Does the HNF-1aG319S variant confer a metabolic advantage to a traditional First Nations lifestyle but promote youth onset type 2 diabetes under modern dietary conditions?

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INTRODUCTION
• Rate of Youth onset-T2D in Manitoba is 20 times the national average, with ~90% of youth with T2D in Manitoba are First Nations Children
• Historically, T2D was rare in Anishininuwak people when they lived as nomadic hunter-gatherers that entail a lifestyle of long periods of fasting, and consumption of traditional diet high in fat and low in glucose
• Relationship between diet, fasting and the G319S variant on T2D development is not understood

What is HNF-1a?
• Hepatic Nuclear Factor-1a (HNF-1a) is a transcription factor expressed primarily in liver, pancreas, and kidney
• Pancreatic Beta cell: Important for B-cell fate, insulin granule maturation and exocytosis, and glucose stimulated insulin secretion
• Liver: Regulates fatty acid synthesis, and gluconeogenesis.
• A variant of the gene, known as HNF-1a G319S, is present in the Anishininuwak people of Central Canada, and is associated with early onset Type 2 Diabetes

Hypothesis
1. The G319S variant increases hepatic fuel production (gluconeogenesis, glycogenolysis and ketogenesis) after a long term fast, in a gene dose-dependent manner.
2. In the pancreatic beta cells, mice with the G319S variant will show a greater depletion of insulin content (less insulin/reduced number of “mature” insulin granules) after a long term fast.

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METHOD
• G319S-expressing C57BL6 mouse model creating using CRISPR/Cas9
• 3 month-old male and female mice were divided into 2 groups: non-fasted (NF) and fasted for 24hr to assess blood glucose (BG) and ketones (BK).
• Livers were collected for gene expression, triglyceride and glycogen contents. Islets were isolated to assess insulin secretion capacity.

RESULTS
I. 24 Hour Fasted Blood glucose and ketones

Question: How does fasting and diet impact beta cell and liver function?

II. Liver Triglycerides

III. Liver Gene Expression

IV. Fasted Plasma Insulin

V. Insulin Secretion Capacity

CONCLUSION
• There is a shift towards increased triglyceride accumulation in 24 hour fasted G/S male mice, and G/S and S/S female mice.
• In addition, there is a decrease in blood glucose in G/S male mice, and an increase in blood ketones in G/S female mice.
• There is an increase in expression of ketogenic genes such as HMGSCR, and these results indicate a shift towards ketone for fuel.
• Finally, there is an increase in GSIS under conditions in female mice, which is also indicated with increased plasma insulin in G/S female mice.