

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 Anishininiwuk people when they lived as nomadic hunter-gatherers that entailed 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 β -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 Anishininiwuk 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.

ACKNOWLEDGEMENTS

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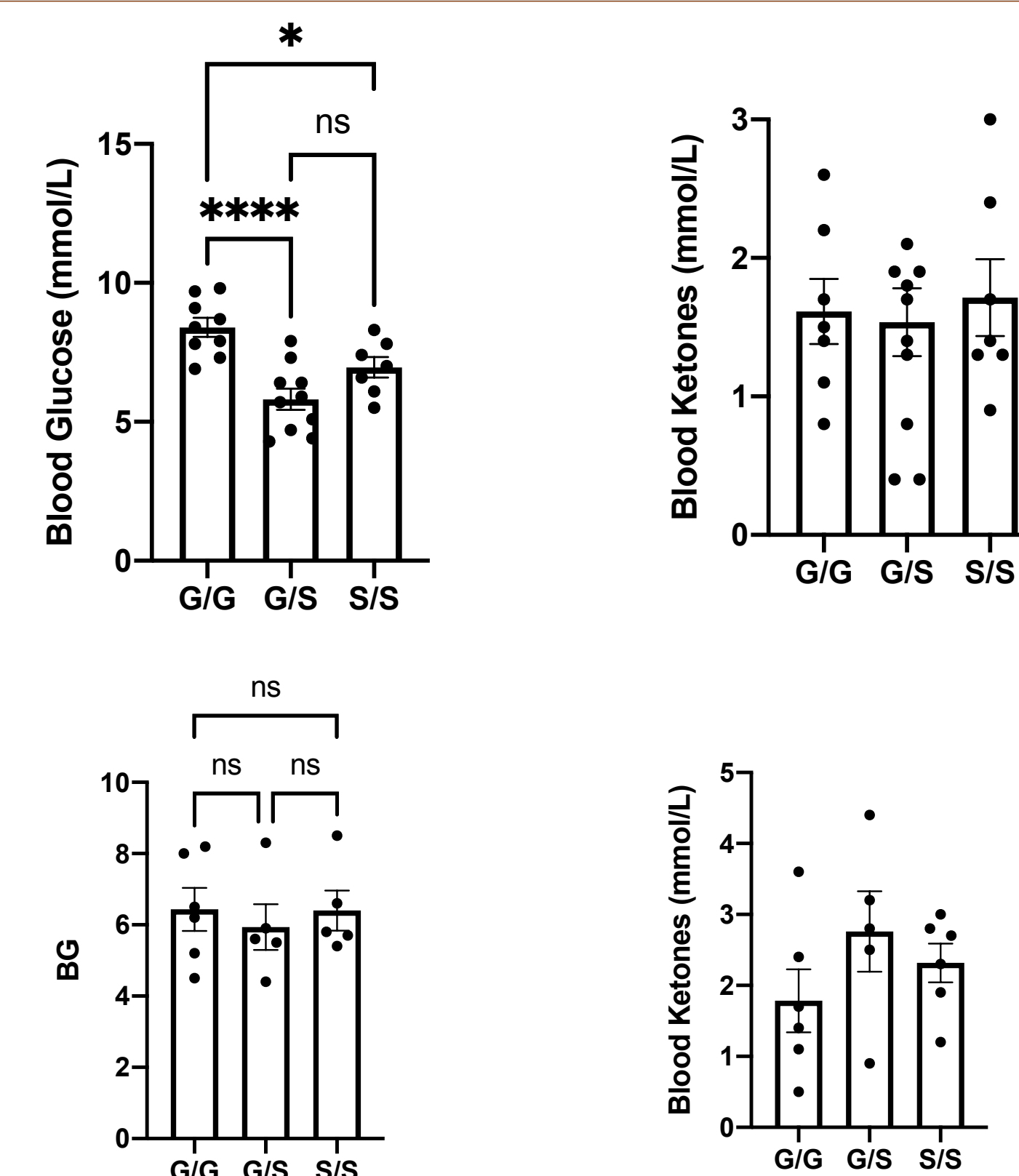
METHOD

- 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.

Question: How does fasting and diet interact with HNF-1a G319S variant and impact beta cell and liver function?

RESULTS

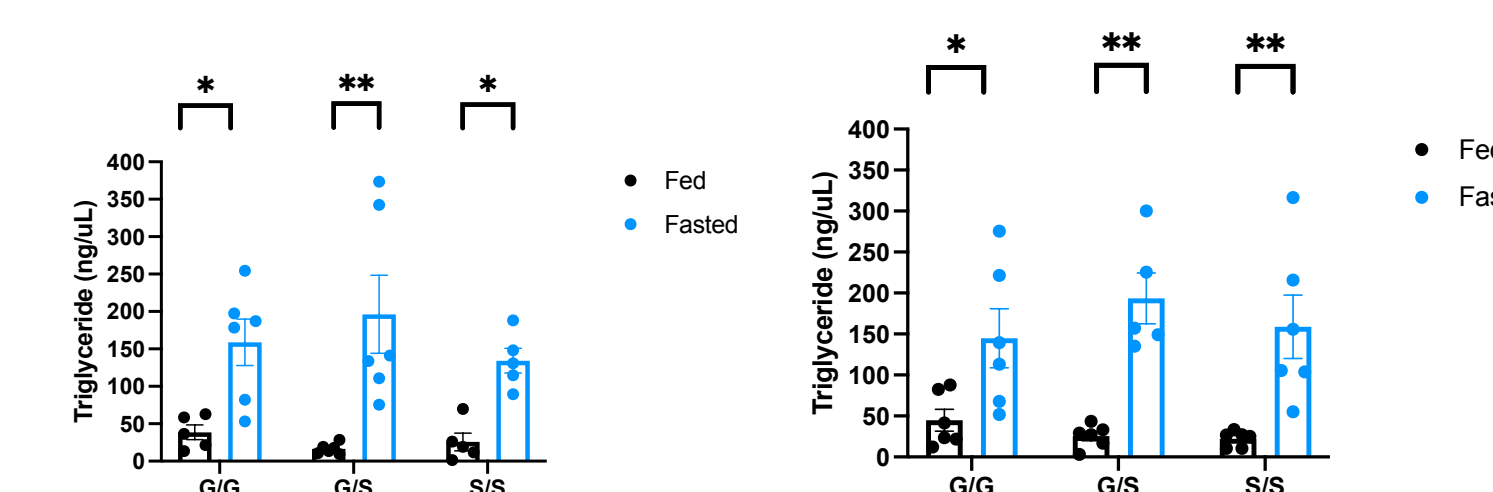
I. 24 Hour Fasted Blood glucose and ketones



3 Month Male and female mice 24 hour fasted blood glucose and blood ketone levels. Data represented as group mean \pm SEM. N=6-10 *p<0.05, **p<0.01, ***p<0.001 determined by 1-way ANOVA

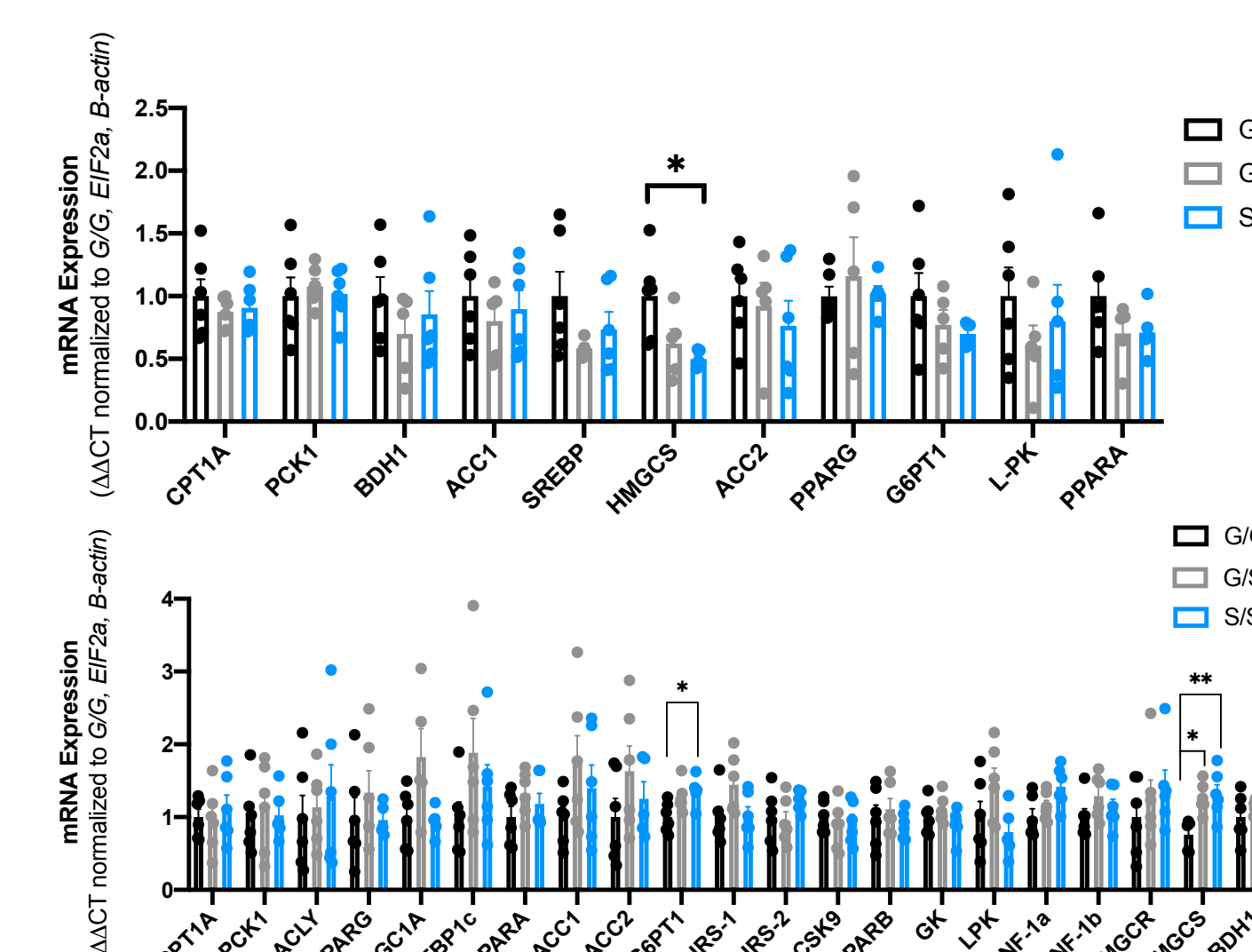
RESULTS

II. Liver Triglycerides



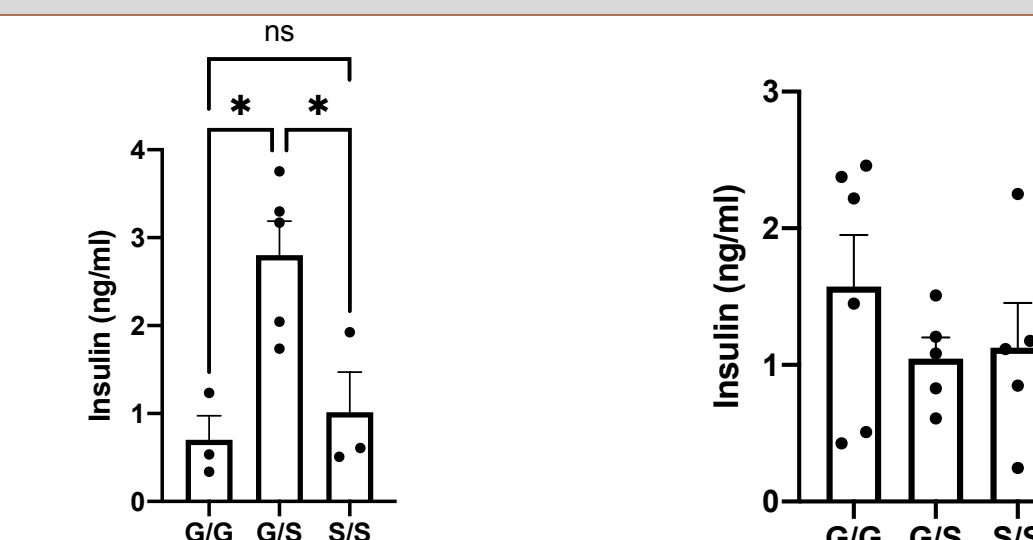
3 Month Male and Female mice 24 Liver triglyceride levels. Data represented as group mean \pm SEM. N=6-10 *p<0.05, **p<0.01, ***p<0.001 determined by 1-way ANOVA

III. Liver Gene Expression



3 Month Male and Female mice 24 Liver triglyceride levels. Data represented as group mean \pm SEM. N=6-10 *p<0.05, **p<0.01, ***p<0.001 determined by 1-way ANOVA

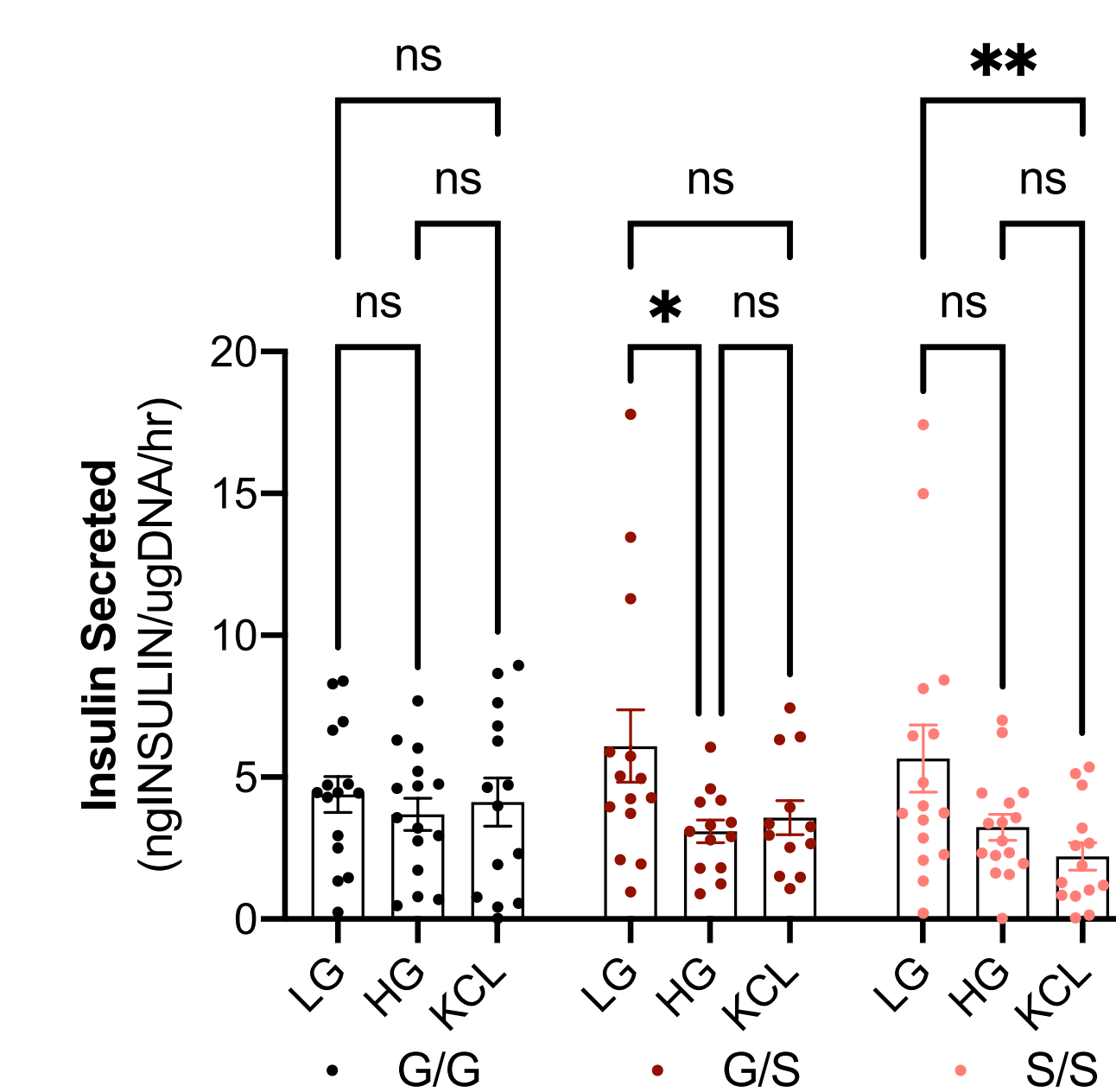
IV. Fasted Plasma Insulin



3 Month male and female mice 24 hour fasted plasma insulin. Data represented as group mean \pm SEM. N=6 *p<0.05, **p<0.01, ***p<0.001 determined by 1-way ANOVA

V. Insulin Secretion Capacity

3 Month HNF1A 24hr Fast Female GSIS



3 Month Female 24 fasted GSIS. Data represented as group mean \pm SEM. N=6-10 *p<0.05, **p<0.01, ***p<0.001 determined by 1-way ANOVA

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 HMGCR, and these results indicate a shift towards ketone for fuel.
- Finally, there is an increase in GSIS under LG conditions in female mice, which is also indicated with increased plasma insulin in G/S female mice.

