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INVESTIGATING THE MOLECULAR AND METABOLIC REGULATORS OF RHYTHMIC INSULIN SECRETION OVER 24 HOURS

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Background:
Manitoban Indigenous Youth are *disproportionately* affected by Type 2 Diabetes(T2D), a condition caused by the failure of healthy β cells. The exact mechanisms underlying β cell failure in T2D remain elusive. More recently, chronodisruption is associated as an important risk factor for developing Type 2 Diabetes (T2D). Healthy β-cells secrete insulin rhythmically over 24hrs to maintain glucose homeostasis. Our lab recently demonstrated rhythmic expression of *Ucp2 over 24hrs* which resulted in daily cycles of insulin secretion capacity; *however,* the regulatory mechanisms that control temporal *Ucp2* expression remain undefined.

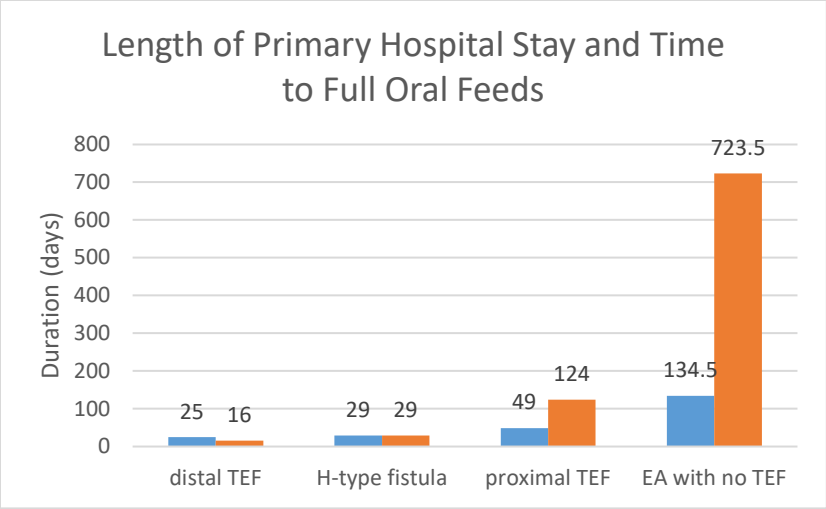
Objective:
The circadian clock regulates daily cycles of *Ucp2* expression and ultimately, daily cycles of GSIS capacity.

Methods:
Bmal1, a core circadian clock machinery component, was knocked down in MIN6 β-like cells using siRNA to establish a cell model of Chronodisruption. We examined the impact of circadian dysfunction on *Ucp2* mRNA expression, GSIS and ATP content were assessed.

Results:
Bmal1 knockdown elevated *Ucp2* mRNA expression 2.4-fold at ZT4 (Zeitgeber time, post-entrainment) comparted to control cells, but had no impact on *Ucp2* expression at ZT16. Upregulation of *Ucp2* at ZT4 was associated with reduced ATP production and impaired GSIS, indicative of reduced mitochondrial uncoupling. Additionally, impaired GSIS observed at 4hrs was ameliorated when a Ucp2-specific inhibitor (Genipin) was applied

Conclusion:
The circadian clock regulates daily cycles of *Ucp2* expression in MIN6 cells, which is a part of an important metabolic switch that aligns GSIS capacity with the time of day. Future studies will explore if these findings are translatable *in vivo* by generating and characterizing a β cell-specific *Bmal1* knockout mouse model.

Figure 1. Length of Hospitalization and Time to Full Oral Feeds



BLUE

Median Length of Stay
*overall 26d (range 0- 268)

RED

Median Time to Full Oral Feeds
*overall 22d (range 6- 3728)