ABSTRACT SUBMISSION FORM

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SEX + GENDER

Exploring the role of sex and gender on health research

CHRD
CHILD HEALTH RESEARCH DAYS

CHRD 2020: Abstract Submission Form

Submitter Name
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Title
Unravelling interactions between sex, diet, and genetics using experimental models of early-onset type 2 diabetes (T2D).

Background
Manitoban Indigenous youth, particularly female adolescents, experience the highest rates of early-onset T2D in Canada. 40% of these youth harbor the G319S variant in the HNF-1α gene. In G319S carriers, clinical evidence implicates pancreatic β-cell dysfunction compounded by modern dietary stress.

Objective
We hypothesize that the G319S variant alters β-cell insulin secretion differentially by sex and by diet.

Methods
CRISPR/Cas9 was used to knock-in the G>A.955 substitution into MIN6 β-cells (G319S-MIN6) and C57/BL6 mice (G/S and S/S) compared to control (G/G). To determine the impact of the G319S variant on β-cell function, insulin secretion and oxygen consumption rates were measured in MIN6 β-cells. To assess whole-body physiology, body weight, insulin sensitivity, and insulin secretion were measured in male and female mice at 6-months-old.

Results
Glucose-stimulated insulin secretion (GSIS) in female G/S islets was reduced 3.5-fold relative to G/G mice, but this impairment was not observed in G319S-MIN6 or in islets from male mice. In these male-derived models, a consistent reduction in basal insulin secretion (BIS) was observed (>2.8-fold). The suppression of BIS may be driven by an observed 1.5-fold elevation in fatty-acid β-oxidation. At the whole-body level, suppressed BIS in male G/S mice translated into reduced fasting plasma insulin (3.4-fold) and elevated blood ketones (2.6-fold), with no changes in body weight or insulin sensitivity.

Conclusion
In a female G/S mouse model, the impairment in GSIS may contribute to accelerated diabetes onset under

modern dietary stress. This will be assessed by placing G319S-expressing mice on a “Western” high-carbohydrate diet. In male-derived models, the G319S variant shifts β-cell metabolism resulting in elevated fatty-acid oxidation and suppressed BIS, possibly triggering ketogenesis and reduced systemic glucose utilization. Whether a high-fat, low-carbohydrate diet (one that resembles the content of traditional food sources) better aligns with metabolic dependencies in male and female mice will be evaluated in future studies.

Theme:
Basic Science

Do you have a table/figure to upload?
No

Are you willing to participate in Goodbear's Den?
Yes

Presenter Status:
PhD Student

What was your role in the project?
All of the above

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