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INVESTIGATING THE CONTRIBUTION OF THE HNF-1AG319S GENE VARIANT TO EARLY-ONSET TYPE 2 DIABETES (T2D) USING MIN-6 B-CELLS AND MICE

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Background:
40% of Manitoban Indigenous youth with T2D carry a unique variant in the HNF-1α gene (HNF-1αG319S). Clinical evidence suggests pancreatic β-cell dysfunction drives T2D development, further compounded by recent changes in diet due to the disruption of traditional food systems. It remains unclear whether the HNF-1αG319S variant accelerates β-cell dysfunction under modern dietary stress (high in saturated fats/refined carbohydrates), or whether this variant confers metabolic resiliency to off-the-land-foods (rich in unsaturated fats/protein).

Objective:

To define how the HNF-1αG319S variant interacts with metabolic fuels to modulate pancreatic β-cell function and whole-body glucose homeostasis.

Methods:
CRISPR/Cas9 was used to knock-in the G>A.955 substitution into MIN6 β-cells ("G319S-MIN6") and C57/BL6 mice. *In vitro*, glucose-stimulated insulin secretion (GSIS), qPCR and fatty acid oxidation assays were performed. *In vivo*, body weight, glucose tolerance, pyruvate tolerance and insulin sensitivity were assessed in male and female mice.

Results:

HNF-1αG319S did not affect GSIS in MIN6 β-cells; however, basal insulin secretion decreased 3.2-fold relative to control ("WT-MIN6"). Under chronic lipotoxic stress, unlike WT-MIN6, G319S-MIN6 maintained 15-fold GSIS, accompanied by a 2-fold increase in carnitine palmitoyltransferase-1A (*Cpt1A*) gene expression and a 2-fold increase in basal and maximal fatty acid oxidation. 6-month-old G319S-expressing female mice fed a chow diet revealed mild glucose intolerance and elevated hepatic glucose production, despite no changes in body weight or insulin sensitivity.

Conclusion:
The HNF-1αG319S variant may confer resiliency to the high fat intake abundant in traditional Indigenous food sources. During fasting/starvation, reduced basal insulin secretion may contribute to improved maintenance of blood glucose via enhanced hepatic gluconeogenesis; however, interaction of this variant with excessive dietary carbohydrate may trigger hyperglycemia and early-onset T2D. Future studies will address whether reduced dietary glucose and increased lipid consumption is protective in G319S-expressing mice.