, forming fewer and smaller cysts. The microvascular environment at different transplant sites will impact the frequency and size of tumors and cysts.

Methods: iPSCs derived from a non-diabetic patient were differentiated to S4 and S6. Cells were transplanted into immunodeficient mice in the kidney capsule, portal vein, subcutaneous tissue, epididymal fat pad, and omentum. Mice were tested for intraperitoneal glucose tolerance (8 and 12 weeks). Serum was analyzed for human C-peptide. At 12 weeks post-transplant (wpt), grafts were assessed for endocrine maturation and off-target growth with histology and immunohistochemistry.

Results: 87.5% (14/16) of S6 and 75.0% (9/12) of S4 transplanted mice survived to endpoint. Cystic and teratogenic growths were seen in 100% of mice transplanted at S4 under the kidney capsule (n=3) and omentum (n=3) and 50% of mice transplanted at the epididymal fat pad (n=2). Cystic structures were lined with ductal epithelial tissue, staining positive for CK19 but without CDX2. Non-endocrine tissue was seen with gastric and alveolar tissues. At 12 wpt, human C-peptide (4-10 pmol) was detected in all S4 mice. S6 cells demonstrated minimal cyst formation in only 21.4% (3/14) of surviving mice at 12 wpt (kidney capsule (n=2) and omentum (n=1)). S6 transplanted mice secreted minimal C-peptide. Comparison of engraftment and angiogenesis at each of the transplant sites is ongoing.

Conclusion: All cysts formed at both stages 4 and 6 were lined with ductal epithelium as identified by CK19 staining. S4 cells result in large cystic growths while more mature S6 cells only form small simple cysts. There was minimal presence of SOX9 in any of the grafts suggesting that the cysts forming are not hyperproliferative in nature. However, the minimal C-peptide secretion at S6 suggests poor cell survival after transplantation. Further work remains to optimize differentiation and transplant protocols and improve survival of cells after transplant.

Abstracts

IMPACT OF 24-HOUR STATIC COLD STORAGE OF NEONATAL PIG PANCREAS ON ISLET RECOVERY AND FUNCTIONALITY

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Introduction: Islet transplantation (ITx) has been shown to restore glycemic homeostasis in a subset of patients with type 1 diabetes (T1D). However, the limited supply of cadaveric human donors, the necessity of multiple donors per recipient, and the large number of islets required for the procedure have led to only a small percentage of T1D patients receiving ITx. Xenotransplantation of neonatal porcine islets (NPIs) may help alleviate shortages by providing a reproducible and readily available source of islets. Xenotransplantation has been gaining popularity with recent breakthroughs of genetically modified pig organs being transplanted into human patients. In the context of islet transplantation, pancreases from genetically modified pigs will be procured and transported to Good Manufacturing Practice (GMP) laboratories for NPI isolation, similar to how typical donor organs are transported to hospitals where recipients are located. Static cold storage (SCS) of the pancreas may extend preservation time such that the organ is still viable for islet isolation upon arrival at GMP facility. Currently, the University of Wisconsin (UW) solution is the standard preservation solution used for pancreases, with up to 12 hours of preservation time. This study aims to examine the impact of 24-hour cold storage of neonatal porcine pancreases (3-5 days old) in UW solution on islet recovery and β-cell function.

Methods: Pancreases from both male and female neonatal piglets were procured (n = 8); half of the pancreases were stored in HBSS (control) and digested immediately post-surgery to isolate NPIs, while the other half were stored in UW at 4°C for 24-hours before NPI isolation. In both cases, NPIs were cultured for a week. Samples were then taken post-culture for flow cytometry, glucose-stimulated insulin secretion (GSIS), DNA content, insulin content and immunohistochemistry. Another cohort of piglets were used under identical conditions (n = 4 /treatment), and those islets were transplanted into the kidney capsule of streptozotocin-induced diabetic B6.129S7-Rag1^{tm1Mom}/J mice (n = 8 / treatment). Data are expressed as mean ± SEM.

Results: Islet yield based on total DNA recovery per pancreas were similar in both experimental conditions (HBSS: 69.18 ± 1.68 µg vs SCS: 73.12 ± 3.76 µg; p = ns). The functionality of the islets, measured by glucose-stimulated insulin secretion, also remained consistent, with a 2.18 ± 0.28 and 2.24 ± 0.12 (p = ns) stimulation index for the control and SCS groups respectively. Additionally, the total number of β-cells recovered (HBSS: $2.37x10^6$ ± 0.44 vs SCS: $1.91x10^6$ ± 0.22; p = ns) was also comparable between the two groups. Currently, as of 10 weeks post-transplant, one mouse in the control group and two mice in the cold-storage group have reversed and achieved normoglycemia, suggesting that SCS treatment does not impair in vivo function.

Conclusion: 24-hour hypothermic storage of neonatal pig pancreases in UW solution showed to have no impact on β-cell function and recovery. Overall, 24-hour cold storage of porcine pancreases demonstrates the potential viability of transporting and utilizing genetically modified pig pancreases to help increase the availability of xenogeneic donor islets.

Abstracts

FEEDING LONG-CHAIN POLYUNSATURATED FATTY ACIDS ALTERED SPLENOCYTE MEMBRANE FATTY ACID COMPOSITION IN A DOSE-DEPENDENT MANNER AND MODULATED CYTOKINE PRODUCTION IN YOUNG WISTAR RATS

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Introduction: Obesity is associated with an increased risk of various health concerns, including pathogen infection and type 2 diabetes. Early life is a critical period for immune system development and long-chain polyunsaturated fatty acid (LCPUFA) supplementation in this period has been shown to support immune development and regulate immune response in food allergy models. However, the potential of such supplementation in early life to prevent obesity-related immune dysfunction remains unclear.

Methods: Wistar dams (n=6) were fed a high-fat diet (20% w/w fat, 1% arachidonic acid (ARA) and 1% docosahexaenoic acid (DHA) of the fat) during suckling. At 3 weeks, offspring were randomized to one of the following high-fat diets (20% w/w fat, n=12/group, 1:1 sex ratio): control diet (0%DHA, 0%ARA), 1%DHA diet (1%DHA, 1%ARA), 2%DHA diet (2%DHA, 1%ARA) or fish oil diet (1%DHA, 1%ARA, 1% eicosapentaenoic acid (EPA)). At 10 weeks, the pups were terminated. The fatty acid composition of splenocyte phosphatidylcholine (PC) and phosphatidylethanolamine (PE) were measured by gas-liquid chromatography. Isolated splenocytes were incubated with lipopolysaccharide (LPS) for 48 hours and supernatant was collected to measure the ex-vivo cytokine production by ELISA. Data were compared by 2-way ANOVA to explore the effects of diet, sex and diet*sex interaction.

Results: There were no diet effects but sex differences in pups' body (male 400±5g vs. female 236±7g) and spleen (male 1.02±0.03g vs. female 0.64±0.02g) weights (both $P<0.001$). In splenocyte PC, the percentage of ARA was not affected by diet or sex, the percentage of EPA was higher in fish oil group and the percentage of DHA was higher in diet groups supplemented with DHA in a dose-dependent manner (both $P<0.001$). In splenocyte PE, the percentage of ARA was higher in males and the percentage of EPA was higher in fish oil group (both $P<0.001$), the percentage of DHA was affected by both diet (higher in diet groups supplemented with DHA in a dose- dependent manner, $P<0.001$) and sex (higher in female, $P=0.011$). Splenocyte ex-vivo production of IL-1β, IL-8, TGF-β, TNF-α and IFN-γ after LPS stimulation were not affected by diet or sex. However, the production of IL-6 was higher in males ($P=0.002$) and the production of IL-17 was higher in females ($P=0.021$). The production of IL-10 was affected by both diet (higher in control and 1%DHA group than 2%DHA and fish oil group, $P=0.05$) and sex (higher in females, $P=0.004$).

Conclusion: In summary, young male Wistar rats had higher ARA and lower DHA levels in splenocyte PE and a higher IL-6 but lower IL-17 and IL-10 production by LPS-stimulated splenocytes. Post-weaning LCPUFA supplementation increased the DHA (in a dose-dependent manner) and EPA (fish oil diet) levels in splenocyte membranes and this resulted in a lower IL-10 production by LPS-stimulated splenocytes, indicating its potential to prevent obesity-related immune dysfunction.

Abstracts

THE EFFECT OF SEX AND BUTTERMILK-DERIVED LIPID-SOLUBLE FORM OF CHOLINE ON IMMUNE DYSFUNCTION IN THE CONTEXT OF OBESITY: PRELIMINARY FINDINGS

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Introduction: Obesity is associated with chronic inflammation, which diminishes the body's ability to mount an effective immune response against infections. Additionally, biological sex influences immune responses. Lipid-soluble forms of choline, such as phosphatidylcholine (PC) and sphingomyelin (SM), have been shown to enhance T-cell response and normalize gut permeability in the context of a high-fat diet (HFD). Buttermilk contains milk-fat globule membrane (MFGM), which is one of the richest dietary sources of both PC and SM. This study aimed to assess how sex differences modulate immune function in response to buttermilk consumption as part of a HFD.

Methods: At 4 weeks of age, male (n=18) and female (n=18) Wistar rats were randomized to consume one of three nutritionally complete HFDs for 12 weeks, each containing 1.5g of total choline/kg of diet but differing in choline forms: 1) Control high-fat diet (CHF, 50% fat, 100% free choline (FC)); 2) HFD + dairy phospholipid extract (PL, 50% fat, 1.5% FC, 58% PC, and 39% SM); and 3) Buttermilk (BM, 50% fat, 40% FC, 13% GPC, 22% PC, and 22% SM). Immune function was assessed by measuring *ex vivo* cytokine production and T cell proliferation in splenocytes after mitogen stimulation (PMA+I (T cell)). Intestinal permeability was evaluated using a bolus of FITC-dextran, and fasting blood glucose was measured with a glucometer.

Results: Following PMA+I stimulation, both the BM and PL groups increased IL-2 production compared to the CHF diet, independently of sex (p-diet=0.011). Female rats exhibited significantly enhanced T cell proliferation and lower fasting blood glucose levels in the context of a HFD compared to male rats (both p-sex<0.05). BM consumption was associated with reduced FITC- dextran levels and lower fasting glucose compared to the CHF diet, although it did not reach statistical significance. Male rats showed increased production of IL-10 compared to female rats (p-sex=0.013). Rats fed with the BM diet increased IL-10 production when compared to both PL and CHF groups, regardless of sex (p-diet=0.008).

Conclusion: Our preliminary data suggest that lipid-soluble forms of choline, derived either from a dairy phospholipid extract or buttermilk, may enhance T cell function by increasing IL-2. However, buttermilk may confer an additional immune advantage over the dairy PL extract by increasing the production of the anti-inflammatory cytokine IL-10 and reducing gut permeability. Additionally, females generally exhibited better T cell proliferation and glucose metabolism than males, consistent with current literature in the field.

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2024 RESEARCH DAY

0800-1635 | 1-040 LKS (Oborowsky Degner Seminar Hall) & LKS Foyer

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