IMPACT OF SHIFTWORK ON RISK OF DIABETES AND CARDIOVASCULAR DISEASE

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Introduction. Insulin is a hormone that regulates uptake of blood glucose in peripheral tissues. When an increase in glucose is detected, the pancreas secretes insulin which stimulates glucose uptake by skeletal muscle and other peripheral tissues for storage. Tight regulation of blood glucose is critical to prevent blood vessel, heart, kidney and nerve damage resulting from hyperglycemia (high blood sugar) in diabetes. Diabetes results from either a failure of the pancreas to secrete insulin or a failure for cells to recognize and respond to insulin (i.e., impaired insulin sensitivity).

Impaired insulin sensitivity is an established risk for type 2 diabetes and just 4 days of insufficient sleep has been shown to decrease insulin sensitivity to pre-diabetic levels in otherwise healthy adults.[1] Alarmingly, this level of sleep loss is similar to what a typical college student could experience during finals week, highlighting quantifiable health consequences to this commonly experienced short-term insufficient sleep. The human circadian system regulates ~24-h physiological sleep wake cycles. Light exposure is the primary time cue that entrains the central circadian clock located in the suprachiasmatic nucleus. At the cellular level circadian clocks are governed by a transcriptional translational feedback mechanism.[2] Shift workers work deep into their physiological night which induces circadian misalignment. Shift work and this associated circadian misalignment has been related to an increased risk of cardiovascular disease, obesity, disrupted glucose tolerance and metabolic syndrome.[3] With shift workers representing ~20% of the global work-force, the adverse physiological consequences of shift-work represent a significant health burden.

The primary aim of this study was to further understand how insulin sensitivity and circadian misalignment are related. All subjects (n=14) completed a 5 day in-laboratory protocol consisting of a control circadian alignment segment and a circadian misalignment segment. Meals were provided and remained constant throughout the study and blood draws were analyzed for insulin and glucose concentrations. We hypothesized post-meal glucose would be elevated during the first day of circadian misalignment versus circadian alignment.

Methods.

Subjects. Inclusion criteria were age 18-39 y; BMI 18.5-24.9; habitual nightly sleep duration >7 h and <9.25 h; low to moderate caffeine use (<500 mg/d); average alcohol use (fewer than two drinks per day and fewer than five drinks per week), and nonsmokers. Exclusion criteria were current or chronic medical/psychiatric conditions; working a shift-work schedule, dwelling below 1,600 m altitude in the year before the study, travel across more than one time zone in the 3 weeks before study, recent self-reported weight loss, and a positive urine toxicology screen. 14

subjects (n=8 females) completed the study. The 14 subjects had a fasting blood glucose of 85.1 ± 5.1 mg/dL and fasting blood insulin of 7.8 ± 3.0 uIU/mLI.

Protocol. Subjects were monitored for 5 days and nights in-laboratory (Fig. 1). Three days prior to check-in at the lab, participants ate an energy balanced diet (neither caloric surplus nor deficit). Three days prior to check-in, participants were not allowed to exercise. Caloric content of energy balanced diets was determined by resting metabolic rate (RMR) using indirect calorimetry. RMR was multiplied by an activity factor of 1.5 to determine final daily calories provided to each subject. Nights 1 and 2 in the laboratory set an arbitrary baseline circadian alignment sleep schedule with a relative 2400 bedtime and 0800 waketime. Day 3 initiated circadian misalignment with a 2 h sleep opportunity (nap) in the afternoon without a night-time sleep opportunity. Day 4 and day 5 provided a sleep opportunity from 0800 to 1800 constituting circadian misalignment. This was to simulate beginning shiftwork after 2 days of adequate and aligned sleep. Subjects were given the same breakfast, lunch, snack, and dinner on each study day with the same intervals with breakfast 1 hour after waketime. On day 2, day 4, and day 5 blood was sampled through an intravenous catheter 30 minutes before and up to 3.5 hours after each meal.
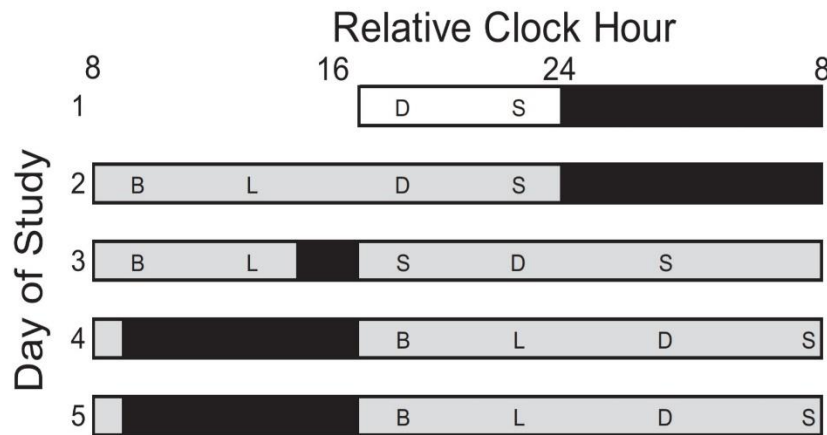

Fig. 1. Protocol and circadian timing (n = 14). (A) In-laboratory protocol with time of day plotted as relative clock hour with scheduled waketime arbitrarily assigned a value of 0800 h and all other times referenced to this. The black rectangles represent scheduled sleep and gray rectangles represent scheduled wakefulness in dim light (<1 lx). On study day 2 subjects were circadian aligned, and on study day 4 subjects were circadian misaligned. B, breakfast; D, dinner; L, lunch; S, snack.

Results.

Average blood glucose (Fig. 2). Subjects consumed identical breakfast meals 1h after scheduled waketime with 0.5 h to consume the entirety of the meal. Fasting glucose (t=-30) was decreased by ~7.4% from Study Day 2 to Study Day 4. At 60 minutes, glucose increased by ~17.2% and ~12.1% on Study Day 4 and Study Day 5 versus Study Day 2, respectively. At 90 minutes, glucose increased by ~43.4% and ~24.3% on Study Day 4 and Study Day 5 versus Study Day 2, respectively. This decrease in blood glucose from Study Day 4 to Study Day 5 suggests potential adaptation to circadian misalignment.

Average blood insulin (Fig. 2). Fasting insulin decreased by ~52.5% and ~27.8% on Study Day 4 and Study Day 5 versus Study Day 2, respectively. At 90 minutes, insulin increased by ~84.3% and ~43.1% on Study Day 4 and Study Day 5 versus Study Day 2, respectively.
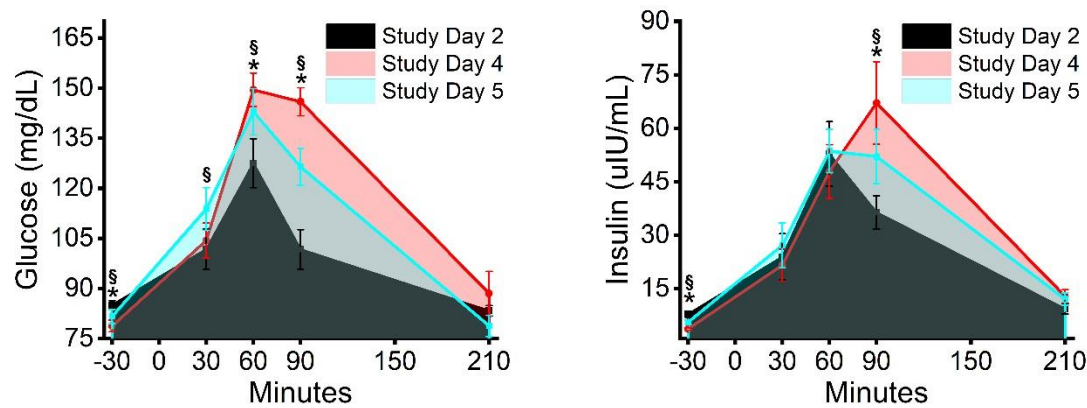
Fig. 2. Effects of circadian misalignment on glucose and insulin (n = 14). The breakfast meal was 1 h after scheduled waketime which constitutes 0 minutes on the graph and subjects were given 30 minutes to consume the meal. The black plot represents blood glucose and insulin on Study Day 2, constituting circadian alighment. The red plot represents Study Day 4 and the cyan plot represents Study Day 5, representing the first and second day of circadian misalignment, respectively. ***** P < 0.05 Study Day 4 versus Study Day 2 circadian alignment at same time point for glucose and insulin (one-tailed t test). **§** P < 0.05 Study Day 5 versus Study Day 2. Data are mean ± SEM.

Blood Glucose and Insulin AUC (Fig. 3). Analyzing the relationship of glucose and insulin using Area Under Curve (AUC) shows glucose, but not insulin, had significant responses to circadian misalignment and shiftwork. Study Day 2 glucose AUC median was 399.0 with 25% and 75% of the data encompassed in an AUC of 392.0 and 445.5 respectively. Study Day 4 glucose AUC median was 484.0 with 25% and 75% of 484.0 and 500.3 respectively. Study Day 5 glucose AUC median was 444 with 25% and 75% of 464.0 and 490.5 respectively. Collectively, glucose AUC increased from Study Day 2 to Study Day 4 and Study Day 5. This suggests higher blood glucose during circadian misalignment. Insulin did not vary significantly from Study Day 2 which had a median of 129.0 with 25% and 75% of 105.5 and 137.5.
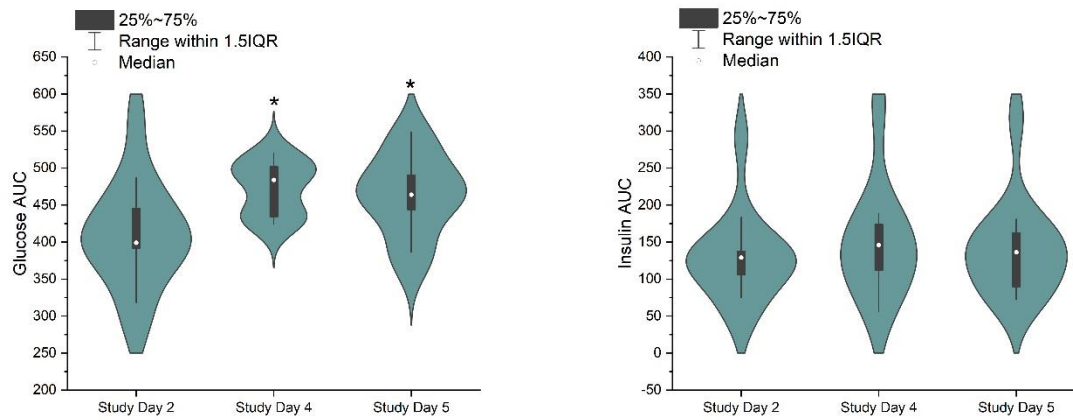
Fig. 3. Effects of circadian misalignment on glucose and insulin AUC (n = 14). Data is from the same breakfast time interval as Fig. 2. This violin plot showcases the data set median in white, 25% and 75% are included in the dark rectangle encompassing the median. The dark line includes data within 1.5 of the Interquartile Range. Outliers are not pictured. The light rounded shape surrounding the box plot, represents individual distribution of data. The wider the shape, the more values in that range. ***** $P < 0.05$ Study Day 4 versus Study Day 2 and Study Day 5 versus Study Day 2 for glucose and insulin (one-tailed t test).

Discussion. Within just two days of circadian misalignment, significant changes in blood glucose and insulin were quantified. While being provided the same meal, at the same offset from waketime, blood glucose was significantly higher at 90 minutes post-meal during both misalignment days. Blood insulin was also significantly higher at 90 minutes. Increased blood glucose and insulin is linked to impaired glucose metabolism and increased risk of diabetes. Epidemiological findings show increased career time in shiftwork to linearly increase risk of diabetes.[3] Our findings suggest dysregulated glucose metabolism during shift-work is one pathway that could mediate this increased risk of diabetes.

Comparing Study Day 4 to Study Day 5 suggests a non-linear trend of metabolic acclimation to circadian misalignment. Glucose at 90 minutes is lower on Study Day 5 versus Study Day 4 ($P < 0.05$). To fully understand if people can adapt to circadian misalignment associated with shiftwork, a protocol over several weeks or months may be required.

Understanding that glucose and insulin impairment can occur with acute exposure to circadian misalignment, mitigation methods must be explored. There may be more physiologically appropriate ways to time meals or control light exposure for people who suffer circadian misalignment like shift-workers or transcontinental travelers. Further biochemical analyses are required to understand cellular and physiological changes in circadian misalignment leading towards downstream consequences noted here.

References:
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