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ORIGINAL ARTICLE

Impairments in glycemic control during Eastbound transatlantic travel in healthy adults

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Abstract

Study Objectives: Repeated bouts of circadian misalignment impair glucose tolerance. However, whether circadian misalignment associated with travel and jet lag impair glucose homeostasis in a free-living population is not known. The goal of the present study was to examine glycemic control during one week of Eastbound transatlantic travel in healthy men and women.
Methods: Seven healthy participants (5 women; age: 35.6 ± 2.5 years, BMI: 23.9 ± 2.4 m/kg^2) traveled from Colorado, USA (GMT-7) to Europe (GMT and GMT+1) and wore a continuous glucose monitor (Freestyle Libre Pro) for 8–14 days before, during, and after travel. Indices of glycemic control were summarized over 24-hour periods and by day and night.
Results: Mean glucose, peak glucose, and time spent in hyperglycemia increased linearly throughout the travel period relative to baseline levels. Mean glucose concentrations rose 1.03 mg/dL (95% CI: 0.34, 1.74) and duration of hyperglycemia increased by 17 min (95% CI: 5.5, 28.6) each 24-hour period. Increases in 24-hour glucose were primarily driven by increases in daytime parameters with rising mean glucose (0.72 mg/dL per day, [95% CI: −0.1, 1.5]) and duration of hyperglycemia (13.2 min per day [95% CI: 4.3, 22.1]). Mean glucose, but not peak glucose or time spent in hyperglycemia, increased each night (0.7 mg/dL per night [95% CI: 0.2, 1.2]).
Conclusions: Eastbound transatlantic travel induced a progressive worsening of glucose metrics during 24-hour, day, and night periods. Future research on managing glycemic control during jet lag in people with metabolic disorders is warranted.
Clinical Trial Registration: None

Statement of Significance

Repeated bouts of circadian misalignment increase the risk for diabetes. Whether such circadian misalignment associated with jet lag impair glucose homeostasis in a free-living population is not known. In this study, Eastbound transatlantic travel impaired glycemic control during 24-hour, day, and night periods, likely due to combination of physiological (e.g. circadian misalignment) and behavioral factors (e.g. energy intake or physical activity). Future research on managing glycemic control during jet lag in people with existing metabolic disorders is warranted.

Key words: jet lag; circadian misalignment; glycemic control; free-living behavior

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Introduction

Circadian misalignment, defined as inappropriately timed sleep- and wake-associated behaviors in relation to the endogenous circadian rhythm [1], is associated with an increased risk of obesity, diabetes, and cardiovascular disease [2–4]. Repeated bouts of circadian misalignment are often unavoidable in modern society (e.g. firefighters, police officers, paramedics, clinical staff, custodial workers, transatlantic travelers). For example, shift workers who chronically experience repeated bouts of acute circadian misalignment have an increased risk of diabetes, which may be compounded by other lifestyle factors including sleep deprivation [5–7]. Indeed, findings from highly controlled laboratory studies demonstrate acute circadian misalignment results in a host of metabolic impairments including increased fasting and postprandial glucose, impaired insulin sensitivity, elevated blood pressure, and increased inflammation [8, 9]. However, the impact of circadian misalignment on metabolic parameters in free-living environments is less well-studied.

Transatlantic travel induces acute circadian misalignment and represents an ecologically relevant opportunity in which to investigate changes in glucose homeostasis in free-living individuals. Therefore, the goal of this study was to examine the acute effects of circadian misalignment associated with jet lag during Eastbound transatlantic travel on glycemic control in healthy young men and women.

Methods

Study population

Seven healthy participants (5 female, 23–39 years old) who were traveling to Europe (GMT or GMT +1) from the continental US (GMT -7) volunteered to participate in this study. All participants were self-reportedly free of cardiovascular disease, diabetes, and any sleep disorders. Participants provided written informed consent, which was reviewed and approved by the Institutional Review Board (IRB) at Colorado State University.

Study design

Healthy participants with planned travel to Europe were recruited for a free-living observational study. Prior to departure, participants met with study personnel for insertion of a continuous glucose monitor (CGM) into the subcutaneous fat on the left or right back side of the iliac crest, depending on preferred sleeping position. In our experience, healthy young individuals prefer to wear a CGM in locations where it can be hidden underneath clothes rather than visible on the upper arm. We have also found that this location will remain in place for a longer duration. Compared with the upper arm placement, the accuracy of this alternative CGM location is 98% [10]. CGMs were inserted at least one day prior to departure and removed when participants returned home. Data analyses were conducted for trip durations for participant ranged from 6 to 14 days.

CGM

CGMs capture acute and dynamic changes in glucose for up to 2 weeks [11]. Interstitial glucose concentrations were assessed by the Freestyle Libre Pro continuous glucose monitor (Abbot, Alameda, CA) CGM every 15 min throughout the study. Glucose concentrations were not displayed on the CGM so participants were blinded to glucose levels. After travel, CGMs were collected from participants and downloaded by research staff.

To examine the acute impact of circadian misalignment due to jet lag, we included CGM data from the day before departure and all days spent in Europe. The day spent in transit (i.e. air travel from origin to destination city in Europe) was excluded. One participant (female, BMI: 24.2 kg/m^2, age: 32 years old) spent only 4 days at their destination and was therefore excluded from analyses. Return journeys were excluded for all participants.

Prior to analysis, CGM data were visually inspected and examined for completeness. All participants wore the CGM for at least 6 days. In 4 participants the CGM was worn for ≥8 days. Glucose values ≤45 mg/dL are indicative of device measurement error and were removed, resulting in <0.10% of data excluded. To be included for analysis, each day was required to have at least 80% of a complete day. Across all participants, a total of 3 days' worth data were excluded because of missing data within a day. After excluding incomplete days of data (5% of total data available), there were 59 days of glucose recordings included in analysis.

Glucose summary metrics

Glycemic control was summarized at baseline (1 day prior to trip departure), and throughout the trip period. Data from the travel day (day 0) were excluded from analyses. For all other time periods, we quantified 24-hour daily glycemic control using the following metrics: mean glucose, total area under the curve (trapezoidal method), peak glucose, glycemic variability (standard deviation and coefficient of variation), and duration of hyperglycemia. Because participants were healthy, we investigated duration of hyperglycemia using two different cut-points: clinically defined 140 mg/dL (HG_{140}) and an individually defined threshold (HG_{IND}). HG_{140} was defined as time spent when glucose was ≥140 mg/dL and HG_{IND} was defined as >2 standard deviations above mean glucose concentrations at baseline for each individual participant. This threshold has been used in previous metrics of glycemic control (e.g. mean amplitude of glycemic excursions, MAGE) [12] to indicate a significant glycemic excursion. By deriving an individualized cut-point for hyperglycemia, we were able to account for inter-individual differences in healthy, normoglycemic participants.

Metrics of glycemic control were also calculated for the day and night of each 24-hour period at baseline and throughout the trip. We defined the timing of the day and night using the clock time that participants reported as their usual sleep and wake timing. Night was defined as the 10-hour window beginning approximately 2 h prior to habitual sleep time to capture approximate melatonin onset [13], and day was defined as the remaining 14 h in the 24-hour period. We used absolute clock times to define day and night to capture the likely behaviors that would be occurring in the origin and destination city. For example, for someone who habitually goes to sleep at midnight, night was defined as 22:00–08:00 at baseline as well as the destination time zone. By defining day and night in this manner, we segment the 24-hour day according to the timing of likely eating and waking behaviors and better capture the participant's behavioral shifts that occur during transatlantic travel.

Statistical analyses

Linear mixed models with repeated measures were used to investigate changes in glycemic control over time. Stratified analyses were conducted to investigate changes in glycemic control occurring during the day and night over time using separate linear mixed models. Secondary analyses expanding linear mixed models by nested splines were performed to model potential non-linear trends in variables over time for 24-hour, day, and night parameters. Significance was set at $p \leq .05$ and data are presented as mean ± standard deviation.

Results

Participant characteristics

Participants were 35.6 ± 2.5 years old with an average BMI of 23.9 ± 2.4 kg/m^2. Participants reported an average habitual sleep duration of 7.9 ± 0.2 h. Average trip duration was 8.9 ± 3.3 days. At baseline, mean glucose concentrations were 84.7 ± 4.6 mg/dL and participants spent 2.4 ± 3.0% of the day above 140 mg/dL (HG_{140}) and 4.0 ± 1.2% of the day in individually defined hyperglycemia (HG_{IND}).

Changes in glycemic control and variability

Compared to baseline, mean 24-hour glucose progressively increased over the course of the travel period by 0.82 mg/dL per day (95% CI: 0.22, 1.4, Figure 1, A, left panel). Twenty-four-hour peak glucose concentration did not significantly increase over time (Figure 1, B, left panel), however, duration of HG_{IND} increased by 12.3 min per day (95% CI: 3.1, 21.7, Figure 1, C, left panel). There were no differences in measures of 24-hour glucose variability (coefficient of variation or standard deviation) over time (data not shown). There was a high degree of individual variability in 24-hour glucose summary metrics and so we present individual data for all glucose summary metrics (mean glucose, peak glucose, and duration of HG_{IND}) in Supplemental Figure 1A-C.

We next investigated glycemic control during the day and night as defined above. Mean day glucose increased significantly over the course of the travel period (0.87 mg/dL per day, 95% CI: 0.02, 1.71, Figure 1, A), as did duration of HG_{IND} (14.9 min per day 95% CI: 5.67, 24.16, Figure 1, C) compared to baseline values. Mean night glucose also increased over the course of the travel period (0.70 mg/dL per day 95% CI: 0.17, 1.22, Figure 1, A, right panel). However, no other glucose summary metrics were significantly different over time during the night (Figure 1, B and C, right panels). Day and night glucose metrics over the course of the travel period are shown for individual participants in Supplemental Figures 2-4.

Non-linear changes in glycemic control and variability were assessed to determine whether there were any signs of a return to baseline in glucose levels during the trip. Non-linear models were not significantly different from linear models, indicating metrics of glycemic control continued to worsen throughout the trip period.

Discussion

In this observational field study, several metrics of daily glycemic control progressively worsened during a period of Eastbound transatlantic travel in free-living healthy adults. Impairments in glycemia were driven primarily by changes during the day when participants were likely awake and eating during the travel period.

There are several mechanisms by which transatlantic travel may impair overall glycemic control. First, Eastbound travel to Europe induces circadian misalignment due to changing time zones, which would require a 7–8 h phase advance of central and peripheral circadian clocks to entrain to the new time zone. The central circadian clock can phase advance by a reported 57 min per day [14]. As a result, an individual who travels briefly to Europe (one week or less), will likely experience circadian misalignment throughout the duration of their entire trip. Figure 2 displays hypothesized biological and behavioral factors over the course of Eastbound transatlantic travel for a participant whose habitually goes to sleep at midnight and wakes at 08:00 in the time zone of origin (night defined as 22:00–08:00 as described above). In this hypothetical scenario, circadian misalignment is predicted to be present for the duration of the travel period. Evidence from laboratory studies demonstrates that circadian misalignment is consistently associated with hyperglycemia, hyperinsulinemia, and impaired insulin sensitivity [8, 15, 16]. Thus, circadian misalignment is likely a key contributor to the continued increase in glucose concentrations observed over the travel period.

Internal desynchrony or misalignment between central and peripheral circadian clocks may also contribute to the observed changes in glucose. Although light remains the strongest zeitgeber for the central clock, non-photic cues such as food intake and physical activity may have an impact on peripheral clock rhythms. For example, Wehrens et al. measured central and peripheral circadian rhythms in healthy adults under constant conditions before and after a 6-day period of a delayed eating schedule [17]. In this study, the delay in food intake did not lead to a shifted central circadian rhythm, but rather delayed the rhythm of the clock gene PER2 in adipose tissue [17]. Further, physical activity may influence peripheral clock rhythms in skeletal muscle. In one such study, mice performed 2 h of daily exercise conducted at the same time each day for 4 weeks [18]. After one month, the circadian rhythm of PER2 in skeletal muscle was shifted by 2–3 h compared to baseline; however, there were no changes in the central circadian rhythm, further demonstrating that non-photic cues impact the rhythm of peripheral tissue clocks [18]. Initial reports in humans also suggest an impact of exercise on the expression of skeletal muscle clock genes in response to acute [19] and chronic exercise [20]. For example, 12-weeks of aerobic exercise in individuals with prediabetes induced a significant increase in the expression of BMAL1 in skeletal muscle at a single timepoint [20]. Whether exercise can shift the entire circadian rhythm of clock genes in human skeletal muscle in not yet known, but may represent a strategy to mitigate the metabolic impairments associated with circadian misalignment [21].

Second, transatlantic travel induces jet lag, which is considered a sleep disorder characterized by daytime fatigue, reduced alertness, and disrupted sleep [22]. Sleep disruption, including reduced sleep duration, can last for several days and up to a week when crossing multiple time zones [23]. Further, insufficient sleep is associated with impaired glucose tolerance, as well as increased glucose concentration and impaired insulin sensitivity [24, 25]. Thus, impairments in glycemia during transatlantic travel are likely also driven by sleep disruption.

Third, eating later in the day, even in the absence of circadian misalignment, has emerged as a risk factor for obesity [26]

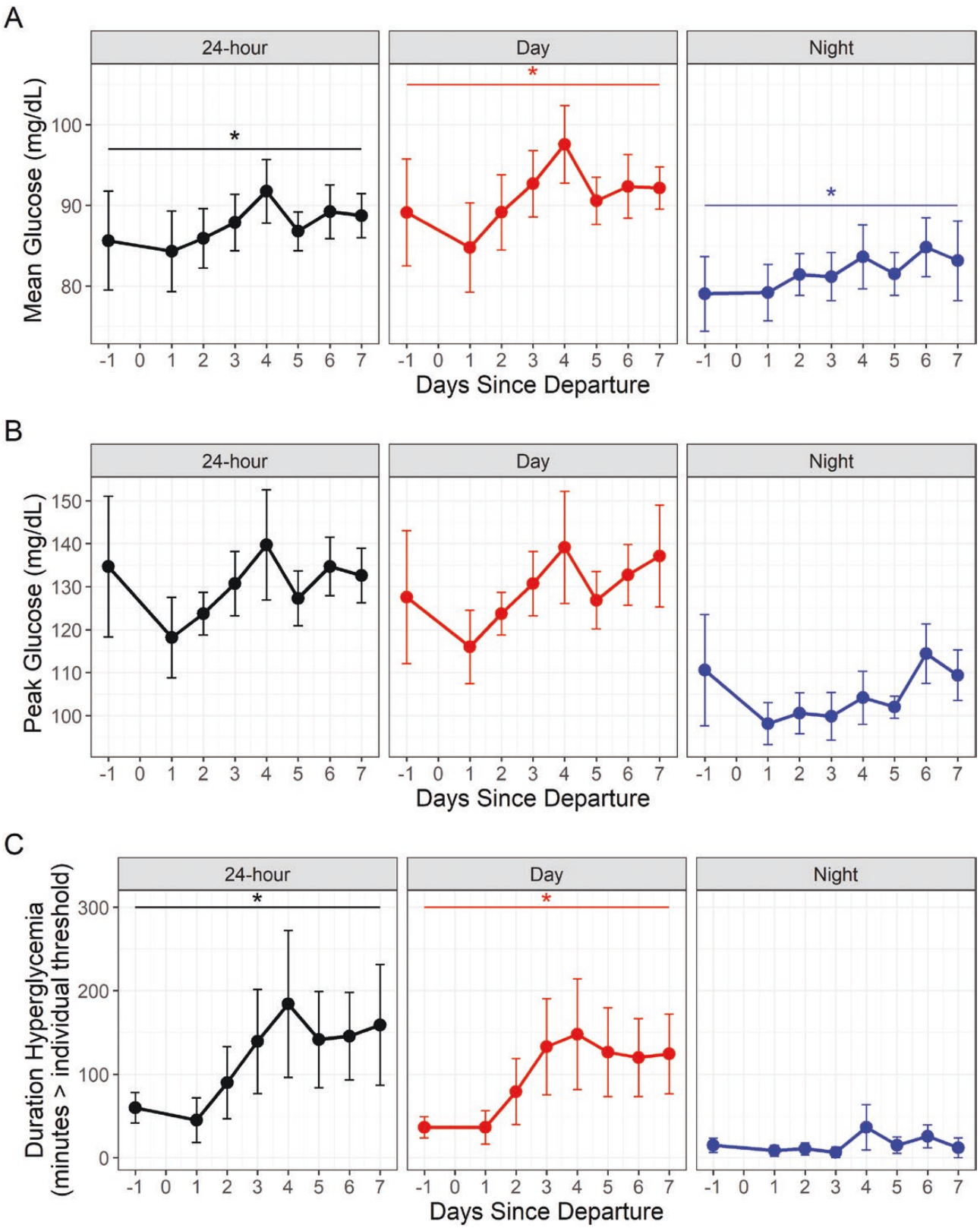

Figure 1. Glucose summary metrics. (A) Mean glucose, (B) peak glucose, and (C) HG_{IND} are summarized over 24-hours (left panel), and during the defined day (middle panel) and night (right panel) periods. Night was defined as a 10-hour window starting 2 h prior to habitual sleep time. Data are presented as mean ± SE. *Significant ($p < .05$) difference over time.

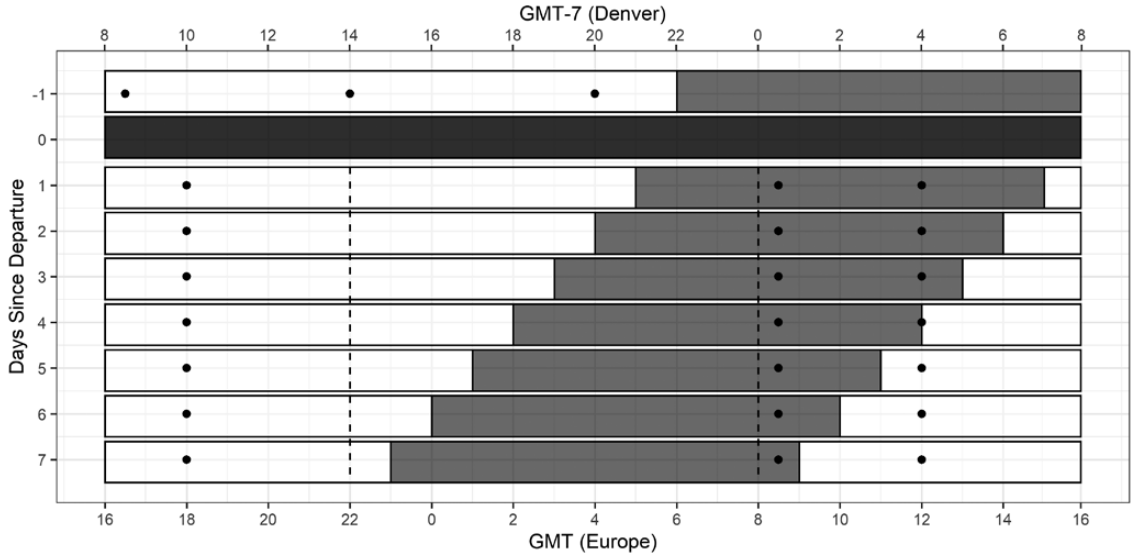

Figure 2. Hypothesized biological and behavioral factors for a participant who habitually goes to sleep at midnight and wakes at 08:00. The night period (defined as the 10-hour window starting 2 h prior to habitual sleep time) is shown in grey during baseline (Day = −1). The travel day (Day = 0, dark grey bar) was excluded due to unpredictable and likely disrupted sleep/wake behavior. The central circadian clock is predicted to entrain at a rate of approximately 1 h per day, as depicted by the phase advance of the grey bars on Days 1–7. Dashed lines represent the period of time that would be classified as Night (and participants would likely be sleeping) according to local time while participants were traveling in Europe. Clock time is displayed on the upper x-axis as GMT-7 (local time zone prior to travel) and on the lower x-axis as GMT (local time zone during travel). Black circles represent potential eating occurrences for someone who typically consumes 3 meals per day.

and is associated with glucose intolerance [27]. Further, eating during the biological night (i.e. when melatonin levels are high and individuals are typically asleep) leads to elevated circulating glucose and insulin concentrations [8, 28]. Even when macronutrient composition is matched, food intake at night results in higher glucose peaks without compensatory hyperinsulinemia compared to a meal consumed during the day [29].

The progressive and immediate worsening of several glycemic control metrics in the current study may reflect repeated episodes of eating during the biological night due to circadian misalignment during travel. Although participants did not record mealtimes, it is likely that participants had several eating events throughout the course of their trip that would fall during the time they would normally be asleep in the time zone of origin, as shown in Figure 2. Though we cannot separate the impact of mistimed eating from circadian misalignment and sleep disruption, eating when participants would normally be sleeping may contribute to elevated glucose levels observed in the present study.

To better understand individual glycemic responses and patterns, we also examined mean glucose levels over time for each individual participant (Supplemental Figure 1A and Supplemental Figure 2). Although there was high variability between subjects, the overall glucose elevation observed on Day 4 was present in most participants. It should also be noted that no participants traveled together or to the same venue, so there was no specific event or meal that occurred on Day 4 in all participants. Without information on sleep and eating behaviors, factors driving this elevation are not clear and will be explored in future studies.

Strengths and Limitations

Strengths of the current investigation include the utilization of wearable technology to capture the physiological the impact of sleep loss and circadian misalignment in an ecologically relevant field study of young healthy adults. Applying CGMs in this setting is novel and demonstrative of the potential of wearable sensors to assess aspects of physiology outside of strict laboratory settings. Furthermore, we calculated several metrics of glycemic control and derived novel individualized thresholds of hyperglycemia (HG_{IND}) to better capture the potential glycemic impairments that may occur in normoglycemic individuals. Recent consensus panels have agreed that individualized thresholds to indicate periods of hyperglycemia are appropriate, though no standards have been defined [12]. Our decision for the threshold of hyperglycemia for HG_{IND} is rooted in previous metrics, like the mean amplitude of glycemic excursions (MAGE), which use the same threshold (2 standard deviations above the mean) to indicate a significant glucose excursion.

Several limitations also exist in the present study that should be acknowledged. For example, although we obtained frequent assessments glucose concentrations and conducted an in-depth assessment of glycemic control, we did not collect detailed information on behavioral factors that impact glucose such as sleep, diet, and physical activity. Travel is associated with changes in eating patterns including altered macronutrient composition (e.g. higher consumption of fatty foods, sweets, and alcohol) and increased eating occasions in restaurants [30]. These changes in dietary habits could translate to increases in circulating glucose concentrations. Physical activity may also have changed, though studies are inconsistent and report both increased [31] and decreased [32] levels during travel. Inclusion of a control group in which participants traveled within the same time zone could have provided insight into behavioral changes associated with travel.

We also did not ask participants to record sleep/wake timing prior to or during the travel period, though we did collect self-reported sleep habits. Future studies should consider incorporating additional wearable technology to objectively

capture behavioral components known to affect glycemic control including sleep, diet, and physical activity to better understand the contributions of circadian misalignment, sleep, and meal intake on glycemic control. In addition, the duration of time required for glycemia to return to baseline levels in the destination time zone is unclear, and an extended assessment period is required to investigate this question. Finally, it must be recognized that our results are limited by the small sample size in the present study.

Conclusions

Significant and immediate deteriorations in glycemic control were observed in young healthy adults without signs of improvement or adaptation over the course of one week of Eastbound transatlantic travel. Elevations in glucose levels were likely driven by a combination of physiological and behavioral factors including continued circadian misalignment, insufficient sleep, and mistimed food intake.

Air travel has increased dramatically over the last decade, resulting in a greater number of people exposed to acute and repeated bouts of circadian misalignment. Further, the Bureau of Transportation Statistics reported over 200 million passengers in the United States traveled internationally in 2018 [33]. With so many individuals exposed to this type of circadian misalignment, important health considerations should be made to mitigate the impact of international travel on glucose homeostasis. It will be particularly important to consider countermeasures to circadian misalignment in frequent travelers at elevated risk for cardiometabolic diseases (e.g. individuals with prediabetes, overweight, or obesity, as well as people with existing sleep disorders). For example, circadian misalignment associated with chronic shift work in people with diabetes is associated with worse glycemic control [34].

Understanding factors responsible for impairments in glycemic control during travel is a necessary step in developing effective methods to manage glycemia during jet lag, particularly in people with existing metabolic disorders.

Supplementary Material

Supplementary material is available at *SLEEP Advances* online.

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Author Contributions

JLB developed the idea and designed the study. JMB, CV, and JLB were involved in the collection, analyses, and interpretation of the data. All authors were involved in writing the paper and had final approval of the submitted and published versions. JLB is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosure Statement

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