Alberta Diabetes INSTITUTE

2025 RESEARCH DAY

08:00-16:35 | 1-040 LKS (Oborowsky Degner Seminar Hall) & LKS Foyer

THURSDAY, OCTOBER 9th

KEYNOTE SPEAKER

Bruce A. Perkins, MD MPH

Sam and Judy Pencer Family Chair in Diabetes Clinical Research

University of Toronto

Co-Sponsored by:

Alberta Diabetes FOUNDATION

UNIVERSITY OF ALBERTA

2025 ADI RESEARCH DAY

Thursday, October 9th | 08:00-16:35 (MT)

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PROGRAM

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

Acknowledgments

The University of Alberta, its buildings, labs and research stations are primarily located on the territory of the Néhiyaw (Cree), Niitsitapi (Blackfoot), Métis, Nakoda (Stoney), Dene, Haudenosaunee (Iroquois) and Anishinaabe (Ojibway/Saulteaux), lands that are now known as part of Treaties 6, 7 and 8 and homeland of the Métis. The University of Alberta respects the sovereignty, lands, histories, languages, knowledge systems and cultures of all First Nations, Métis and Inuit nations.

We extend our sincere appreciation to all those who contributed to the success of the 2025 ADI Research Day.

We gratefully acknowledge:

- **Dr. Bruce Perkins**, our keynote speaker, for his insightful and thought-provoking address.
- **Alberta Diabetes Foundation**, for their generous co-sponsorship and continued support of diabetes research and innovation.
- **Presenters and poster contributors**, for sharing their research and advancing scholarly dialogue.
- **Session chairs, judges and moderators**, for facilitating meaningful discussions and ensuring the smooth flow of the program.
- **The ADI Trainee Working Group members**, for their tireless efforts in planning and coordinating every aspect of the event.
- **Volunteers**, for their enthusiasm and assistance throughout the day.
- **Funding agencies and research sponsors**, whose support empowers the pursuit of knowledge and innovation.
- **Collaborating departments and institutions**, for fostering interdisciplinary engagement and academic excellence.
- **ADI members,** for participating in and supporting our annual event

We are deeply grateful for the collective effort and commitment that made today a meaningful celebration of inquiry, collaboration, and discovery.

NOTE FROM THE DIRECTOR

Welcome to the 2025 Alberta Diabetes Institute Research Day. This annual event has become a highlight of our calendar, offering a vibrant space for our trainees—from first-year undergraduate students to postdoctoral fellows—to share their research, connect with peers, and celebrate the spirit of scientific inquiry.

With the support of our ADI Trainee Working Group, ADI Members, Trainees, and Administrative staff, we've curated a day filled with engaging oral and poster presentations that reflect the diversity and depth of diabetes research happening across the institute. These sessions are more than just updates—they're opportunities to spark new ideas, build collaborations, and inspire future directions. Throughout the day, you'll hear from trainees at all levels, with dedicated oral and poster sessions designed to showcase their work and encourage meaningful dialogue.

It is a pleasure to welcome Dr. Bruce Perkins, Professor of Medicine at the University of Toronto, as our keynote speaker and judge. Dr. Perkins is a leader in clinical diabetes research, known for his work in diabetic complications and precision medicine. His presence here today brings valuable insight and inspiration, and we are grateful to our Trainee Working Group for extending the invitation. We're especially pleased to offer opportunities for direct interaction with Dr. Perkins over lunch.

We are deeply thankful for the continued support of our donors and partners, including the Alberta Diabetes Foundation, DRIFCan, and others whose generosity enables the ADI to thrive. A heartfelt thank you goes to our Trainee Working Group (supported by Dr. Vincent Rogers), as well as our volunteers, judges, session chairs, and support staff. Your efforts make this day possible.

We hope today leaves you inspired, challenged, and energized to continue pushing the boundaries of diabetes research. Enjoy the day, ask questions, make connections, and above all—celebrate the incredible work being done across our institute.

Dr. Peter Senior

Director, Alberta Diabetes Institute

Dr. Charles A. Allard Chair in Diabetes Research

KEYNOTE

Bruce A. Perkins, MD MPH

The ADI is excited to announce this year's keynote speaker, Dr. Bruce A. Perkins.

Professor, Endocrinologist, Epidemiologist and Clinician-Scientist in the Faculty of Medicine. He holds the Sam and Judy Pencer Family Chair in Diabetes Clinical Research and directs the Leadership Sinai Centre for Diabetes. His research platform, research leadership, clinical practice, and advocacy work has focused entirely on strategies to improve the lives of those, like himself, living with type 1 diabetes. Using cohort and trial methods, his research has focused on 1) Early biomarkers and mechanisms of diabetes complications, and 2) complications prevention through artificial pancreas technologies, add-on-to-insulin drug therapies, as well as immunomodulation and cell-based therapies.

He is Vice-Chair of the Executive of the historic "DCCT/EDIC" Study, and co-leads the Innovations in Type 1 Diabetes Goal Group within Diabetes Action Canada, a national patient-oriented research strategy. He has been awarded the Canadian Diabetes Association/CIHR Young Scientist Award, and the Gerald Wong Service Award from Diabetes Canada, for his research and advocacy.

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

Welcome Dr. Perkins!

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SCHEDULE

MORNING SESSION

WELCOME

08:00	Welcome to the 2025 ADI Research Day	Refreshments in the LKS Foyer
08:15	Opening Remarks	Dr. Peter Senior, ADI Director
08:25	Introduction to the Keynote Speaker	Honyi Ong — ADI Trainee Working Group President

KEYNOTE

08:30 - 09:30	**Dr. Bruce A. Perkins** Sam and Judy Pencer Family Chair in Diabetes Clinical Research, University of Toronto	Keynote Speech

POSTER PRESENTATION - SENIOR

09:45	AKM Shahid Ullah Anderson Lab	Post-Doctoral Fellow	**Page 1**	LOCALIZED IMMUNOMODULATION IN T1D: POTENTIAL OF PANCREATIC DUCT INFUSION FOR TARGETED T-CELL INTERVENTION
09:45	Alice Missagia Springer Haqq Lab	PhD Student	**Page 2**	DIAGNOSTIC ASSESSMENTS AND TREATMENT PATHWAYS OF INSULIN RESISTANCE IN PEDIATRIC OBESITY
09:55	Arghyadip Bose Korbutt Lab	PhD Student	**Page 3**	OPTIMIZING THE SUBCUTANEOUS SPACE FOR ISLET TRANSPLANTATION USING MESENCHYMAL STROMAL CELL-LOADED SCAFFOLDS
9:55	Camilla Fonseca Rezende Haqq Lab	PhD Student	**Page 4**	THREE-DIMENSIONAL OPTICAL BODY COMPOSITION SCANNING AND CARDIOMETABOLIC HEALTH: A NARRATIVE REVIEW
10:05	Eamon Fitzpatrick Hull Lab	MSc Student	**Page 5**	INVESTIGATION OF NON-PRODUCTIVE ISLET ANGIOGENESIS IN A MOUSE MODEL OF hIAPP AGGREGATION
10:05	Emad Ghazizadeh Stroberg Lab	PhD Student	**Page 6**	MESOSCALE SIMULATION OF SHEET-TO-TUBULE TRANSFORMATION IN THE ENDOPLASMIC RETICULUM BY CURVATURE-PROMOTING PROTEINS
10:15	Luisa P. Soares Tsai Lab	PhD Student	**Page 7**	MATERNAL FACTORS MODULATE OFFSPRING MICROBIOME AND IMMUNITY TO MITIGATE DIABETES DEVELOPMENT
10:15	Magnus Stenlund Ussher Lab	MSc Student	**Page 8**	CHRONIC KETONE ESTER SUPPLEMENTATION PRESERVES EXERCISE CAPACITY IN OBESE MICE

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10:25	Nastaran Mojibi Richard Lab	PhD Student	**Page 9**	DIETARY OAT PROTEIN HYDROLYSATE AND b-GLUCAN ENHANCE GLYCEMIC CONTROL IN DIET-INDUCED OBESE MICE
10:25	Reihane Taheri Proctor Lab	PhD Student	**Page 10**	A RANDOMIZED CONTROLLED TRIAL TO ASSESS THE EFFICACY OF FISH OIL SUPPLEMENTATION TO IMPROVE IMPAIRED NON-FASTING LIPID METABOLISM IN YOUTH
10:35	Xiang Xiao Kaul Lab	PhD Student	**Page 11**	PROGNOSTIC U-SHAPE OF GLYCEMIC CONTROL AND CONSISTENT REVASCULARIZATION BENEFIT IN PATIENTS WITH DIABETES AND MULTIVESSEL DISEASE
10:35	Yosdel Soto Proctor Lab	Research Associate	**Page 12**	EXPRESSION, CHARACTERIZATION, AND ANTIATHEROGENIC EFFECTS OF THE ANTI-SULFATED GLYCOSAMINOGLYCANS mAb chP3R99 FROM CHO-K1
10:45	Qian Wang Buteau Lab	Research Associate	**Page 13**	BCAR1, A NOVEL REGULATOR OF FUNCTIONAL BETA-CELL MASS

ORAL PRESENTATION - JUNIOR

11:00	Soren Stachniak Pepper Lab	Undergraduate Student	**Page 14**	EXAMINING THE IMPACT OF LOCALIZED RAPAMYCIN ON ISLET GRAFT INSULIN SECRETION IN RESPONSE TO HYPERGLYCEMIA
11:15	Assa Akbarysedigh Mager Lab	MSc Student	**Page 15**	IMPACT OF A HOME-BASED LIFESTYLE INTERVENTION ON FUNCTIONAL OUTCOMES IN FRAIL AND NON-FRAIL ADULTS WITH DIABETIC KIDNEY DISEASE (DKD): A 6-MONTH RANDOMIZED CONTROLLED TRIAL
11:30	Illia Levin Rayat Lab	MSc Student	**Page 16**	GENE AND PROTEIN EXPRESSION OF ENDOCRINE, VASCULAR, NEURAL, AND EXTRACELLULAR MATRIX MOLECULES DURING THE FIRST WEEK OF NEONATAL PORCINE ISLET CULTURE
11:45	Pei Yu (Alex) Liu Anderson Lab	Undergraduate Student	**Page 17**	CO-INHIBITORY RECEPTORS AND TREGS SHAPE $CD4^+$ T CELL RESPONSES TO SELF AND FOREIGN PEPTIDES
12:00	Reid McClure Boule Lab	PhD Student	**Page 18**	FASTED EXERCISE TRAINING REDUCES NOCTURNAL HYPOGLYCEMIA IN OVERWEIGHT ADULTS WITH TYPE 1 DIABETES USING AUTOMATED INSULIN DELIVERY
12:15	Zofia Czarnecka Shapiro Lab	MSc Student	**Page 19**	GLYCEMIC CONTROL AND RISK OF RECURRENT HYPOGLYCEMIA AFTER TOTAL PANCREATECTOMY

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SCHEDULE

TRAINEE LUNCH

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

AFTERNOON SESSION

POSTER PRESENTATION - JUNIOR

13:35	Assa Akbarysedigh Mager Lab	MSc Student	**Page 20**	DOES FI IMPACT DIET QUALITY AND INTAKE OF ULTRA-PROCESSED FOODS IN ADULTS WITH DIABETIC KIDNEY DISEASE.
13:35	Emily Grapel Ferdaousi Lab	Undergraduate Student	**Page 21**	ROLE OF LIPOCALIN-2 IN FERROPTOSIS AND GLUCOCORTICOID-INDUCED β-CELL DYSFUNCTION
13:45	Januki Somatillaka Hull Lab	Undergraduate Student	**Page 22**	ANALYZING PANCREATIC DUCTAL ORGANOIDS AS A HUMAN PRIMARY CELL-BASED MODEL TO STUDY CYSTIC FIBROSIS-RELATED DIABETES
13:45	Jodie Harbarenko Chan Lab	MSc Student	**Page 23**	METABOLIC AND INFLAMMATORY OUTCOMES OF THE KETOGENIC DIET (KETO-IM): INTERIM CARDIOVASCULAR RESULTS
13:55	Mark Biollo Anderson Lab	Undergraduate Student	**Page 24**	THYMIC SLICE MODEL OPTIMIZATION AND BTLA'S ROLE IN NEGATIVE SELECTION
13:55	Raahim Aqueel Chan Lab	Undergraduate Student	**Page 25**	RELATIONSHIP OF ADHERENCE TO ASSIGNED DIETARY PATTERN WITH OUTCOMES OF THE KETO-IM TRIAL
14:05	Savanna Tippe MacDonald Lab	Undergraduate Student	**Page 26**	INVESTIGATING THE ROLE OF SREBP-1 IN STEM CELL-DERIVED BETA CELL FUNCTION FOR TYPE 1 DIABETES TREATMENT
14:05	Shawn Duckett MacDonald Lab	MSc Student	**Page 27**	CHARACTERIZING α-CELLS FROM MICE FED A HIGH-FAT DIET
14:15	Todimu Abifarin MacDonald Lab	Undergraduate Student	**Page 28**	CYTOKINE-INDUCED PROTEIN TRANSLOCATION BETWEEN CYTOPLASM AND PLASMA MEMBRANE IN HUMAN PANCREATIC ISLETS
14:15	Victoria Johnston Hull Lab	MSc Student	**Page 29**	ANALYSIS OF PANCREATIC MICROVASCULATURE ALTERATIONS IN CYSTIC FIBROSIS WITH MULTIPLEXED IMMUNOFLUORESCENCE

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14:25	Vipra Patel Rayat Lab	Undergraduate Student	**Page 30**	MATURE NK CELLS MAY BE AN ATTRACTIVE TARGET TO IMPROVE PIG ISLET XENOGRAFT SURVIVAL
14:25	Yasaman Mojibi Eslami Richard Lab	MSc Student	**Page 31**	PRELIMINARY FINDINGS OF THE KETO-IM STUDY: THE EFFECTS OF SATURATED AND UNSATURATED FAT SOURCES ON IMMUNE FUNCTION IN INDIVIDUALS AT RISK OF OR DIAGNOSED WITH TYPE 2 DIABETES
14:35	Zeelkunvarba Gohil Richard Lab	Undergraduate Student	**Page 32**	EFFECT OF FAT SOURCES IN KETOGENIC DIETS ON T CELL FUNCTION IN DIET INDUCED OBESE MICE

ORAL PRESENTATION - SENIOR

14:50	Nerea Cuesta Gomez Korbutt Lab	PhD Student	**Page 33**	INFLUENCE OF SEX ON NEONATAL PORCINE ISLET MATURATION AND FUNCTION UPON TRANSPLANTATION IN MICE
15:05	Tanin Shafaati Ussher Lab	PhD Student	**Page 34**	SYSTEMIC GIP RECEPTOR ACTIVATION INDUCES DIASTOLIC DYSFUNCTION IN MICE WITH TYPE 2 DIABETES
15:20	Jihong Lian Lehner Lab	Research Associate	**Page 35**	ARYLACETAMIDE DEACETYLASE (AADAC) REGULATES HEPATIC LIPID HYDROLYSIS AND DE NOVO LIPID SYNTHESIS
15:35	Summer Helmi Pepper Lab	Post-Doctoral Fellow	**Page 36**	ADVANCING BIOREACTOR-BASED MATURATION OF NEONATAL PORCINE ISLETS: TOWARDS SCALABLE BETA CELL REPLACEMENT THERAPY
15:50	Masaaki Naganuma Dyck Lab	Post-Doctoral Fellow	**Page 37**	KETONE THERAPY PREVENTS SEMAGLUTIDE-INDUCED LOSS OF SKELETAL MUSCLE MASS
16:05	Alice Carr Senior Lab	Post-Doctoral Fellow	**Page 38**	BASELINE INSULIN SECRETION DETERMINES THE RESPONSE TO ABATACEPT IN STAGE 1 TYPE 1 DIABETES

CLOSING REMARKS

16:25 - 16:35	Dr. Peter Senior, ADI Director	Awards announced

AWARDS

Poster Presentation - Junior

- Best Presentation Award
- Honourable Mention

Poster Presentation - Senior

- Best Presentation Award
- Honourable Mention

Oral Presentation - Junior

- Best Presentation Award
- Honourable Mention

Oral Presentation - Senior

- Best Presentation Award
- Honourable Mention

We sincerely thank all participants for their valuable contributions and for dedicating their time to present — your involvement was integral to the success of the 2025 Alberta Diabetes Institute Research Day!

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Zeelkunvarba **Gohil** Richard Lab	32	EFFECT OF FAT SOURCES IN KETOGENIC DIETS ON T CELL FUNCTION IN DIET INDUCED OBESE MICE
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AKM Shahid **Ullah** Anderson Lab	**1**	LOCALIZED IMMUNOMODULATION IN T1D: POTENTIAL OF PANCREATIC DUCT INFUSION FOR TARGETED T-CELL INTERVENTION
Qian **Wang** Buteau Lab	**13**	BCAR1, A NOVEL REGULATOR OF FUNCTIONAL BETA-CELL MASS
Xiang **Xiao** Kaul Lab	**11**	PROGNOSTIC U-SHAPE OF GLYCEMIC CONTROL AND CONSISTENT REVASCULARIZATION BENEFIT IN PATIENTS WITH DIABETES AND MULTIVESSEL DISEASE

Alberta Diabetes INSTITUTE

ABSTRACTS

MORNING SESSION

POSTER PRESENTATION

SENIOR

Pages 1-13

UNIVERSITY OF ALBERTA

Alberta Diabetes INSTITUTE

ABSTRACT

LOCALIZED IMMUNOMODULATION IN T1D: POTENTIAL OF PANCREATIC DUCT INFUSION FOR TARGETED T-CELL INTERVENTION

AKM Shahid Ullah, Colin Anderson

Background: Autoimmune destruction of pancreatic β-cells, primarily mediated by autoreactive T-cells, is the principal driving force resulting in Type 1 Diabetes (T1D). Currently practiced systemic immunotherapies lack tissue specificity and their broad immunosuppression limit clinical utility.

Objectives: The aim of our study is to explore a novel approach to conduct localized immune modulation by administering low dose antibodies directly into the pancreatic duct of non-obese diabetic (NOD) mice. We hypothesized that, localized delivery of low dose T-cell targeting antibodies directly into the pancreas can selectively modulate pancreatic microenvironment which will delay the development of T1D and reverse new onset T1D.

Methods: In our ongoing study, we delivered a combination of antibodies targeting CD4, CD8 and PD-1 locally in the pancreas through the intraductal route (ID) and systemically (IP) in non-obese diabetic (NOD) mice. Blood glucose levels and body weight of the mice were measured weekly, and flow cytometry was performed on blood to assess the effect of antibodies on T-cell and B-cell populations.

Results: Our preliminary results demonstrated that the group of ID delivery of antibodies remained non-diabetic for a longer period compared to IP delivery and PBS control group. Body weight remained unchanged across all groups. Flow cytometry on blood showed no significant effect on CD19+ B-cells. CD4+ T-cells showed a decreasing trend in the control group and remained unchanged in the antibody receiving groups. CD8+ T-cells showed an increasing trend in the ID antibody group and did not change in the IP or PBS control group. Among the CD4+ and CD8+ T-cell subsets, central memory cells tended to rise while naïve and effector-memory populations were stable. Although our results so far are inconclusive, we are expanding sample size and incorporating additional treatment groups to validate these findings and exploring the potential for reversing early-stage diabetes by delivering the antibody combinations locally.

Conclusions: The direct and site-specific immunotherapy may offer a viable alternative to conventional systemic approaches to prevent or delay the onset of T1D. Our investigation is laying a foundation for a minimally invasive and organ specific immunotherapy strategy which could contribute to a ‘paradigm shift’ of systemic immunosuppression to precision immunomodulation therapy for autoimmune T1D.

ABSTRACT

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

Alice M. M. Springer, Camilla F. Rezende, Edward C. Deehan, Faria Ajamian, Carla M. Prado, Andrea M. Haqq[1], Flavio T. Vieira[2]

[1]Co-Corresponding Author: haqq@ualberta.ca

[2]Co-Corresponding Author: teixeir1@ualberta.ca

Background: Insulin resistance (IR) is characterized by reduced insulin sensitivity, which leads to compensatory hyperinsulinemia and may progress to hyperglycemia, increasing the risk of type 2 diabetes mellitus (T2DM) and other metabolic disorders, such as metabolic syndrome. Pediatric obesity is rising worldwide and represents a major risk factor for IR and thus, T2DM. In the pediatric population, T2DM progresses more aggressively, with rapid deterioration and early complications. This highlights the urgent need for early identification and management of IR in childhood; however, there is no diagnostic consensus, and treatment options remain limited.

Objectives: This narrative review explores current IR diagnostic approaches and potential treatment pathways in pediatric patients with obesity.

Methods: A non-systematic literature search was conducted in Scopus and MEDLINE to identify studies published within the past 10 years. Search terms included pediatric populations, obesity, IR, T2DM, and therapeutic interventions.

Results: The most frequently used tools for assessing pediatric IR were fasting-based indices, particularly the Homeostatic Model Assessment of Insulin Resistance and the Quantitative Insulin Sensitivity Check Index. These are simple and widely applied but lack standardized cut-offs. The hyperinsulinemic–euglycemic clamp remains the gold standard, and the Matsuda Index, derived from the oral glucose tolerance test, provides broader insight into insulin sensitivity; however, they are reserved for research settings. Lipid-derived indices such as the triglyceride-to-glucose (TyG) index and the triglyceride/high-density lipoprotein ratio are promising low-cost alternatives; however, further validation is needed before clinical routine use in pediatrics. Regarding treatment, lifestyle modification through dietary improvement, regular physical activity, and weight management constitutes the primary approach to care. Reducing ultra-processed foods and improving quality of carbohydrate intake, with a preference for foods with a lower glycemic load, improves metabolic health, with fiber supplementation providing additional benefits. Metformin is the most commonly used pharmacological agent for insulin resistance in pediatric obesity. Glucagon-like peptide-1 receptor agonists have demonstrated significant improvements in BMI, glycemic control, and insulin sensitivity in adolescents, but robust evidence in younger pediatric populations is not yet available. Integrated strategies combining behavioral interventions, fiber supplementation, and pharmacotherapy may achieve greater and long-term health improvements than monotherapy interventions.

Conclusions: Fasting-based indices represent the most practical approach for assessing IR; however, the absence of standardized cut-offs limits their clinical application. Behavioral interventions remain the primary strategy for IR management, with additional benefits observed with increased fiber intake and pharmacological therapies.

ABSTRACT

OPTIMIZING THE SUBCUTANEOUS SPACE FOR ISLET TRANSPLANTATION USING MESENCHYMAL STROMAL CELL-LOADED SCAFFOLDS

Arghyadip Bose, Purushothaman Kuppan, Joy Paramor, Jessica Worton, Karen Seeberger, Chelsea Castro, Mandy Rosko, Andrew R. Pepper, Gregory S. Korbutt, Nerea Cuesta-Gomez

Background: Intraportal islet transplantation is a viable cell-replacement therapy for type 1 diabetes (T1D) but widespread application is limited. Currently, alternative sources of islets are being explored due to donor shortage. Extrahepatic transplant sites allowing easy access for monitoring and retrieval are necessary for successful translation. The subcutaneous (SC) space is an appealing option due to its minimally invasive nature, extensive surface area, and ease of access. However, inherent hypovascularity limits its effectiveness, leading to the exploration of "pre-vascularization" strategies. Mesenchymal stromal cells (MSCs) are pro-angiogenic and can be easily derived from low-purity islet (LPI)-fractions (a byproduct of islet isolation). We hypothesize that delivering LPI-MSCs with a poly (lactic-co-glycolic) acid and gelatin (PLGA+G) scaffold subcutaneously will create a highly vascularized site capable of supporting islet survival and function.

Objectives: Herein, we aim to use LPI-MSCs to improve vascularization in the SC space and assess the role of MSC-mediated vascularization in the engraftment and function (measured as improved reversal of hyperglycaemia) of neonatal porcine islets (NPIs) transplanted into the SC space.

Methods: LPI-MSCs stimulated for 24 hours with 10 ng/ml TNF-α, IL-1β and IFN-γ were coated onto electrospun PLGA+G scaffolds, followed by implantation into the SC space of non-diabetic B6.129S7-Rag1tm1Mom/J mice. Unstimulated LPI-MSC-coated scaffolds and uncoated scaffolds alone were used as controls (n=6/group, M/F). Two- and four-weeks post-implant, grafts were assessed for vascularization with a lectin perfusion assay and immunofluorescence for vascular markers CD31 and α-smooth muscle actin (α-SMA). In separate cohorts, 3000 NPIs were transplanted into the MSC-conditioned SC spaces of diabetic B6.129S7-Rag1tm1Mom/J mice (n=3 stimulated; n=5 for unstimulated). PLGA+G alone (n=8) and transplants under the kidney capsule (KC; n=9) were used as controls. Blood glucose levels were monitored weekly until reversal of diabetes, with intraperitoneal glucose tolerance tests performed every 4 weeks.

Results: Blood vessel number ($p=0.0007$; $p<0.0001$), area ($p=0.0006$; $p<0.0001$) and size ($p<0.0001$; $p<0.0001$) were significantly increased in the stimulated-MSC group compared to unstimulated-MSCs and uncoated controls at 2 weeks. Metabolic follow-up data indicates significantly faster diabetes reversal ($p=0.0192$) only in the unstimulated group compared to KC controls, along with improved glucose tolerance; stimulated group recipients could not reverse diabetes.

Conclusions: This data demonstrates that (unstimulated) LPI-MSCs are enhancing vascularization in the SC space, which correlates to improved NPI engraftment and function. However, despite improved vascularization of the SC space by stimulated MSCs, NPIs failed to reverse diabetes in recipients, potentially due to generation of non-functional, immature neo-vessels.

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ABSTRACT

THREE-DIMENSIONAL OPTICAL BODY COMPOSITION SCANNING AND CARDIOMETABOLIC HEALTH: A NARRATIVE REVIEW

Camilla F. Rezende, Alice M. M. Springer, Jonathan P. Bennett, Geoff D. C. Ball, Faria Ajamian, Carla M. Prado, Andrea M. Haqq, Flavio T. Vieira

Background: Body composition (BC) refers to different body compartments, including fat mass, muscle mass, and bone mineral content. Imbalances between these compartments, particularly increased visceral adipose tissue and reduced muscle mass, play a central role in the development of cardiometabolic conditions like insulin resistance and type 2 diabetes. While gold-standard techniques such as dual-energy X-ray absorptiometry, computed tomography, and magnetic resonance imaging provide accurate assessments, their high cost and limited availability restrict routine use. In clinical practice, cardiometabolic risk stratification based on BC often relies on surrogate markers such as body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR). Though indicative of disease risk, these metrics may not fully capture fat or muscle mass quantity and distribution. In this context, three-dimensional optical (3DO) body scanners emerged as a promising alternative. Using low-cost cameras, 3DO systems capture detailed body surface information, generate a virtual 3D avatar, and estimate BC through segmental and whole-body anthropometric measurements. Therefore, 3DO technology may offer a practical tool to identify individuals at cardiometabolic risk beyond conventional measures.

Objectives: To explore current evidence on the association between 3DO body scanners and cardiometabolic health.

Methods: A non-systematic literature search was conducted across scientific databases. Articles were screened for relevance based on their focus on the relationship between 3DO body scanners and cardiometabolic health.

Results: 3DO body scanners provide precise, automated, non-invasive measurements of waist and hip circumferences while also generating detailed estimates of whole-body and regional BC. Compared with manual tape-based methods, 3DO assessments are cost-effective, minimize observer bias, and allow repeated evaluations, making them suitable for screening and clinical monitoring of cardiometabolic health. Evidence from clinical studies indicates that 3DO improves the prediction of cardiometabolic conditions beyond traditional anthropometric assessments with the ability to identify at -risk individuals who would otherwise be misclassified, such as those with a normal BMI but elevated visceral adipose tissue. Moreover, machine learning using 3DO scan data can create advanced models for risk prediction, further strengthening their potential as a practical tool for early prevention and management of cardiometabolic disorders. By enabling more precise risk stratification, 3DO technology may help guide targeted interventions, such as personalized nutrition counseling, physical activity programs, or early pharmacological treatment.

Conclusion: Incorporating 3DO technology into clinical practice offers an accessible and cost-effective approach to enhance cardiometabolic disease risk stratification, supporting earlier prevention and targeted interventions.

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ABSTRACT

INVESTIGATION OF NON-PRODUCTIVE ISLET ANGIOGENESIS IN A MOUSE MODEL OF hIAPP AGGREGATION

Eamon Fitzpatrick, Rebecca Hull-Meichle

Background: Islet beta cells require close communication with their associated vasculature for optimal endocrine function and to maintain beta cell survival. These beta cells release the peptide human islet amyloid polypeptide (hIAPP) during normal insulin secretion. In type 2 diabetes hIAPP aggregates as amyloid within the islet. This aggregation is cytotoxic to the beta cell and has several deleterious effects on the islet vasculature, including inflammation, loss of vessel density and dissociation of vascular pericytes. In the brain, aggregation of Alzheimer's disease-associated amyloid leads to a vascular phenomenon known as non-productive angiogenesis (NPA). NPA results in non-functional blood vessel growth, which leads to vascular destabilization and inflammation. This phenotype closely resembles the changes we see in islet vasculature adjacent to amyloid deposits, but NPA has not previously been investigated in this context. We hypothesize, therefore, that hIAPP aggregation results in NPA, which could explain the deleterious effects of hIAPP within the islet vasculature.

Objectives: Identify markers of NPA within the islet.
Determine if NPA is localized around aggregations of hIAPP within the islet.
Determine if deleterious changes, such as vessel density loss or vascular pericyte dissociation, are associated with both amyloid aggregates and markers of NPA.

Methods: Sections of frozen pancreas from hIAPP transgenic mice and non-transgenic littermates were stained with thioflavin S (amyloid), lectin (blood vessels), and antibodies for insulin (islets), neural-glial antigen 2 (pericytes), and Nidogen 2 (NPA). Stained sections were imaged using widefield and confocal fluorescence microscopy, and images were analysed using the QuPath software.

Results: Amyloid aggregation has been observed within a new cohort of transgenic mice. In the islets of amyloid positive animals, we have confirmed amyloid-associated vascular pathologies, namely a reduction in blood vessel density alongside an increase in pericyte number. Pericytes have displayed an altered morphology from wildtype controls. The protocol for identifying NPA in the islets is currently being optimized.

Conclusions: NPA is likely to be a component of the pathology of islet amyloid deposition. By investigating NPA in the hIAPP context, we hope to elucidate the cellular mechanisms underlying the deleterious effects of amyloid within the islet vasculature. Understanding the mechanisms by which hIAPP aggregation contributes to islet dysfunction is necessary to allow future research to approach ways to alleviate or prevent the damage to the islet.

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ABSTRACT

MESOSCALE SIMULATION OF SHEET-TO-TUBULE TRANSFORMATION IN THE ENDOPLASMIC RETICULUM BY CURVATURE-PROMOTING PROTEINS

Emad Ghazizadeh, Wylie Stroberg

Background: The endoplasmic reticulum (ER) is a highly dynamic organelle that undergoes continuous remodeling between tubular and sheet-like structures, driven by the Rtn and Reep protein families.

Objectives: Understanding the physical principles underlying these transitions is crucial for elucidating the ER's role in cellular homeostasis and disease.

Methods: In this study, we employ mesoscale simulations to investigate the mechanisms by which curvature-promoting proteins regulate ER morphology. Specifically, we explore the influence of protein intrinsic curvature, protein concentration, and protein stiffening on tubulation dynamics.

Results and Conclusions: Our results indicate that increasing the intrinsic curvature of proteins lowers the protein coverage threshold required for tubulation, while enhanced membrane stiffness facilitates curvature propagation at lower protein coverage. A phase diagram is constructed to map the conditions necessary for membrane remodeling, identifying critical curvature and protein coverage thresholds that drive ER transformation. These findings establish a quantitative framework for ER shape regulation, shedding light on the interplay between protein-membrane interactions and mechanical properties in ER morphogenesis. By integrating computational predictions, this study advances our understanding of ER structural dynamics and its implications for cellular function.

ABSTRACT

MATERNAL FACTORS MODULATE OFFSPRING MICROBIOME AND IMMUNITY TO MITIGATE DIABETES DEVELOPMENT

Luisa P. Soares, Erin Strachan, Tingting Ju, Alejandro Schcolnik-Cabrera, Henry Wang, Masoud Akbari, Carol Huang, Olivier Julien, Benjamin P. Willing, Xavier Clemente-Casares, Sue Tsai

Background : 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 and promotes a responsive immune reaction that fosters long-lasting tolerance and helps prevent the development of immune-mediated pathologies. Whether maternal dysbiosis can alter offspring immune development and potentially contribute to the development of autoimmune diseases such as type I diabetes (T1D), remains largely unknown.

Objectives and Methods: Using a nonobese diabetic (NOD) mouse deficient in immunoglobulin A (IgA), we examined if and how maternal dysbiosis derived from IgA deficiency influenced offspring T1D onset.

Results: Our findings reveal that dysbiosis in IgA-deficient (IgA-/-) NOD dams significantly lowered diabetes incidence in their offspring, when compared to those born from IgA-sufficient NOD dams. Weaning pups reared by dysbiotic IgA-/- dams contain significant yet transient changes in the gut microbiome, with reduced colonic abundance of Akkermansia muciniphila, and a heightened gastrointestinal immune activity. In adulthood, these pups are protected long term from islet autoimmunity, as measured by degree of insulitis and T1D onset. Regarding the maternal factors in play, IgA-/- breast milk proteome is significantly altered, including an increase in immunoglobulin G (IgG) levels and a change in microbiome specificity. Neonatal colonization of germ-Free NOD pups with dysbiotic IgA-/- donor microbiome is not sufficient to confer T1D protection. However, pups reared by germ-free NOD dams that had received a fecal microbiome transfer (FMT) from dysbiotic IgA-/- dams prior to pregnancy replicate the T1D protection observed in the SPF cohort, when compared to pups reared by germ-free NOD dams that are FMT recipients of IgA-sufficient NOD microbiome.

Conclusions: Our data indicates that maternal dysbiosis confers protection against diabetes development in offspring and that neonatal exposure to maternal factors is sufficient to afford long-term protection against T1D.

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ABSTRACT

CHRONIC KETONE ESTER SUPPLEMENTATION PRESERVES EXERCISE CAPACITY IN OBESE MICE

Magnus Stenlund, Sally R. Ferrari, Lynn Dong, John Ussher

Introduction: Obesity is a multifactorial disease characterized by the excessive accumulation of body fat. This increase in adiposity, combined with alterations in whole-body metabolism, lead to several physiological perturbations, including inflammation, insulin resistance, mitochondrial dysfunction, and oxidative stress. Ketones are an endogenously produced fuel source that have their production increase during fasting to provide fuel for the brain, but recent studies have demonstrated that ketones can benefit cardiometabolic syndrome. For example, ketones have been shown to exert epigenetic effects that could reduce the oxidative stress associated with obesity. They also engage anti-inflammatory signaling that could reduce the inflammatory environment associated with obesity. Therefore, we postulated that supplementing obese mice with ketones would improve some of the adverse aspects of obesity and improve metabolic health.

Methods: In this study, male C57BL/6J mice were subjected to a standard chow diet (lean mice) or 60% high-fat diet (HFD) for 4-wks to induce obesity. Following 4-wks of diet supplmentation, mice remained on their original diet and were randomized to treatment with either a ketone ester (KE) supplement or volume-matched vehicle control. Body composition was assessed at the beginning and the end of the study, and body weight and blood glucose measurements were collected every wk. Glucose tolerance, endurance exercise capacity, and anaerobic exercise capacity were assessed following 4 wks of KE treatment. Mice were euthanized at the end of the study and muscle tissues were collected for biochemical analyses

Results: We observed no changes in body mass or composition with KE supplementation in obese mice, though glucose tolerance was improved when KE was administered immediately prior to testing. Exercise treadmill testing also demonstrated that KE supplementation preserved endurance exercise capacity in obese mice. This was complemented by an increase in HSL phosphorylation in the gastrocnemius muscles of obese mice treated with KE.

Conclusions: The results from this study demonstrate the therapeutic potential for KE supplementation in obese mice to improve exercise capacity and metabolic health.

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ABSTRACT

DIETARY OAT PROTEIN HYDROLYSATE AND b-GLUCAN ENHANCE GLYCEMIC CONTROL IN DIET-INDUCED OBESE MICE

Nastaran Mojibi, Stephanie Tollenaar, Alexander Makarowski, Lingyun Chen, Michael Gänzle, Jean Buteau, and Caroline Richard

Background: Oat protein hydrolysate (OPH) generated with Alcalase and Flavourzyme has demonstrated potential glucoregulatory bioactivities in vitro, particularly by inhibiting a-amylase, a-glucosidase, and dipeptidyl peptidase-4. However, the effect of OPH in vivo remains unexplored. On the other hand, oat b-glucan (BG), a soluble fiber, has been well studied for its glucose and cholesterol lowering effect.

Objectives: We aimed to explore the potential effects of OPH, alone and in combination with oat BG on glucose metabolism in obese mice.

Methods: At 4 weeks of age mice were fed a 60 % high-fat diet (HFD) for 8 weeks to induce obesity. Afterwards, mice either remained on HFD (n=24) or were randomized into four diet groups: HFD with 25% of protein replaced by either oat protein (OP, n=11), OPH (OPH; n=11), or OPH in combination with 10% of fiber replaced by b-glucan (OPH+BG; n=11), or modifying BG alone (BG; n=10), for 5 weeks. Fasting blood glucose (FBG), oral glucose tolerance test (OGTT), and insulin tolerance test (ITT) were assessed at weeks two, three, and four of the intervention, respectively. Insulin and glucagon-like peptide-1 (GLP-1) levels were measured from 15-minute OGTT plasma by ELISA. At week five, a subset of HFD-fed mice (n=18) underwent a meal tolerance test (MTT) consisting of an oral dose of dextrose (40% w/v) combined with either OP, OPH, or casein (all 5% w/v).

Results: There were no differences in food intake among groups, whereas body weight gain was lower in the OPH group compared to other groups. The incremental area under the curve (iAUC) for the OGTT was lower in mice fed the OPH+BG diet compared to other groups. However, no differences were observed in the iAUC for the ITT nor in the insulin and GLP-1 levels for OGTT at 15 min. Similarly, the MTT showed no differences in glucose or insulin levels.

Conclusion: While the OPH diet appears to prevent weight gain in the context of a HFD, it did not improve insulin sensitivity or glucose tolerance. The OPH+BG diet improved glucose tolerance in obese mice which seems to be independent of GLP-1. Furthermore, a single oral dose of OP or OPH did not improve the glucose response in obese mice compared to casein. Altogether, these data suggest that the glucose lowering effect is mostly attributable to the combination of oat b-glucan and protein hydrolysate.

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ABSTRACT

A RANDOMIZED CONTROLLED TRIAL TO ASSESS THE EFFICACY OF FISH OIL SUPPLEMENTATION TO IMPROVE IMPAIRED NON-FASTING LIPID METABOLISM IN YOUTH WITH OBESITY

Reihane Taheri, Spencer D Proctor, Donna Vine, Geoff Ball, Michael Khoury

Introduction: Cardiovascular diseases (CVD) remain among the leading causes of death in Canada. While CVD typically manifests in adulthood, the etiology of CVD begins in childhood. Obesity and dyslipidemia are among the major risk factors for CVD. Dyslipidemia is defined as elevated levels of low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG). New evidence in adults showed that in addition to LDL-C and TG, non-fasting remnant cholesterol (RC) is an independent risk factor for CVD. In our previous studies, we found that while other fasting lipid biomarkers are normal in youth with obesity, non-fasting RC and TG are elevated. These findings reinforced the importance of the management of non-fasting RC and TG in youth with obesity to reduce risk of CVD in future. In adults, dietary fish oil supplementation has been shown to reduces plasma TG and RC effectively. To date, we do not know if fish oil will lower fasting and/or non-fasting, TG, and/or RC in youth with obesity. Therefore, we aim to assess the efficacy of 3g/d dietary fish oil supplementation on reduction of non-fasting RCand TG in youth with obesity.

Study Design: This is an open pilot study (n=20) to provide preliminary evidence to initiate a larger randomized, double-blinded, placebo-controlled efficacy study in youth (boys and girls) with overweight and obesity aged 14-20 years (n=92 total). Participants will be randomized and allocated to either intervention group who are supplemented with 3g/day of fish oil [1500mg of Eicosapentaenoic acid (EPA)+500mg docosahexaenoic acid (DHA)] as per Health Canada guidelinesfor this age (n=46), or the placebo group who are supplemented with 3g/day olive oil (n=46) for 8 weeks. At the beginning and end of the study, the background dietary intake, physical activity, weight, and body composition of participants will be taken. Fasting and non-fasting blood sample will be collected to measure ApoB48, ApoB100, total cholesterol (TC), LDL-C, HDL-C, RC, and TG. For non-fasting measurement, we will provide individualized milkshake, and every 2 hours we will collect blood sample until 8 hours. We received Human Ethics approval (Pro00091319) for this study and are actively recruiting. For recruiting participants, we are using two strategies: 1- recruiting from Pediatric Center for Weight and Health (PCWH) in Misericordia hospital, and 2-recruiting from community. For recruiting from the community, we advertised aposter in social media (erase.ca website, Instagram and Facebook), recreation centers in Edmonton, University of Alberta weekly digest and campus, and McEwan University campus. We have recruited 5 patients to date, and we are broadening our study in community through uploading recruitment video in YouTube. We anticipate to recruit n=20 for the pilot study by March 2026.

Expected outcomes: We expect fish oil supplementation improves non-fasting TG, RC, and apoB48 levels and improve the body's ability to metabolize fat in youth with obesity. The results of this project will provide proof for the potential efficacy of a safe, nutritional approach to improve fat intolerance and reduce CVD risk in youth with obesity.

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ABSTRACT

PROGNOSTIC U-SHAPE OF GLYCEMIC CONTROL AND CONSISTENT REVASCULARIZATION BENEFIT IN PATIENTS WITH DIABETES AND MULTIVESSEL DISEASE

Xiang Xiao, Anamaria Savu, Kevin R. Bainey, Dean Urich, Roopinder K. Sandhu, Padma Kaul

Introduction: The influence of glycemic control (HbA1c) on outcomes after coronary revascularization in high-risk patients with diabetes (DM) and multivessel disease (MVD) is unclear. We aimed to evaluate the dual role of baseline HbA1c as both an independent prognostic factor and a potential effect modifier of the comparative effectiveness of percutaneous coronary intervention with drug-eluting stents (PCI-DES) versus coronary artery bypass grafting (CABG).

Methods: Our population-based retrospective cohort study included 3,726 patients with DM and MVD who underwent PCI -DES (n=2,297) or CABG (n=1,429) within 90 days following a cardiac catheterization (January 1, 2013, to March 31, 2019) in Alberta, Canada. Cox proportional hazards models weighted by the inverse probability of PCI-DES versus CABG were used to examine the associations between revascularization type, baseline HbA1c and outcomes. The primary outcomes were major adverse cardiovascular events (MACE) and all-cause mortality at 1 year. The secondary outcome was major adverse cardiovascular and cerebrovascular events (MACCE) at 1 year. HbA1c was included as a categorical and continuous variable using restricted cubic splines to characterize its non-linear prognostic effect and to test for an interaction with revascularization type.

Results: At 1 year, PCI-DES was associated with a similar risk of MACE (HR=1.24; 95% CI: 0.97, 1.58; P=0.09) and all-cause mortality (HR=1.27; 95% CI: 0.92, 1.74; P=0.15), but a significantly higher risk of MACCE (HR=2.10; 95% CI: 1.72, 2.58; P<0.0001), compared to CABG and independent of HbA1c. Patients with HbA1c levels of 7.0–8.5% had the lowest risk of MACE (HR=0.79; 95% CI: 0.64, 0.98) compared to those with HbA1c <6.5%, a trend that was also present for all-cause mortality. The association was further confirmed by restricted cubic analyses, which demonstrated a non-linear U-shaped association with both MACE (P non-linearity=0.005) and all-cause mortality (P non-linearity=0.01). However, the interaction between HbA1c and revascularization type was not statistically significant, although point estimates indicated a potential U-shaped trend favouring CABG over PCI-DES at intermediate HbA1c levels (around 7.0%–8.5%), while for MACCE, this benefit was observed across all HbA1c levels.

Conclusions: In patients with DM and MVD, glycemic control demonstrates a dual role. It is a significant, non-linear prognostic factor, with the lowest risk for MACE and mortality observed at intermediate HbA1c levels. However, it is not a significant effect modifier, as the relative effectiveness of CABG versus PCI-DES remained unchanged across all levels of glycemic control.

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ABSTRACT

EXPRESSION, CHARACTERIZATION, AND ANTIATHEROGENIC EFFECTS OF THE ANTI-SULFATED GLYCOSAMINOGLYCANS mAb chP3R99 FROM CHO-K1 AND HEK293 CELLS

Yosdel Soto, Leidy M Valencia, Yoandra Martínez Montano, Jose A Gómez, Víctor Brito, Arletty Hernández, Roger Sarduy, Aymé Fernández Calienes, Spencer Proctor.

Background: Atherosclerotic vascular disease is driven by arterial retention of ApoB-containing lipoproteins mediated by glycosaminoglycan (GAG) chains of proteoglycans. The chimeric chP3R99 monoclonal antibody (mAb) targets chondroitin sulfate (CS) sites to block lipoprotein–proteoglycan interactions. Because production in NS0 cells was inefficient, new serum-free CHO-K1 and HEK293 variants were generated.

Objective: To determine whether CHO-K1– and HEK293-derived chP3R99 retain the parental NS0 antibody's structural characteristics, antigen recognition, biodistribution to aorta, impact on arterial LDL retention, and antiatherogenic activity.

Methods: Heavy/light chain genes were cloned into pL6WBlast, co-transduced into CHO-K1 and HEK293 cells, and stable clones were selected. Purified mAbs were compared with the NS0 antibody by SDS-PAGE, size-exclusion chromatography, and PNGase F deglycosylation; CS binding and in-vitro recognition of atherosclerotic lesions were assessed. Biodistribution (1 mg IV; n=3) and LDL retention after a single 1 mg IP dose were evaluated in Sprague Dawley rats. In New Zealand White rabbits, atherosclerosis was induced with Lipofundin 20% (2 mL/kg IV, daily ×8 days) and passive chP3R99 was administered IV (total 6 mg; n=6–7).

Results: CHO-K1 and HEK293 lines produced chP3R99 with high yield and low aggregation. New variants showed ~150 kDa molecular mass, ~99% purity, and similar hydrodynamic diameters (12.5–13.7 nm) to the NS0 mAb. Despite cell-line-specific glycosylation, CS binding and lesion recognition were preserved in vitro. In rats, chP3R99 from both CHO-K1 and HEK293 specifically accumulated in aorta to a similar extent, resulting in a significant reduction of arterial LDL retention ($p<0.05$). In rabbits, passive administration of the new variants effectively reduced atherosclerosis and 60% of treated animals did not develop lesions under the Lipofundin regimen (n=6–7), consistent with preferential aortic accumulation.

Conclusions: CHO-K1- and HEK293-derived chP3R99 maintain the NS0 antibody's structural integrity, antigen recognition, aortic targeting, and antiatherogenic activity. These results support further preclinical development of any of the chP3R99 variants to limit proteoglycan-mediated lipoprotein retention and atherogenesis.

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ABSTRACT

BCAR1, A NOVEL REGULATOR OF FUNCTIONAL BETA-CELL MASS

Qian Wang, Austin Bautista, Patrick MacDonald, Jean Buteau

Background: We recently characterized the protein kinase Lyn as a promising molecular target in diabetes treatment. Indeed, activation of Lyn promoted beta-cell mass expansion and restored glucose tolerance in both T2D and T1D mouse models. The underlying molecular mechanisms remains poorly understood since Lyn targets in β-cells are largely unknown. We therefore performed a phospho-proteomics study to identify key signaling molecules that are phosphorylated in response to Lyn activation. One hit of interest was Bcar1 since it has been associated with T2D and decreased β-cell function in a previous GWAS study. We herein sought to explore the biological action of Bcar1 in β-cells, and test the hypothesis that Bcar1 regulates β-cell proliferation and function.

Methods: The biological action of Bcar1 was first examined by performing gain- and loss-of-function experiments using overexpression and siRNA-mediated knock-down, in INS832/13 cells and human islet cells. β-cell proliferation was determined via PCNA or ki67 staining, and BrdU incorporation assay. Apoptosis was evaluated by TUNEL assay. β-cell function was assessed by GSIS, patch-clamp, and respiration seahorse assay. Key results were confirmed in vivo, using our novel model with β-cell-specific deletion of Bcar1 (βBCAR1-ko).

Results: Transient overexpression of Bcar1 increased β-cell proliferation, and prevented β-cell apoptosis. Conversely, Bcar1 knock-down inhibited β-cell proliferation and protection. Glucose-stimulated insulin secretion and ATP production were impaired following Bcar1 knockdown in INS cells. Consistently, Bcar1 knockdown in human islet cells decreased their exocytotic capacity. Loss of Bcar1 disrupted β-cell mitochondrial networks and attenuated mitochondrial function, indicating a key role of BCAR1 in maintaining mitochondrial health. Our data were reiterated in βBCAR1-ko mice, which displayed decreased β-cell area and impaired glucose tolerance.

Conclusion: Our study characterizes Bcar1 as a novel regulator of β-cell mass and function. Bcar1 may represent a promising molecular target for diabetes therapeutic interventions.

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ABSTRACTS

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ABSTRACT

EXAMINING THE IMPACT OF LOCALIZED RAPAMYCIN ON ISLET GRAFT INSULIN SECRETION IN RESPONSE TO HYPERGLYCEMIA

Soren Stachniak, Joy Paramor, Chelsea Castro, Karen Seeberger, Riley Reid, Evan Pullishy, Purushothaman Kuppan, Bryan Lum, Jessica T. Y. Yue, Andrew R. Pepper

Background: Pancreatic islet transplantation (ITx) is a highly effective and promising approach to restoring near-normal blood glucose regulation in individuals with type 1 diabetes. To date, immunosuppression poses a significant challenge, limiting patient eligibility for ITx to a subset of individuals. One such immunosuppressant, rapamycin (rapa), exerts potent immunosuppression by interacting with the mammalian target of rapamycin (mTOR) kinase in immune cells. Of concern in ITx, elevated or prolonged rapa dosages may be counterproductive to normal glycemic regulation, even when administered locally.

Objective: This study aims to assess the dose-dependent effects of rapa delivered alongside islets at the ITx site. We hypothesize that islet graft-localized rapa will elicit a temporal attenuation of the recipient's glucose responsiveness and insulin sensitivity.

Methods: To elucidate the local effects of rapa administered at the ITx site, we encapsulated rapa into microparticles (MPs) composed of poly(lactic-co-glycolic acid) (PLGA). Syngeneic islets and MPs were co-transplanted into diabetic BALB/c mice beneath the kidney capsule and monitored for three weeks post-transplant. Rapa dosages included three experimental groups: empty MPs (n = 11), low-dose 0.1 mg/kg MPs (n = 11), and high-dose 0.2 mg/kg MPs (n = 11). After three weeks, hyperglycemic clamp experiments were used to assess graft islet function. Following hyperglycemic clamps, key metabolic tissues (cardiac and skeletal muscle, visceral and subcutaneous white adipose tissue, the liver, and graft) were collected for polymerase chain reaction (PCR) assessment of three genes involved in glucose homeostasis and tissue metabolism: protein kinase B (AKT), insulin receptor substrate 1 (IRS-1), and glucose transporter 4 (GLUT4).

Results and Conclusions: Hyperglycemic clamp experiments demonstrated reduced glucose clearance and insulin secretion three weeks post-ITx in rapa-treated recipients compared to those transplanted with E-MPs. This suggests that ITx β-cells may be adversely affected by rapa exposure, resulting in reduced insulin secretion under prolonged hyperglycemic conditions. PCR findings corroborate the differences observed between the empty MP and rapa-treated groups, showing reductions in GLUT4 expression in cardiac and skeletal muscle, as well as AKT expression in cardiac muscle and graft tissue, and IRS-1 in the liver of treated mice.
While local rapa has been shown to prolong allograft function, it is essential to consider the effects of the drug on β-cells to assess its viability as an immunosuppressant in ITx. Continued evaluation of rapa, its analogs, co-therapies, and MP technologies could potentially reduce the immunosuppressive burden that currently restricts patient eligibility for ITx.

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ABSTRACT

IMPACT OF A HOME-BASED LIFESTYLE INTERVENTION ON FUNCTIONAL OUTCOMES IN FRAIL AND NON-FRAIL ADULTS WITH DIABETIC KIDNEY DISEASE (DKD): A 6-MONTH RANDOMIZED CONTROLLED TRIAL

Assa Akbarysedigh, Kaitlyn Visser, Vera Mazurak, Normand Boulé, Angela Juby, Stephanie Thompson, Patricia Manns, Kailash Jindal, Peter Senior, Diana Mager

Background: Frailty is a common co-morbid condition for adults with diabetic kidney disease (DKD), defined as a state of increasing vulnerability which may lead to impairments in mobility, reduced muscle strength, and increased difficulties in performing activities of daily life (ADL).

Objective: This randomized clinical trial evaluated the impact of 6-month resistance exercise (RE) intervention on muscle strength, functional, and physical performance in frail (F) and non-frail (NF) adults with DKD.

Methods: Adults with DKD aged 50-85 years (n=60 Frail (28M/32F), n=59 non-frail; 25M/34F) were randomized into intervention and standard of care (CON) groups. They were evaluated for frailty status using the validated Clinical Frailty Scale (CFS) (Frail: score ≥4, Non-frail: score ≤3). Validated tools to measure functional and physical performance included the Short Physical Performance Battery Tests (SPPB), consisting of balance, gait speed, and sit-to-stand tests. Muscle strength (MS) was measured using hand-grip dynamometry.

Results: At baseline in the RE and CON groups, no significant differences were observed between F and NF in BMI (31.6 ± 9.4 F vs 32 ± 9.4 kg/m² NF), and HbA1C (7.1 % (6.6-8.4) F vs 6.9 % (6.7-7.6) NF) ($p>0.05$). In contrast, frail participants were older (76.9 ± 7.2 F vs. 66 ± 7.6 years NF), had longer duration of DM (20 (13.7-26) F vs 11.9 (6-19.7) years NF), and lower eGFR (38.5 (32.3-49.5) F vs 71.5 (58-92.3) ml/min NF) ($p<0.05$). Similar patterns were observed in CON group. Six-month RE significantly reduced CFS score (from 4 (4-4) to 4 (3-4), $P<0.05$) and increased MS (from 25.5 (21.3-31.8) to 30 (21-33.3) kg, $P<0.05$), gait speed score (from 3 (2-4) to 3.5 (3-4), $P<0.05$), and balance score (from 4 (3-4) to 4 (3-4), $P<0.05$) but no difference in total SPPB score was observed.

Conclusion: Home-based six-month RE contributed to improvements in MS, physical performance, and frailty in frail adults with DKD.

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ABSTRACT

GENE AND PROTEIN EXPRESSION OF ENDOCRINE, VASCULAR, NEURAL, AND EXTRACELLULAR MATRIX MOLECULES DURING THE FIRST WEEK OF NEONATAL PORCINE ISLET CULTURE

Illia Levin, Jeongbeen Kim, Adnan Black, Kieran Purich, Wenlong Huang, Yizhao Zhou, Gina R. Rayat

Background: Isolation of neonatal porcine islets disrupts the endocrine hormones, extracellular matrix (ECM), vasculature, and neural components of the pancreas. The fate of the endocrine, ECM, vasculature, and neural molecules as well as the formation of clusters of islet cells while in culture in vitro has not been fully elucidated.

Objective: The aim of this study was to evaluate the transcriptional and histologic changes in endocrine hormones, ECM, vascular, and neural molecules during the in vitro culture of neonatal porcine islets to test our hypothesis that dynamic changes in these molecules occur when islet cells form into clusters.

Methods: Pancreas from neonatal pigs were surgically procured and processed by mechanical and enzymatic digestion to isolate islets. Digested tissues were cultured for 7 days with changing media on days 1, 3, 5, and 7 of culture. Samples on days 3, 5, and 7 were collected for RT-qPCR and immunostaining assays to determine the gene and protein expression of endocrine hormones (insulin, glucagon, and somatostatin), ECM (collagen IV, fibronectin, laminin 1), vascular (vascular endothelial-cadherin [VE-cadherin], CD31, and von Willebrand Factor [vWF]), and neural molecules (Ephrin A5 receptor, ubiquitin carboxy terminal hydrolase L1 [UCHL1], and protein gene product 9.5 [PGP 5.9], respectively. Results were compared between the samples collected.

Results: Preliminary results showed higher relative insulin, glucagon and somatostatin gene expression in islets cultured for 7 days compared to islets cultured for 3 days. This trend coincided with the protein expression of insulin in the immunostained images of islets. There was no detectable gene expression for ECM molecules such as laminin-α1, collagen I, and fibronectin but protein expression was detected. For vascular molecules, VE-cadherin relative gene expression was decreased in islets on day 7 compared to day 3 of culture. The same trend was observed in protein expression. EPHA5 receptor gene expression showed variability but was lower in islets cultured for 7 days. There was no detectable gene expression for neural marker UCHL1 but an increase in PGP9.5 protein expression was observed in islets cultured for 7 days.

Conclusion: These results describe the important changes in endocrine hormones, ECM, vascular, and neural molecules occurring in neonatal porcine islets during culture in vitro, which help us understand the molecules involved in the formation of islets clusters. The next step is to process all samples we have collected to demonstrate reproducibility of our results.

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ABSTRACT

CO-INHIBITORY RECEPTORS AND TREGS SHAPE CD4$^+$ T CELL RESPONSES TO SELF AND FOREIGN PEPTIDES

Pei Yu (Alex) Liu, Mark Biollo, Marcos Petersen, Troy Baldwin, and Colin Anderson

Background: Autoimmune diseases, such as type 1 diabetes, arise when tolerance to self-antigens breaks down, resulting in the erroneous attack of T-cells on our body's own cells. A key mechanism in preventing autoreactivity and maintaining tolerance is the T-cell receptor (TCR), which allows T-cells to discriminate between high- and low-affinity peptide–MHC ligands and regulate T-cell response. The affinity of the peptide–MHC interaction is therefore crucial in shaping T-cell activation and maintaining self tolerance. This selective response is regulated by coinhibitory receptors, such as B and T lymphocyte attenuator (BTLA), programmed death-1 (PD-1), and CD5. Regulatory T-cells (Tregs) are another key component of peripheral tolerance, helping suppress activation of self-reactive T-cells. However, how coinhibitory receptors interact with each other or with Tregs to regulate immune responses remains poorly understood.

Objectives: Our aim is to determine how coinhibitory receptors, such as BTLA and PD-1, regulate CD4 T-cell activation and expression of other co-inhibitory receptors across high- and low-affinity peptide–MHC interactions, and how their absence may influence Treg-mediated suppression.

Methods: In this study, we used ovalbumin (OVA323-339) peptide specific OTII CD4 T-cells to investigate how coinhibitory receptors regulate proliferation and Treg-mediated suppression. Genes for coinhibitors were individually or combinatorially deleted using CRISPR/Cas9. Cells were stimulated with high- and low-affinity OV A peptides, and proliferation was assessed using CellTrace Violet (CTV). Tregs were generated by culturing naive OTII CD4 T-cells with OVA-pulsed APCs and IL-2 plus TGF-β. Modified T-cells from wild-type and BTLA knock-out (KO) mice were co-cultured with peptide-pulsed APCs with and without Tregs, and flow cytometry was used to analyze proliferation and receptor expression.

Results: Preliminary results suggest that CD4 T-cells deficient for BTLA and PD-1 show enhanced activation and expression of other coinhibitory receptors in response to both high and low affinity peptides when compared to wild-type T-cells. Furthermore, coculture with Treg cells affected proliferation and coinhibitory receptor expression on BTLA and PD-1 deficient T-cells differently when compared to wild-type T-cells.

Conclusion: Our results suggest that coinhibitory receptors, such as BTLA and PD-1, act to regulate CD4 T-cell activation and TCR affinity when presented with high and low affinity peptides. They may also act in regulating Treg-mediated suppression. Together, these findings suggest the importance of co-inhibitory receptor networks in shaping peripheral tolerance and may provide insight into the potential mechanisms behind distinguishing TCR affinity.

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ABSTRACT

FASTED EXERCISE TRAINING REDUCES NOCTURNAL HYPOGLYCEMIA IN OVERWEIGHT ADULTS WITH TYPE 1 DIABETES USING AUTOMATED INSULIN DELIVERY

REID D MCCLURE, NAEEM HUSSEIN, PETER A SENIOR, JANE E YARDLEY & NORMAND G BOULÉ

BACKGROUND: For people with type 1 diabetes (PwT1D), fasted (before breakfast) exercise, especially high-intensity interval or resistance exercise, is less likely to cause hypoglycemia compared to fed state (after breakfast + breakfast insulin dose) exercise. However, no long-term study of fasted exercise training has been performed.

OBJECTIVE: This trial is designed to determine the effects of 12 weeks of 3 times weekly fasted vs fed exercise training in 20 adults with T1D > 5 years duration, BMI>25, waist circumference associated with metabolic syndrome, using continuous glucose monitoring (CGM) and insulin pumps as usual care.

METHODS: Here we present preliminary findings in 4 participants (n=1 completed three months, n=2 completed 2 months, n=1 completed one month) using automated insulin delivery (AID) doing fasted exercise training, comparing exercise vs non exercise days and considering daytime separately from night-time. We used paired t-tests to compare daytime (6:00-23:59) and post-exercise overnight (0:00-5:59) CGM outcomes (time in range, below range, above range, mean glucose, SD and CV), daily insulin dosage and carbohydrate intake on days when participants did and did not complete a supervised exercise session.

RESULTS: The percent time below range (<3.9 mmol/L) during the night (midnight-6AM), was lower following exercise (p=0.01; Table 1). No significant differences were detected in daytime CGM outcomes (Table 1), or insulin dosing and carbohydrate intake (Table 2).

CONCLUSION: These results suggest that for PwT1D who use AID and exceed recommended time in range targets, fasted exercise training reduces nocturnal hypoglycemia compared with non-exercise days, without affecting insulin dosing.

Table 1. CGM outcomes from the daytime (6:00-23:59) and overnight post-exercise period (0:00-5:59) on exercise and non-exercise days. Data shown as mean ± SD.

Metric	Exercise (n days=90)	Non-Exercise (n days=176)	p-value
Daytime			
Time in range 3.9-10 (%)	79.6 ± 15.4	78.7 ± 16.0	0.64
Time below range <3.9 (%)	2.3 ± 3.9	3.0 ± 4.8	0.21
Time above range >10.0 (%)	18.1 ± 16.1	18.4 ± 16.2	0.90
Mean glucose (mmol/L)	8.0 ± 1.3	7.9 ± 1.3	0.52
SD	2.2 ± 0.8	2.2 ± 0.8	0.84
CV	27.0 ± 7.2	27.8 ± 8.8	0.40
Overnight			
Time in range 3.9-10 (%)	81.3 ± 23.9	78.3 ± 28.1	0.36
Time below range <3.9 (%)	1.6 ± 4.2	3.7 ± 9.0	0.010
Time above range >10.0 (%)	17.1 ± 23.8	18.1 ± 27.1	0.77
Mean glucose (mmol/L)	7.8 ± 1.9	7.9 ± 2.1	0.84
SD	1.5 ± 0.9	1.5 ± 0.9	0.77
CV	18.6 ± 8.3	18.9 ± 11.1	0.82

Table 2. Insulin pump dosing and carbohydrate entries on exercise and non-exercise days. Data shown as mean ± SD.

Metric	Exercise (n days=95)	Non-Exercise (n days=240)	p-value
Total Daily Dose (units)	65.7 ± 36.0	63.3 ± 34.0	0.15
Total Daily Bolus Dose (units)	40.2 ± 22.0	38.3 ± 21.1	0.16
Total Daily Basal Dose (units)	25.7 ± 14.7	24.99 ± 13.9	0.40
Total Daily Carbohydrate intake (grams)	191.5 ± 88.3	178.5 ± 65.8	0.36

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ABSTRACT

GLYCEMIC CONTROL AND RISK OF RECURRENT HYPOGLYCEMIA AFTER TOTAL PANCREATECTOMY

Zofia Czarnecka, Kevin Verhoeff, Alice L. J. Carr, Anna Lam, Peter Senior, Robin Lucciantonio, Tatsuya Kin, Andrew R. Pepper, David L. Bigam, Khaled Dajani, Blaire Anderson, A.M. James Shapiro

Background: Total pancreatectomy (TP) is performed selectively for pancreatic malignancies, chronic pancreatitis, and autoimmune conditions. Historically, TP was feared due to loss of insulin and counter-regulatory hormones, as well as the risk of severe hypoglycemic events (SHEs). While TP with islet auto-transplant (TPIAT) can preserve some function, past studies reported 41% post-operative SHE rates. However, advancements in insulin therapies and continuous glucose monitors (CGMs) may improve outcomes.

Objective: To evaluate risk of severe hypoglycemia after total pancreatectomy (TP).

Methods: This single center observational study analyzed TP patients from 2009-2024 comparing three groups: TP-alone, TPIAT insulin-independent and TPIAT insulin-dependent patients. CGMs (Dexcom G7) were provided for the study if patients did not already have one. Demographics, outcomes, survival, emergency department visits, and glycemic control were assessed.

Results: Among 147 TP cases, 76 underwent TP alone and 71 TPIAT. In the TP-alone patients, two deaths (2/76; 2.63%) occurred due to hypoglycemia. Pre-operatively, TP-alone patients had higher HbA1c (7.1±2.2%) than TPIAT patients (5.9±1.3%; $p<0.001$). In the first month post-operatively, TP-alone patients had higher HbA1c than TPIAT-insulin dependent patients, but no difference over 10 years. Hypo/hyperglycemia-related hospital visits, median time in target range (TP: 53.5%, IQR: 36.5-68.5 vs. TPIAT insulin-dependent: 59.0%, IQR: 43.3-67.5), and glycemic variability (coefficient of variation; 31.3%, IQR 28.3-35.0 vs 32.3%, IQR 28.7-35.5) were similar between TP-alone and TPIAT-insulin dependent groups. In 14 days of CGM capture, no severe hypoglycemia was observed in TP-alone patients (<3.0 mmol/L).

Conclusions: Advancements in insulins and CGMs provide acceptable outcomes after TP without supplemental islet transplantation, and lower risk of SHE than previously reported. This encouraging data may aid surgical decision-making and patient selection for surgery.

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ABSTRACTS

AFTERNOON SESSION

POSTER PRESENTATION

JUNIOR

UNIVERSITY OF ALBERTA

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ABSTRACT

DOES FI IMPACT DIET QUALITY AND INTAKE OF ULTRA-PROCESSED FOODS IN ADULTS WITH DIABETIC KIDNEY DISEASE

Assa Akbarysedigh, Yuxin Guo, Kaitlyn Visser, Peter Senior, Caroline Richard, Diana Mager

Background: Evidence suggests that adults with diabetic kidney disease (DKD) in Canada often have low diet quality (DQ), relying heavily on processed and ultra-processed foods.

Objective: To determine whether the presence of household FI impacts the DQ of adults with DKD.

Methods: This is a case-control prospective study with 25 adults aged 18-80 years diagnosed with DKD (stage I-V CKD). FI was evaluated using the validated Hunger Vital Sign Screener (HVS) and the US Household 18-Item Food Security Survey Module (HFSSM-18). Diet intake was assessed using 3-day food records and evaluated for DQ by the Canadian Healthy Eating Index (HEI-C) and the NOVA classification system for processed and ultra-processed foods.

Results: The prevalence of food insecurity was 28% (7 / 25) based on HFSSM-18. No significant differences were observed between food secure (FS) (N=18) and food insecure (FI) (N=7) participants in age (72.6 ± 7.5 FS vs 73 ± 6.2 years old FI, P>0.05), BMI (28.5 ± 4.8 FS vs 28.4 ± 6.5 kg/m2 FI, P>0.05), and eGFR (57.9 ± 21.8 FS vs 52.5 ± 30 ml/min FI, P>0.05). In terms of DQ, there were no significant differences between FS and FI participants in HEI-C scores (62.9 ± 10.8 FI vs 58.3 ± 14.6 FS, P>0.05) or in the intake of unprocessed (51.5 % ± 27.2 FI vs 38.5 % ± 19.8 FS, P>0.05) and processed/ultra-processed foods (45.3 % ± 29.2 FI vs 61.6 % ± 19.9 FS, P>0.05).

Conclusion: Among individuals with DKD, 28% were food insecure. There were no significant differences in DQ or intake of unprocessed and processed/ultra-processed foods between FI and FS individuals with DKD.

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ABSTRACT

ROLE OF LIPOCALIN-2 IN FERROPTOSIS AND GLUCOCORTICOID-INDUCED β-CELL DYSFUNCTION

Emily Grapel, Eliora Begna, Lee Ann Atkesone, Mourad Ferdaoussi

Background: Glucocorticoid (GCs)-induced diabetes mellitus (GIDM) is an iatrogenic metabolic disorder characterized by hyperglycemia resulting from pancreatic β-cell dysfunction and reduced insulin sensitivity in target tissues. GCs are anti-inflammatory and immunosuppressant medications that are highly effective in a wide range of clinical conditions. The role of ferroptosis, an iron-dependent form of cell death, in mediating the effects of GC remains unexplored.

Objectives: This study aims to investigate the contribution of ferroptosis to β-cell dysfunction and to identify circulating factors that protect against GC-induced metabolic disturbances, using mouse models in vivo and isolated human and mouse islets ex vivo.

Methods: Mice were treated with dexamethasone (0.42 mg/kg/day) or vehicle administered via drinking water. Isolated human and mouse islets, as well as the insulin-secreting cell line INS-832/13, were treated with dexamethasone (0.5 µM) in the presence or absence of the ferroptosis inhibitor liproxstatin-1 (0.5 µM) or lipocalin-2 peptide (LCN2, 2 µg/mL). Gene expression was measured by qPCR, and protein expression by western blot.

Results: We observed a divergent effect of dexamethasone between ex vitro and in vivo models. In isolated human islets, dexamethasone impaired insulin secretion and reduced the expression of ferroptosis-related markers (GPx4 and SLC7A11). Treatment with the ferroptosis inhibitor liproxstatin-1 restored insulin secretion in mouse islets, suggesting a role for ferroptotic pathways in dexamethasone-induced β-cell dysfunction. Surprisingly, in vivo dexamethasone treatment improved glucose tolerance in mice, despite inducing significant insulin resistance. This paradoxical improvement suggests the presence of protective circulating factors. To explore this, we identified LCN2 as a hepatokine that is undetectable under basal conditions but strongly induced in the liver following dexamethasone treatment. In INS-832/13 cells, LCN2 enhanced insulin gene (Ins2) expression ($p=0.0090$). A trend toward higher ferritin heavy chain 1 (FTH1, $p=0.0986$) suggested a role in iron sequestration. Anti-ferroptosis markers were upregulated by Lcn2, including SLC7A11 ($p=0.04$), and Ferroptosis Suppressor Protein 1 (FSP1, $p=0.0348$), promoting antioxidant defense. Exposure to the ferroptosis inducer, RSL3 (1µM), revealed an increase in the Lcn2 transporter SLC22A17 at the protein level (n=2), suggesting signaling of Lcn2 as a compensatory factor against ferroptosis.

Conclusion: Lcn2 is a potential regulator of β-cell survival under GC stress by enhancing insulin transcription, promoting iron storage, and modulating ferroptosis pathways. Future studies will work to define the mechanistic role of Lcn2 and evaluate its therapeutic potential to mitigate GIDM.

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ABSTRACT

ANALYZING PANCREATIC DUCTAL ORGANOIDS AS A HUMAN PRIMARY CELL-BASED MODEL TO STUDY CYSTIC FIBROSIS-RELATED DIABETES

Januki Somatillaka, Birbickram Roy, Ayodeji Aderibigbe, Rebecca Hull-Meichle

Background: Cystic fibrosis (CF) is a genetic disease caused by loss-of-function mutations in the cystic fibrosis transmembrane regulator (CFTR) gene coding for an anion channel responsible for bicarbonate and chloride transport across epithelial-lined tissues. When mutated, the pancreas is one of the first organs to be affected due to its high expression of CFTR. A major complication of CFTR mutations in the pancreas is cystic-fibrosis related diabetes (CFRD). CFRD is characterized by ductal plugging, fibrotic replacement, and islet remodeling. However, the etiology of CFRD is poorly understood with no well-established human cell-based models to study this disease. Thus, we wanted to explore the use of organoids as a potential model.
Organoids are 3D cell cultures derived from stem cells or primary tissues of model animals and humans, of various organs. Cultured in extracellular matrix-based hydrogels, such as Matrigel, organoids can undergo long-term expansion and maintain the 3D structure, morphology, physiology, and genetic information of their tissue of origin across several passages. Overall, the organoid system is standardized to support the cultivation of specific cell types making organoids a promising model for CFTR analysis in pancreatic duct cells.

Objectives: To use human donor tissue to assess the feasibility of generating and utilizing pancreatic ductal organoids as an in vitro human primary cell-based model for CF and CFRD research.

Methods: To do this, primary acinar tissue from five randomly selected donors was used to seed four organoid cultures and passaged three times. Growth rate measurements paired with rt-qPCR and forskolin-induced swelling (FIS) assay were conducted to assess organoid growth, mRNA expression of target genes, and physiological function of residual CFTR, respectively.

Results: Organoids were generated and cultured in all donor samples across passages with the highest and lowest growth rates being relatively consistent in the same two donors. Prompted to proliferate, CFTR expression steadily declined as the organoids obtained stem cell markers and lost differentiated duct cell markers over time, with swelling among donors being either quite similar or increased when treated.

Conclusions: Overall, we were able to successfully generate CFTR-expressing cells within weeks with detectable—though variable—swelling even as CFTR levels declined. This suggests that organoids could be used as a model for CF and CFRD to aid in the progression of understanding novel mechanisms and the etiology underlying the disease.

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ABSTRACT

METABOLIC AND INFLAMMATORY OUTCOMES OF THE KETOGENIC DIET (KETO-IM): INTERIM CARDIOVASCULAR RESULTS

Jodie Harbarenko, Jessy Azarcoya Barrera, Alexander Makarowski, Paulina Blanco, Rose Yeung, Laurie Mereu, Caroline Richard, Catherine Chan

Introduction: The ketogenic diet (KD) has become trendy for weight loss, and is gaining interest as a dietary pattern for improving glucose control in individuals at risk of or living with type 2 diabetes (T2D). Increased LDL cholesterol (LDL-C) is a concern due to the high saturated fat content of KD, with potentially negative cardiovascular impacts. Indeed, nutrition recommendations highlight the benefits of unsaturated fats (UFA) from eating patterns like the Mediterranean Diet. This study compared the efficacy of two KDs differing in fatty acid content (i.e.-rich in SFA or UFA) for changes in cardiovascular risk factors.

Hypothesis: Replacing SFA in a KD with a UFA source, like canola oil, will lower circulating LDL-C levels in overweight/ obese adults with prediabetes or T2D after a 6 month intervention.

Methods: A 3-arm randomized-controlled trial comparing 1) KD high in SFA from butter and coconut oil (KETO-Sat) (n=12), 2) KD high in UFA from canola oil (KETO-Can) (n=7), 3) a low-fat diet (LFD) (n=8) based on current Diabetes Canada nutrition guidelines. The study is enrolling adults aged 18 to 70 years, having overweight or obesity (BMI >23 kg/ m2 Asian or South Asian, BMI >25 kg/m2 non-Asian), and glycated hemoglobin (HbA1c) >5.7% at screening/baseline. Participants are counselled by nutrition experts for 6 months, with anthropometrics, HbA1c and lipids measured at baseline and 6 months. Reported in this interim analysis are within-group changes in values using paired t-test and $p \leq 0.05$ for statistical significance.

Results: Body weight decreased significantly in all groups (all $p<0.02$), with greater losses in KD (8.4% in KETO-CAN and 10.2% in KETO-SAT), than in LFD (3.2%). HDL-C increased significantly in both KD groups ($P<0.02$), while LDL-C increased slightly in the KETO-Sat group with non-significant decreases in KETO-Can and LFD. Triglycerides and total cholesterol to HDL-C ratio (C/HDL) decreased significantly in the KD groups (all $p<0.01$) after 6 months. A significant reduction was found in HbA1c across groups ($P<0.01$).

Conclusions: KD is an effective dietary pattern for weight loss, with greater losses compared to LFD after 6 months . Although no significant findings are seen with LDL-C, both LFD and KETO-Can supported decreased levels, with KETO-Can improving HDL-C as well. Both KD improved C/HDL which may be supportive of reduced CVD risk. As expected, LFD elicited benefits on weight and HbA1c. These results demonstrate possible health benefits from all diets.

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ABSTRACT

THYMIC SLICE MODEL OPTIMIZATION AND BTLA'S ROLE IN NEGATIVE SELECTION

Mark Biollo, Marcos Petersen, Alex Liu, Troy Baldwin, and Colin Anderson

Background: Type 1 Diabetes is an autoimmune disease that occurs when an individual's immune system attacks insulin-producing beta cells due to a failure to distinguish self from non-self. Type 1 Diabetes and other autoimmune diseases can be due to a breakdown in central tolerance, a T cell quality control process during negative selection (NS) in the thymus. During NS, many highly self-reactive T cells are deleted before they enter peripheral circulation.

Objectives: While several models exist to study NS, a relatively new in vitro system known as the thymic slice model (TSM) has emerged as a promising tool. We aimed to optimize the TSM to study NS using OT-II TCR-transgenic mice, which recognize ovalbumin (OVA) as their cognate antigen. Specifically, we evaluated BTLA's, a co-inhibitory receptor, role in NS by comparing OT-II BTLA wild-type (WT) and knockout (KO) thymocytes. BTLA is known to dampen TCR signaling. We hypothesized that OT-II BTLA KO thymocytes would undergo more robust deletion than OT-II BTLA WT thymocytes upon exposure to OVA, as the absence of BTLA would be expected to allow them to reach the threshold for NS more readily.

Methods: The TSM involves overlaying 3 million thymocytes, from different transgenic mice in equal ratios, onto 400 µm-thick cross-sectional slices of a thymic lobe. After a 24–48-hour incubation with OVA, the slices are dissociated, and the cells are analyzed by flow cytometry. In our experiments, polyclonal thymocytes were mixed with either or both OT-II BTLA WT and KO thymocytes and overlaid onto wild-type thymic slices. We then used the ratio of thymocyte populations under varying OVA concentrations to evaluate NS.

Results: At 20 µM OVA, we observed clear evidence of NS in both OT-II BTLA WT and KO thymocytes. However, we did not consistently detect a significant deletion difference between BTLA WT and KO across experiments. Interestingly, we found that CD4 single-positive (SP) WT cells surviving OVA induced NS had very high BTLA expression.

Conclusions: Although we did not observe differences in deletion efficiency when comparing OT-II WT:polyclonal and OT-II KO:polyclonal ratios, these preliminary findings suggest that BTLA may reduce NS, as evidenced by high BTLA expression in cells surviving NS. These surviving cells with higher levels of co-inhibitors when exposed to high levels of antigen may indicate a waste reduction or energy conservation model.

ABSTRACT

RELATIONSHIP OF ADHERENCE TO ASSIGNED DIETARY PATTERN WITH OUTCOMES OF THE KETO-IM TRIAL

Raahim Aqueel, Jessy Azarcoya Barrera, Alexander Makarowski, Paulina Blanco Cervantes, Jodie Harbarenko, Paulina Aldana Hernandez, Caroline Richard, Catherine Chan

Background: The ketogenic diet (KD) is a low-carbohydrate, high-fat diet that improves weight and glycemic control in people with or at risk for type 2 diabetes. KD versions high in saturated fat may raise LDL cholesterol (LDL-C), while unsaturated fat based variants may lessen adverse lipid changes. Low-fat diets (LFD) are comparators. A key factor in clinical benefit is adherence, yet few studies report outcomes by adherence level.

Objectives: To compare adherence patterns and their association with cardiometabolic outcomes in participants randomized to KETO-SAT, KETO-CAN, or LFD for six months.

Methods: Adults aged 18–70 years with HbA1c ≥5.7% and overweight/obesity were randomized to KETO-SAT (n=21), KETO-CAN (n=19), or LFD (n=16). Adherence was determined from 24-hour dietary recalls as the proportion of days with <10% of energy from carbohydrate. Low adherence was <40% of days, moderate 40–75%, and high >75%. For LFD, adherence was based on days with ≤30% of energy from fat. Blood ketones in the KETO groups were examined to validate carbohydrate restriction. Primary outcomes were LDL-C and triglycerides; secondary outcomes included HbA1c and body weight.

Results: Most participants were low compliance, particularly in KETO-SAT (19 low, 2 moderate) and KETO-CAN (17 low, 1 moderate, 1 high), while LFD had more high adherers (11 low, 2 moderate, 3 high). At 6 months, carbohydrate intake decreased in both KETO groups ($p<0.0001$) while fat intake increased ($p<0.0001$). Blood ketones rose in KETO arms, confirming restriction. Triglycerides decreased in both KETO groups ($p<0.0001$) but not in LFD ($p=0.27$). LDL-C did not change significantly in any group. HbA1c decreased across all diets (KETO-CAN $p=0.0011$, KETO-SAT $p=0.0016$, LFD $p=0.0018$). Body weight decreased in both KETO groups ($p<0.0001$) and in LFD ($p=0.0128$). Higher adherence groups generally showed greater improvements in triglycerides, HbA1c, and weight than low adherence groups, though small numbers of moderate and high adherers limited statistical power.

Conclusions: Both KETO variants reduced triglycerides, HbA1c, body weight, and carbohydrate intake, while LDL-C did not change in any group. KETO-CAN may have supported better inflammatory results, while LFD produced smaller, less consistent improvements. Many participants achieved benefits despite not meeting strict adherence definitions, suggesting that improvements in some outcomes may not require very low carbohydrate intake. These findings indicate that both diet quality and how adherence is defined can influence observed effects.

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ABSTRACT

CHARACTERIZING α-CELLS FROM MICE FED A HIGH-FAT DIET

Shawn Duckett, Aliya F Spigelman, Nancy P Smith, Patrick E MacDonald

Background: Hyperglycemia in type 2 diabetes mellitus (T2D) is partly caused by pancreatic α-cells which over-produce glucagon. While cellular mechanisms underlying altered α-cell behavior in T2D are poorly understood, subpopulations of α-cells in diabetes have immature phenotypes and compensatory increases in identity factors, correlating with impairment of glucagon exocytosis and adoption of a 'β-cell-like' electrophysiologic phenotype. Further experiments using diabetes models are required to demonstrate whether loss of α-cell identity and acquisition of some β-cell functional properties contribute to inappropriate glucagon secretion. Mice fed a 60% fat diet may be a useful model of α-cell dysfunction.

Objective: Assess whether α-cells from mice fed a 60%-fat diet exhibit functional characteristics that parallel immature functional phenotypes previously reported in diabetes.

Methods: Age-matched C57Bl6 mice were fed either a high-fat diet (HFD) or chow diet (CD). Body weight, blood glucose, plasma insulin, and plasma glucagon were monitored during ad libitum feeding or following a 6 hour fast. After 14-18 weeks on the HFD, pancreatic islets were isolated by collagenase digestion. Then, glucagon secretion was measured from whole islets upon perifusion with buffer containing 1 mM glucose or GIP and alanine. Separate batches of islets were dispersed into single cells, and whole-cell patch-clamp was used to measure functional parameters of single α-cells, including exocytosis in response to depolarization (from -70 to 0 mV) with or without the P/Q type calcium channel inhibitor, agatoxin.

Results: Mice fed a HFD exhibited elevated weight, blood glucose, plasma glucagon, and plasma insulin. Blood glucose, or plasma glucagon and insulin in vivo may predict glucagon secretion from isolated islets in response to 1 mM glucose or GIP and alanine in vitro, respectively. Agatoxin reduced the median exocytosis of α-cells from CD mice from 26.3 to 9.2 fF/pF, although this did not reach statistical significance due to a large heterogeneity in α-cell responses. The median exocytosis of α-cells from HFD mice was 18.6 fF/pF in controls and 11.6 fF/pF with agatoxin.

Conclusions: Mice exhibit large heterogeneity in their responses to HFD up to 18 weeks. More biological replicates or a more robust model will be necessary to assess α-cells. Investigating whether including sucrose in the diet (high fat high sucrose), or whether starting HFD at a younger age produces a more consistent or robust α-cell phenotype will be explored.

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ABSTRACT

CYTOKINE-INDUCED PROTEIN TRANSLOCATION BETWEEN CYTOPLASM AND PLASMA MEMBRANE IN HUMAN PANCREATIC ISLETS

Todimu Abifarin, Xiong Liu, Savanna Tippe, Patrick E. Macdonald

Background: Type 1 diabetes (T1D) is an autoimmune disease in which insulin-producing pancreatic β-cells are selectively destroyed by the immune system. This destruction is mediated in part by pro-inflammatory cytokines that induce mitochondrial dysfunction, endoplasmic reticulum (ER) stress, and apoptosis. While cytokine-induced β-cell death has been extensively studied, much less is known about how cytokines alter protein localization, particularly at the plasma membrane. Membrane proteins are critical for cell signalling, immune surveillance, and therapeutic intervention, with over 60% of approved drugs targeting them. Understanding how early cytokine exposure reshapes the membrane protein landscape could reveal novel therapeutic targets to preserve β-cell survival in T1D.

Objectives: This project aimed to develop and validate a biochemical fractionation approach to investigate how early cytokine exposure affects the localization of membrane-associated proteins in the β-cell. By applying this technique to human islets, we sought to determine whether cytokine treatment alters the distribution of key immune-related proteins and establish a framework for identifying additional biomarkers relevant to T1D pathogenesis.

Methods: Human islets from 5 donors without diabetes were cultured for 24 hours in the presence or absence of a pro-inflammatory cytokine cocktail consisting of TNF-α (1 ng/mL), IFN-γ (1 ng/mL), and IL-1β (0.5 ng/mL). Next, islets were subjected to sequential biochemical fractionation. First, cytosolic proteins were released using a selective permeabilization buffer and collected after centrifugation. The remaining pellet was solubilized in a membrane buffer to extract membrane-associated proteins, which were recovered following a final centrifugation. Protein fractions were analyzed by Western blot to verify the fidelity of separation and assess cytokine-induced changes.

Results: Western blotting revealed the membrane-associated Na⁺/K⁺ ATPase localized exclusively to the membrane fraction, while the cytoplasmic-associated GAPDH was restricted to the cytoplasmic fraction. Primary histocompatibility complex class I (MHC I), a membrane-associated biomarker of inflammation, was detected only in the membrane fraction and displayed increased abundance in cytokine-treated islets relative to controls.

Conclusions: Our study establishes a reliable approach to investigate membrane-associated protein translocation in human islets under inflammatory stress. The observed upregulation of MHC I supports the cytokine stress response model and underscores the utility of this method for identifying additional membrane-associated proteins involved in β-cell dysfunction. Our findings validate this method for tracking protein redistribution under cytokine stress and establish a foundation for identifying molecular targets to protect β-cells, thereby informing the development of new therapeutic strategies for T1D.

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ABSTRACT

ANALYSIS OF PANCREATIC MICROVASCULATURE ALTERATIONS IN CYSTIC FIBROSIS WITH MULTIPLEXED IMMUNOFLUORESCENCE

Victoria Johnston, Birbickram Roy , Rebecca Hull-Meichle

Background: Cystic fibrosis (CF) is the most common genetic recessive disorder affecting children in Canada and is caused by mutations in the CFTR gene. In the pancreas, these mutations result in pancreatic insufficiency, dysregulated blood-glucose homeostasis, and potentially cystic fibrosis-related diabetes (CFRD).
CFRD affects up to 50% of adults with CF, but its etiology remains unclear. Dysfunction of pancreatic islets in CFRD is not attributed to a loss of islets, per se, but to alterations in the pancreatic microenvironment, including microvasculature. Islets exhibit highly vascularized architecture, receiving up to 20% of the pancreatic blood flow despite making up only 1% of pancreatic mass. The microvasculature plays a critical role in supporting islet function by facilitating the transport of insulin from β-cells and glucagon from □-cells, hormones essential for glucose homeostasis. Furthermore the microvasculature secretes essential factors that regulate β-cell activity and growth.
Alterations to pancreatic microvasculature are also seen in T1D and T2D with fragmentation, thickening of capillaries, and phenotypic changes, which impact insulin secretion. Given the pivotal role of blood vessels in maintaining islet function and the observed changes in T1D and T2D, we predict they are involved in the etiology of CFRD.

Objectives: Our goal is to quantify the changes in the pancreatic microvasculature in CF and CFRD including the following investigation parameters: intra-islet and exocrine vessel density, vessel size, sex, CF specific mutation, location of activated stellate cells in relation to intra-islet vasculature and fibrotic vasculature, spatial analysis of vessels and α-SMA positive cells.

Methods: A multiplexed immunofluorescence protocol was applied to human autopsy pancreatic tissues from CF/CFRD donors and ND controls with the following antibodies: Insulin (β-cells), Glucagon (□-cells), CD31 (vasculature), and α-SMA (activated pancreatic stellate cells). The protocol included HIER with EDTA buffer, incubation with 0.3% H2O2 in methanol to block peroxidase activity, and application of a TrueView autofluorescence quenching kit. Samples were imaged with a Leica Thunder widefield microscope at 200x magnification. An analysis pipeline was created using QuPath, including pixel intensity threshold based classifiers and machine learning classifiers, to analyze our objectives.

Results: Preliminary data indicates that there is reduced intra-islet and exocrine vasculature in CF/CFRD pancreas samples compared to ND controls. Further samples will be included in the near future for further analysis.

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ABSTRACT

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ABSTRACT

MATURE NK CELLS MAY BE AN ATTRACTIVE TARGET TO IMPROVE PIG ISLET XENOGRAFT SURVIVAL

Vipra Patel, Brett Wickware, Illia Levin, Andrew Poholka, Gabriel Nemet, Gina R. Rayat

BACKGROUND: There are approximately 9.5 million people living with type 1 diabetes worldwide, including 1.85 million youth under 20. In low-income countries, children diagnosed before age 10 are expected to live only 13 additional years on average. Previous research has shown long-term survival of transplanted pig islets in pre-clinical animal models indicating the potential of pig islet transplantation as an alternative treatment for individuals with type 1 diabetes. However, the human immune response to pig islets has not been fully elucidated.

OBJECTIVE: This study investigates the immune response of individuals with type 1 diabetes using flow cytometry assay to identify key immune cells involved in the recognition and destruction of pig islets.

METHODS: To assess the human immune response to pig islets, a xenogeneic mixed lymphocyte culture reaction was conducted using peripheral blood mononuclear cells (PBMC) from individuals with type 1 diabetes (n=3) stimulated with pig islets. Pig islet stimulators were treated with 25µg/mL Mitomycin C (for 10×10⁶ cells) to metabolically inactivate them, ensuring only human PBMC responder cell response was measured. Human PBMC–pig islet co-cultures were harvested on Day 5 and stained with immune-specific antibodies T cells (CD3, CD4, CD8), macrophages (CD68, HLADR, CD163), natural killer cells (CD56, CD16, CD57), and regulatory T cells (FoxP3, PD-1).

RESULTS AND CONCLUSIONS: The proportion of CD4+ and CD8+ T cells were comparable between PBMC stimulated (63.1%; 25.5%, respectively) and not stimulated (65.6%; 25.7%) with pig islets. The professional antigen presenting macrophage population (CD68+HLADR+CD163+) and T reg population (CD4+or CD8+FoxP3+PD1+) were undetected in PBMC stimulated and not stimulated with pig islets. The mature NK cell population (CD56+CD16+CD57+) was higher in PBMC stimulated with pig islets (48.6%) compared to unstimulated PBMC (24.8%). In contrast the immature NK cell population (CD56+CD16-CD57-) was lower in PBMC from individuals with type 1 diabetes and stimulated with pig islets (23.0%) compared to unstimulated PBMC (53.3%). These results suggest a strong mature NK cell response against pig islets in individuals with type 1 diabetes and may be an attractive approach to target these cells to improve pig islet xenograft survival.

Supervisor: Dr. Gina R. Rayat, Department of Surgery
Stipend Support for Vipra Patel Provided by
Alberta Diabetes Institute Summer Studentship Award and CIRTN CREATE Summer Studentship

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ABSTRACT

PRELIMINARY FINDINGS OF THE KETO-IM STUDY: THE EFFECTS OF SATURATED AND UNSATURATED FAT SOURCES ON IMMUNE FUNCTION IN INDIVIDUALS AT RISK OF OR DIAGNOSED WITH TYPE 2 DIABETES

Yasaman Mojibi, Alexander Makarowski, Paulina Blanco Cervantes, Laurie Mereu, Catherine Chan, Caroline Richard

Background: Ketogenic diets (KD) are becoming popular for weight loss and glycemic control. Yet, they are often high in saturated fatty acids (SFA), which may increase systemic inflammation as they are a natural ligand for the toll-like receptor 4. Since hyperglycemia and inflammation both negatively affect immune function, substituting heart-healthy oils such as canola oil (high in monounsaturated and polyunsaturated fatty acids) for SFA may improve immunity.

Objectives: This study compared the immune function of a KD high in unsaturated fats to a KD high in SFA in participants with overweight/obesity and at risk of or having type 2 diabetes.

Methods: Male and female adult participants with a BMI>25 kg/m2 and glycated hemoglobin (HbA1c) ≥ 5.7% were randomized to consume a low-fat diet (LFD, fat: ≤30% total energy (TE); n=15) supplemented with whole grains or a KD (carbohydrate: ≤10% TE; fat: 60-70% TE) supplemented with either butter and coconut oil (KD-Sat; n=21) or canola oil (KD-Can; n=18) for 6 months. Body weight measures and fasting blood were taken at baseline, 3 months and 6 months. HbA1c and T cell phenotypes were measured in fasting blood, and T cell proliferation, and ex vivo cytokine production for tumor necrosis factor-alpha (TNF-α) and interleukin 2 (IL-2) after anti CD3/CD28 or phytohemagglutinin (PHA) stimulation of peripheral blood mononuclear cells, respectively. A paired T test was used to assess changes at 3 and 6 months from baseline.

Results: Body weight and HbA1c decreased significantly after 3 and 6 months in all groups ($p<0.05$). Although not statistically significant, only KD-Can had an apparent 1.1 times fold increase in T cell proliferation at 6 months relative to LFD where no change was seen for KD-Sat. Only KD-Can had an increase in TNF-α and IL-2 production after PHA stimulation at both 3 and 6 months, while TNF-α production in KD-Sat was reduced significantly at 6 months. The proportion of helper T cells expressing CD25 (the IL-2 receptor) was not different among the groups.

Conclusion: Our preliminary findings confirm that while both KDs are effective at improving body weight and glycemic control, only KD-Can exhibited improvements in T cell function after 6 months intervention similar to the standard of care LFD.

(Funded by Results Driven Agriculture Research, Alberta Canola, MITACS)

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ABSTRACT

EFFECT OF FAT SOURCES IN KETOGENIC DIETS ON T CELL FUNCTION IN DIET INDUCED OBESE MICE

Zeelkunvarba Gohil, Jordan S. F. Chan 2, 3, Yasaman Mojibi 1, Alexander Makarowski 1, Jessy Azarcoya-Barrera 1, Carolina Gonzalez Hernandez 1, Sally R. Ferrari 2, 3, John R. Ussher 2, 3, Caroline Richard 1.

1 Department of Agricultural, Food and Nutritional Sciences, University of Alberta, Canada.
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3 Alberta Diabetes Institute, University of Alberta, Canada.

Background: Obesity is a chronic disease characterized by excess adiposity. It leads to macrophage infiltration in adipose tissue, and proinflammatory cytokine release, which ultimately decreases T cell function by lowering interleukin-2 (IL-2) and interferon-γ (IFN- γ) production. The ketogenic diet (KD) is a high-fat, low-carbohydrate diet used for weight loss and glycemic control by triggering metabolic ketosis, converting fat to ketones. However, KDs are often high in saturated fats (SF) which are known to be pro-inflammatory and negatively impact the immune system. Therefore, a KD high in unsaturated fats (UF) may confer beneficial effects on immune function.

Objectives: To determine the effect of a KD supplemented with unsaturated versus saturated fats on T cell function in a diet-induced obesity mouse model.

Methods: C57BL/6J mice were fed either a commercial high-fat diet (HFD; Research Diets D12492; 60% kcal from lard, n=20) to induce obesity, or chow (PicoLab 5L0D, n=3) for 12 weeks. The mice remained on chow (n=3), or HFD (n=5), or were randomized to one of three experimental diets (n=5/group) for 8 weeks: HFD modified with canola oil (KETO-Can) or coconut oil and butter (KETO-Sat), and Chow (HFD-chow). Post-intervention, splenocytes were isolated and stimulated with Phorbol 12-Myristate 13-Acetate + Ionomycin (PMAi; a T cell mitogen). Cytokine production was measured by ELISA. T cell subsets were identified using flow cytometry and data was analyzed with FlowJo software. Statistical analyses were performed using a one-way ANOVA.

Results: At the end of the intervention, the reduction in body weight (BW) was similar across the KETO-Can, KETO-Sat, and HFD-Chow groups, and significantly greater than the HFD group. No significant changes were observed in T helper cell (Th) and CD25+ Th proportions. The KETO-Sat and HFD-Chow groups produced significantly more IL-2 than the HFD group however, IL-2 production in the KETO-Can group was not significantly different from all 4 groups. All dietary groups produced significantly more IFN-γ compared to HFD, while only KETO-Sat produced significantly more TNF-α than HFD.

Conclusions: While no changes were seen in the proportion of Th and Th cells expressing the IL-2 receptor (CD25), IL-2 and IFN-γ (a Th1 cytokine) production increased with KDs irrespective of fat sources suggesting improved T cell function. The increased production of TNF-α in the KETO-Sat group only, another Th1 cytokine known to increase IL-2 production, may suggest a less efficient T cell response when compared to the KETO-Can group.

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ABSTRACT

INFLUENCE OF SEX ON NEONATAL PORCINE ISLET MATURATION AND FUNCTION UPON TRANSPLANTATION IN MICE

Nerea Cuesta Gomez, Chelsea Castro, Mandy Rosko, Karen Seeberger, Gregory S. Korbutt

Background: Neonatal porcine islets (NPIs) mature into a mixed population of endocrine cells that can restore glucose control in mice, pigs, and non-human primates, representing a potential alternative islet source for clinical beta cell replacement therapy. However, it remains unclear how conditions in the recipient influence the maturation and function of these cells. Studies using stem cell-derived islets have shown accelerated islet maturation in female recipients compared to males. Investigating the relevance of host sex in islet transplantation is vital for addressing sex-specific disparities in health outcomes.

Objectives: Herein, we investigated the impact of host sex on NPIs implanted under the kidney capsule of male and female B6.129S7-Rag1tm1Mom (B6/Rag−/−) mice.

Methods: 3,000 NPIs were transplanted under the kidney capsule of streptozotocin-induced diabetic male and female mice for in vivo functional assessment. All mice were monitored for reversal of hyperglycemia and glucose clearance at 8 - and 20-weeks post-transplant. Grafts were assessed for cell composition and insulin content.

Results: Female mice demonstrated improved glucose clearance at 8- ($p=0.007$) and 20-weeks ($p=0.0096$) post-transplant compared to their male counterparts. Improved glucose clearance correlated with accelerated diabetes reversal in females (8 weeks vs 12 weeks in males, $p=0.0277$) and increased rates of euglycemic achievement (17/ 18 in females vs 14/19 in males, $p=0.0107$). However, grafts collected from male mice exhibited an increased percentage of Insulin+ cells ($p=0.0056$) as well as increased insulin content ($p<0.0001$).

Conclusion: The sex of the host influences the maturation and function of NPIs showcasing the relevance of understanding the role of sex as a biological variable in islet transplantation to improve medical outcomes and address the ethical, legal, and social implications associated with this procedure. Ignoring these differences leads to inequalities in treatment and outcomes, which is why it is essential to consider sex as a key factor to ensure that advancements in islet transplantation are equitable, safe, and effective for all patients.

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ABSTRACT

SYSTEMIC GIP RECEPTOR ACTIVATION INDUCES DIASTOLIC DYSFUNCTION IN MICE WITH TYPE 2 DIABETES

Tanin Shafaati, L. Dong, J.S.F. Chan, M. Stenlund, S.R. Ferrari, F, Eaton, S.A.T Dakhili, J.R. Ussher

Background: The majority of people living with type 2 diabetes (T2D) will eventually succumb to cardiovascular diseases. This includes diabetic cardiomyopathy (DbCM), which is often defined as ventricular dysfunction independent of macrovascular disease, while being characterized by diastolic dysfunction. Glucose-dependent insulinotropic polypeptide (GIP) is an incretin hormone produced by enteroendocrine cells that promotes insulin secretion to improve glycemia in people with T2D. With the recent development of GIP receptor (GIPR) and glucagon-like peptide-1 receptor (GLP-1R) coagonist therapies (i.e. Tirzepatide) for the treatment of T2D, a better understanding of how GIPR activation impacts cardiac function is needed, especially in light of studies reporting that GIPR knockout mice are protected against myocardial infarction.

Objective: We investigated the effects of systemic GIPR activation on cardiac function in mice with experimental T2D.

Methods: 10-week-old male C57BL/6J mice were placed on a high-fat diet for 12 weeks and were administered streptozotocin (75 mg/kg body weight) at week 4 to induce T2D. Starting at week 8, mice were treated with either vehicle control (VC) or the GIPR agonist, D-Ala2 GIP (24 nmol/kg body weight), twice daily for 4 weeks. Cardiac function was assessed via ultrasound echocardiography pre- and post-treatment.

Results: Treatment with D-Ala2 GIP had no impact on body weight or parameters of systolic function (e.g. ejection fraction) in mice with T2D. However, systemic GIPR activation led to diastolic dysfunction (e.g. increased E/e' ratio) when compared to their VC treated counterparts, while also appearing to decrease posterior wall thickness.

Conclusion: In contrast to GLP-1R agonists, GIPR activation may not be associated with salutary actions on cardiac function in T2D.

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ABSTRACT

ARYLACETAMIDE DEACETYLASE (AADAC) REGULATES HEPATIC LIPID HYDROLYSIS AND DE NOVO LIPID SYNTHESIS

Jihong Lian, Randal Nelson, Russell Watts, and Richard Lehner

BACKGROUND: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is characterized and initiated by the accumulation of triacylglycerols (TG) and cholesteryl esters (CE) in the liver. Although it is well established that dysfunction of lipase(s) in hepatic lipid turnover is related to the development of MASLD, the regulation of hepatic lipolysis is not fully understood. Furthermore, enzymes catalyzing hepatic CE hydrolysis at neutral pH in hepatocytes are still unknown. Arylacetamide deacetylase (AADAC) is an ER-localized type II membrane protein and was also identified in liver lipid droplet proteome. Our studies have shown that AADAC catalyzes TG and CE hydrolysis, and AADAC deficient mice present with increased TG and CE concentrations in the liver and increased de novo lipogenesis in hepatocytes.

OBJECTIVES: To elucidate the molecular mechanisms of AADAC in regulating hepatic lipid metabolism.

METHODS: Protein structure prediction by AlphaFold revealed tyrosine residues in the transmembrane domain of AADAC that interact with the lid helix which may regulate substrate access to the active site. As part of a putative inverted Cholesterol Recognition/interaction Amino acid Consensus (CRAC) motif, these tyrosine residues may mediate regulation of AADAC activity by cholesterol. Esterase activity of AADAC was measured after site-directed mutagenesis of these tyrosine residues and after modulation of membrane cholesterol concentrations. To explore the global impact of AADAC ablation on hepatic lipid metabolism, we performed RNA sequencing (RNA-seq) to generate a comprehensive transcriptomic profile of livers collected from WT and AADAC KO mice after one week of high-fat, high-cholesterol western-type diet feeding.

RESULTS: Mutagenesis of tyrosine residues eliminated esterase activity of AADAC, showing their important role in the catalytic function. Cholesterol depletion in AADAC expressing cells increased its esterase activity, while increased cholesterol concentration reduced the activity, suggesting that ER cholesterol is an important regulator of AADAC activity. Lipogenic genes, as well as pathways that support de novo lipid synthesis, were systematically upregulated in the liver of AADAC KO mice.

CONCLUSION: We demonstrated that AADAC is a lipase responsible for performed neutral lipid turnover in the liver. Additionally, AADAC may regulate de novo lipogenesis by modulating ER cholesterol concentration through its CE hydrolase activity.

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ABSTRACT

ADVANCING BIOREACTOR-BASED MATURATION OF NEONATAL PORCINE ISLETS: TOWARDS SCALABLE BETA CELL REPLACEMENT THERAPY

Summer Helmi, Mandy Rosko, Karen Seberger, Chelsea Castro, Andrew R. Pepper, Greg Korbutt.

Introduction: Type 1 diabetes (T1D) is characterized by the targeted destruction of pancreatic beta cells, leading to a lifelong reliance on external insulin and ongoing risk of severe metabolic complications. Despite advances in insulin delivery, current treatments cannot fully mimic natural glucose regulation, leaving many patients exposed to significant health complications. Cell replacement therapy has become a promising approach to achieve euglycemia. Neonatal porcine islets (NPIs) offer a sustainable source of beta cells suitable for xenotransplantation, but current methods for differentiation and maturation are limited by low cell yield and functionality, which hampers clinical development.

Objectives: This study aimed to optimize the differentiation and maturation of NPIs in a GMP-compliant, dynamic bioreactor system to increase islet recovery, functionality, and suitability for scalable beta cell replacement therapy in T1D.

Methods and Results: NPIs were cultured using a PBS Mini Vertical-Wheel Bioreactor® at seeding densities of 4.5K and 6K islets/mL (Bio 4.5, Bio 6) and compared against traditional static plate-based (2K/ml) differentiation. Bioreactor cultures, particularly the Bio 6 condition, demonstrated significantly improved DNA retention and insulin recovery (Bio 6: 34.14 ± 1.31% DNA, 244.14 ± 20.4%, $P<0.001$, 0.001insulin recovery; Plate: 17.45 ± 2.14% DNA, 100 ± 14.85% insulin, $P<0.05$). The proportional representation of beta, alpha, and ductal cells was similar across all conditions; however, overall beta cell recovery in the bioreactor group was markedly higher (Bio 6: 129.86 ± 8.7%; Plate: 80.82 ± 4.7%, $P < 0.001$). Glucose-stimulated insulin secretion assays confirmed that bioreactor-derived NPIs retained glucose responsiveness (stimulation index, Bio 6: 1.80 ± 0.09 vs. Plate: 1.96 ± 0.18), with improved aggregate morphology and reduced islet size, factors previously linked to enhanced vascularization and graft survival. Pilot transplantation studies in diabetic immunodeficient B6.129S7-Rag1tm1Mom/J mice demonstrated that bioreactor-matured NPIs resulted in accelerated normalization of blood glucose levels compared to plate-cultured controls, indicating improved in vivo function.

Conclusions: Dynamic bioreactor-based culture of NPIs significantly enhances cell yield, viability, and functional performance, thereby addressing a key bottleneck in the clinical translation of porcine islet xenotransplantation for T1D. These findings support the scalability and therapeutic potential of this approach, enabling progress toward more effective and accessible cell replacement therapies.

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ABSTRACT

KETONE THERAPY PREVENTS SEMAGLUTIDE-INDUCED LOSS OF SKELETAL MUSCLE MASS

Masaaki Naganuma; Yasser Abuetabh; Mya A. Schmidt; Ramana Vaka; Matthieu C.P. Zolondek; Jody L. Levasseur; Daniela Y. Morales-Llamas; Mahmoud A. El-Ghiaty; Shelly Braun; Darius Sahid; Laibah Khan; Ethan Kwan; Danica K. Roth; Mourad Ferdaoussi; Richard Fahlman; and Jason R.B. Dyck

Background: Glucagon-like peptide 1 receptor agonists (GLP-1RAs), such as semaglutide, are effective in the treatment of obesity, resulting in profound weight loss. However, numerous clinical trials have shown that up to 40% of this weight loss is attributed to loss of fat-free mass, which includes skeletal muscle. Given the importance of skeletal muscle for overall health and mobility, it is possible that the loss of skeletal muscle may negatively impact patients in the longer-term. Although numerous pharmacologic strategies to preserve skeletal muscle mass in patients taking GLP-1RAs have been proposed or tested, the timeline for their clinical approval remains lengthy, highlighting the urgent need for more immediate therapeutic options. We have recently demonstrated that semaglutide-induced weight loss in obese mice results in the downregulation of skeletal muscle β-hydroxybutyrate dehydrogenase 1 (BDH1), a key enzyme involved in ketone metabolism, thus implicating ketone metabolism as a potential mediator of skeletal muscle loss.

Objectives: Given that: 1) the loss of BDH1 in skeletal muscle limits ketone utilization and negatively impacts mitochondrial function by preventing necessary mitochondrial remodeling during times of energetic stress observed during fasting and 2) ketones have been shown to play a major role in maintaining skeletal muscle mass in normal physiology, we speculated that supplementation of ketones during semaglutide treatment could drive ketone utilization in skeletal muscle to protect from loss of mass.

Methods: To achieve chronic elevation of circulating ketone levels, we administered a highly palatable oral ketone supplement, bis-octanoyl (R)-1,3-butanediol (BO-BD), and found that 0.114 g/mL in drinking water effectively induced long-lasting increases in the primary ketone, β-hydroxybutyrate. To investigate the role of this ketone therapy on semaglutide-induced loss of skeletal muscle mass, we fed mice a high-fat diet for 17 weeks to induce obesity. Following this, mice were switched back to a regular chow diet to mimic the lifestyle intervention employed in the STEP1 clinical trial. Mice were then randomized to receive either vehicle (phospho-buffered saline), semaglutide (30 nM/kg/day, intraperitoneally), or semaglutide and BO-BD in their drinking water.

Results: Our data show that ketone supplementation prevented detrimental mitochondrial changes, maintained skeletal muscle mass, and improved muscle function, all while still allowing for normal loss in fat mass.

Conclusions: Based on these findings, we propose that oral supplementation of ketones during semaglutide-induced weight loss is a safe and effective protective strategy that can be rapidly deployed to prevent the loss of skeletal muscle mass during semaglutide treatment of obesity.

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ABSTRACT

BASELINE INSULIN SECRETION DETERMINES THE RESPONSE TO ABATACEPT IN STAGE 1 TYPE 1 DIABETES

Alice Carr, Alfonso Galderisi, Peter Taylor, Jacopo Bonet, David Cuthbertson, Jay Sosenko, Emily K Sims, Carmella Evans-Molina, Chiara Dalla Man, Heba M Ismail, Brandon Nathan, Alessandra Petrelli, Peter A Senior, Jennifer L Sherr, Kevan Herold, William E Russell, Antoinette Moran, Colin Dayan

Background: Abatacept, a CTLA-4 immunoglobulin that inhibits T cell costimulation, was tested for 12 months in people with stage 1 type 1 diabetes in the TrialNet abatacept prevention study to delay disease progression. Despite a modest increase of AUC C-peptide at 12 months in the treated group, the primary endpoint was not met. However, stage 1 type 1 diabetes is metabolically heterogeneous, and C-peptide AUC alone may not capture this.

Objectives: In this post hoc analysis, we adopt the oral minimal model (OMM) to describe insulin secretion trajectory over 48 months and explore how baseline OMM-derived insulin secretion may determine treatment response.

Methods: Insulin secretion (Phitot) was computed using the OMM from the oral glucose tolerance test conducted at baseline and every 6 months up to 48 months from randomization. Within treatment arms, participants were stratified into high- and low-secretors based on baseline Phitot ≥33rd or <33rd centile, respectively, to investigate differential effects of treatment by metabolic phenotype. Trajectories were explored using locally estimated scatterplot smoothing (LOESS) and segmented mixed effects regression. Cumulative incidence of disease progression (Stage 2 or Stage 3 type 1 diabetes), was assessed using Kaplan-Meier curves, stratified by baseline low- and high-secretor groups for each treatment group, censored to 48 months, and compared using Log-rank tests. Cox proportional hazards models were used to calculate hazard ratios (HRs) to estimate the relative risk of progression associated with treatment for each secretor group.

Results: Analysis included 203 participants (96 abatacept and 107 placebo), with 40% of the abatacept group and 50% of the placebo group progressing to Stage 2 or 3 over 48 months. The high-secretor subgroup receiving abatacept exhibited 1.1-year longer progression-free time (p=0.009) with a 49% lower hazard for progression compared to their placebo counterpart (HR 0.51 (95%CI 0.29, 0.89), p=0.018), while abatacept had no effect in the low secretor subgroup (p= 0.9). In addition, treatment of abatacept preserved Phitotal up to 12 months after treatment cessation, with Phitotal increasing over the first 24 months in those receiving abatacept vs. a declining trend in the placebo group (p=0.005), and the effect waning at 24 months after randomization (p=0.9).

Conclusions: Insulin secretion assessed by the OMM enables identification of a treatment responder subgroup to a 12-month course of abatacept, with delayed disease progression. This is the first evidence that an immune intervention administered in stage 1 type 1 diabetes can modulate insulin secretion and slow disease progression in type 1 diabetes.

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2025 RESEARCH DAY

08:00-16:35 | LKS 1-040 (Oborowsky Degner Seminar Hall) & LKS Foyer

THURSDAY, OCTOBER 9th

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