EARLY-ONSET TYPE 2 DIABETES IN INDIGENOUS YOUTH

Examining the role of the HNF-1G319S variant in pancreatic function

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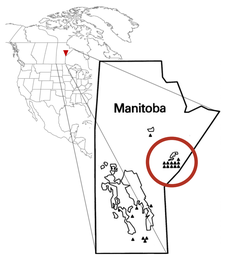
INTRODUCTION

40% of Manitoban Indigenous youth with T2D carry at least one copy of the variant S-allele:

- a single nucleotide substitution in the hepatocyte nuclear factor-1α (HNF-1αG319S) gene.
- Clinical evidence suggests β-cell dysfunction drives T2D.
- HNF-1α is a key transcription factor for β-cell glucose sensing and mitochondrial function.
- **The mechanism through which the G319S variant impacts β-cell function has yet to be defined.**



Dietary Influences:

- The G319S variant was present *prior* to T2D diagnoses.
- The variant may confer an advantage when consuming traditional high fat/high protein foods, but may accelerate T2D when paired with a modern high carbohydrate diet.
- **The relationship between diet and the G319S variant remains unknown.**

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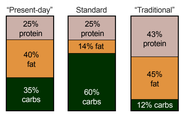
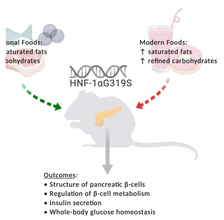


AIM

To determine how the G319S variant interacts with macronutrients affecting:

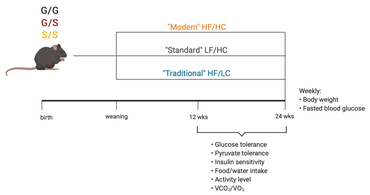
1. The structure and function of pancreatic β-cells;
2. The regulation of β-cell metabolism, insulin secretion, and whole-body glucose homeostasis.



METHODS

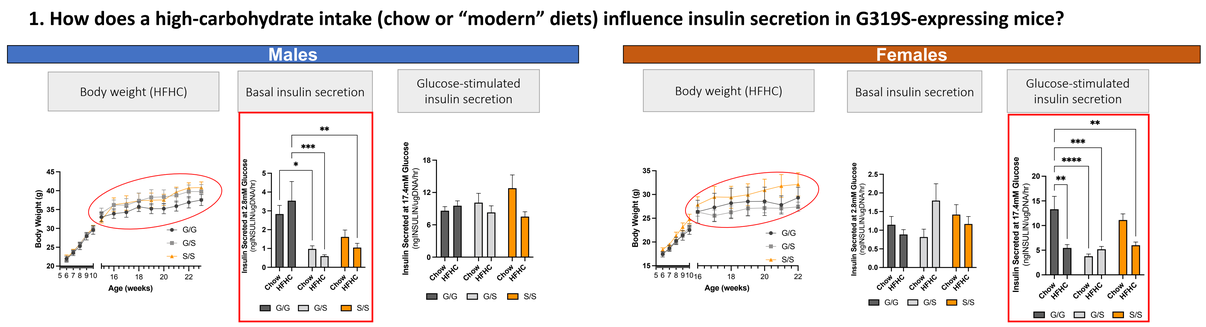
CRISPR/Cas9 was used to knock-in the G>A.955 substitution C57/BL6 mice (male and female). Mice were weaned onto: (1) standard chow, (2) a "traditional" high-fat, low-carbohydrate (HFLC) diet, or (3) a "modern" high-fat, high-carbohydrate (HFHC) diet for 12 or 24 weeks. β-cell function was assessed by glucose-stimulated insulin secretion (GSIS). Metabolic outcomes were assessed by glucose and pyruvate tolerance tests.

Statistics: calculated by one-way or two-way ANOVA.



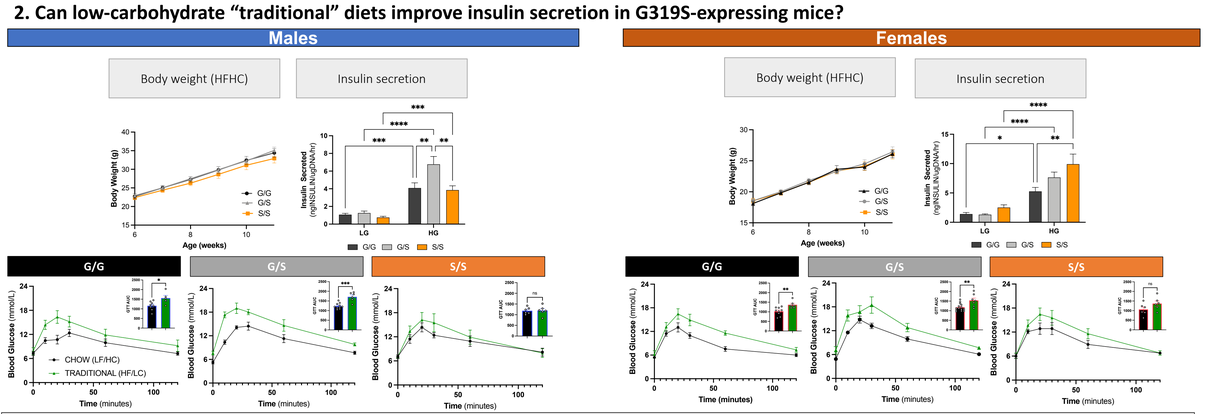
RESULTS

1. How does a high-carbohydrate intake (chow or "modern" diets) influence insulin secretion in G319S-expressing mice?



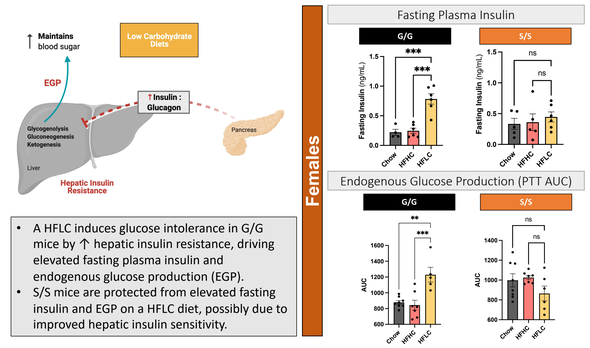
♂ In males, a chow diet suppresses basal insulin secretion in G319S-expressing islets, which is further reduced by a HFHC diet. This is in the absence of impairments in GSIS.
♀ In females, a chow diet impairs glucose-stimulated insulin secretion, which is worsened by a HFHC diet. This is in the absence of changes in basal insulin secretion.

2. Can low-carbohydrate "traditional" diets improve insulin secretion in G319S-expressing mice?



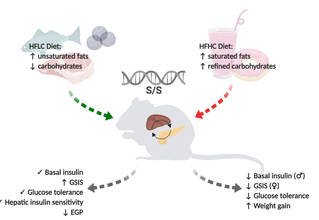
♂/♀ The HFLC diet restores basal insulin secretion (LG), improves GSIS capacity (HG), and normalizes body weight in G319S-expressing mice.
♂/♀ The HFLC diet induces glucose intolerance in G/G and G/S mice, but homozygous S/S mice appear to be protected. The underlying mechanism is addressed in panel (3).

3. How are S/S mice protected from glucose intolerance on a low carbohydrate "traditional" diet?



- A HFLC induces glucose intolerance in G/G mice by ↑ hepatic insulin resistance, driving elevated fasting plasma insulin and endogenous glucose production (EGP).
- S/S mice are protected from elevated fasting insulin and EGP on a HFLC diet, possibly due to improved hepatic insulin sensitivity.

CONCLUSION



- A short-term HFLC diet, designed to reflect traditional food sources, improves insulin secretion and whole-body metabolic outcomes for G319S-expressing mice.
- A long-term HFHC diet, designed to reflect present-day food sources, impairs insulin secretory responses and worsens metabolic outcomes in G319S-expressing mice.

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ACKNOWLEDGEMENTS

We would like to acknowledge the communities, families, clinicians, nurses, and researchers committed to the diagnosis, research, and treatment of T2D in Indigenous youth. TSM is funded by a CIHR Vanier Scholarship and a PIKE-Net Graduate Fellowship.

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