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EXAMINING THE ROLE OF THE HNF-1A G319S VARIANT IN LIVER FUNCTION AND EARLY-ONSET TYPE 2 DIABETES

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Background:
Type 2 diabetes (T2D) diagnoses in Anishininiiwuk (Oji-Cree) linguistic group of central Canada are among the highest in the world, and a private genetic variant known as HNF-1a G319S present in this population has been associated with earlier onset of T2D. Historically, Anishininiiwuk peoples were nomadic hunter-gatherers which entailed a lifestyle of long periods of fasting and significant energy expenditure, and during this time T2D in Anishininiiwuk communities were rare.

Objective:
While the G319S variant is currently the strongest genetic predictor of diabetes, it is currently unclear if the G319S variant provides a metabolic advantage in the fasted/starved state.

Methods:
CRISPR-Cas9 was used to create a knock in mouse model to examine how the G319S variant impacts hepatic fuel production and determine if the G319S variant confers a metabolic benefit in the fasted state.

Results:
Pyruvate tolerance tests (PTT) performed on 24-week mice showed that female mice with one or two copies of the variant S-allele (G/S or S/S) fed a standard chow diet displayed elevated endogenous glucose production after a 12 hour fast. Ketone analysis from urine also showed elevated ketone levels in mice with two copies of the variant allele (S/S).

Conclusion:
Female mice that carry the S allele who are fed a chow diet show greater endogenous glucose production and greater ketone production, indicative of a greater capacity to generate and mobilize endogenous fuels. While these early studies are promising and supportive of our hypothesis, future studies will include gene expression analysis, blood hormone analysis, measurement of glycogen content, and investigation of both oxygen consumption and carbon dioxide release after a 12 hour and 24 hour fast.