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The Impact of Circadian Misalignment on Cardiometabolic Health

Cynthia Marie Mills
University of North Dakota

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THE IMPACT OF CIRCADIAN MISALIGNMENT ON CARDIOMETABOLIC
HEALTH

by

Cynthia Marie Mills
Bachelor of Science, University of Central Florida, 1999

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Abstract

The circadian system is important in all living organisms because it generates a 24-hour rhythm for physiological and behavioral processes enabling anticipation and adaptation to daily changes in the environment. The prevalence of cardiometabolic diseases, which are linked to lifestyle choices, has been rising at an alarming rate. Modernization and globalization are two of many factors to blame for lifestyle changes resulting in circadian disruption. The purpose of this literature review is to explore circadian misalignment with regards to its mechanism and impact on cardiometabolic health and to determine possible interventional measures. The primary focus is on lifestyle change, particularly sleep, as an interventional measure for circadian misalignment. Studies were included if they included a cardiometabolic disease risk factor studied in the context of circadian alignment/misalignment or sleep duration/architecture. The data indicates that circadian misalignment and sleep deprivation impede cardiovascular function and cause a decrease in glucose tolerance and insulin sensitivity; however, restoring circadian rhythmicity and correcting for sleep deprivation improves several health indices including glucose tolerance, insulin sensitivity, blood pressure, and cardiac remodeling.

Keywords: circadian rhythm, circadian misalignment, chronotype, social jet lag, shift-work, delayed sleep phase, advance sleep phase, irregular sleep, sleep deprivation, non-24-hour, free running, and phase angle.

The Impact of Circadian Misalignment on Cardiometabolic Health

Introduction

The circadian system serves one of the most important functions present in almost all organisms because it generates 24-hour rhythms in physiological and behavioral processes enabling anticipation and adaptation to daily changes in the environment (Baron & Reid, 2014). Globalization and modernization, night shift work, and nighttime light exposure have resulted in disruption of sleep which in turn disrupts the circadian system, causing increased prevalence of cardiovascular disorders and metabolic diseases (Chen & Yang, 2015; Krishnan & Lyons, 2015; Paschos, 2015). The circadian system is vital in the regulation of glucose metabolism; if a disturbance occurs in the circadian system, cardiovascular and metabolic diseases will likely be experienced. Therefore, the purpose of this paper is to review the literature about causes, effects, and interventions for circadian misalignment. The primary focus of the literature review is to establish whether lifestyle changes, especially sleep adjustment, can address circadian dysregulation in order to improve an individual's cardiometabolic profile.

Statement of the Problem

Weight loss, physical activity, and nutritional modification are all lifestyle changes currently recommended for improving cardiometabolic health; however, sleep hygiene is rarely addressed though mounting evidence suggests that both sleep deprivation and circadian misalignment contribute to the development of cardiometabolic diseases.

Research Questions

Does adequate sleep at the appropriate time have the potential to halt pathological progression and improve cardiometabolic health before overt disease ensues?

Should adjusting one's chronotype to reduce sleep debt, social jet lag, and circadian misalignment be included in lifestyle modification recommendations?

Research Methods

To prepare this article, the author searched CINAHL, Clinical Key, Cochrane, PsycINFO, PubMed, ResearchGate, and ScienceDirect databases and selected articles to provide a broad overview of the field of circadian misalignment, focusing primarily on cardiovascular disease, diabetes, obesity, circadian rhythm, and sleep disruption. The search included the following key words, phrases and MeSH terms: circadian rhythm, circadian misalignment, chronotype, social jet lag, shift-work, delayed sleep phase, advance sleep phase, irregular sleep, sleep deprivation, non-24-hour, free running, and phase angle. The initial search encompassed the past five years (2012 – 2017) but was expanded to include the past ten years (2007 – 2017) to obtain important preliminary research. Studies were included if they included a cardiometabolic disease risk factor studied in the context of circadian alignment/misalignment or sleep duration/architecture. This article is not a systematic review encompassing all published articles of circadian misalignment. Although the review includes important animal studies, it mostly focuses on human studies of healthy participants beginning with observational studies that provide insight into the prevalence of circadian rhythm and sleep disruption and their effects on cardiometabolic health, then progressing to the effects of sleep timing and length on cardiometabolic health.

The Circadian System

Living organisms are subjected to environmental changes which are imposed by the continuous 24-hour rotation of the earth around its axis (Fuhr, Abreu, Pett, & Relógio, 2015). In order to be prepared for environmental changes, organisms have developed a circadian clock. The circadian clocks are endogenous timekeeping systems that have evolved to anticipate the behavioral and physiological needs of most living organisms. According to Fuhr et al. (2015), the mammalian circadian clock is organized hierarchically by a master pacemaker which is found in the suprachiasmatic nucleus (SCN) of the hypothalamus. Intrinsically photosensitive retinal ganglion cells containing melanopsin transmit light-dark information to the SCN allowing the SCN to synchronize biological processes with the external environment. The paraventricular hypothalamic nucleus then relays the circadian information from the SCN to subsidiary peripheral oscillators which are present in almost all cells of the body (Lin, Huang, & Juan, 2015). At a molecular level, interconnected transcriptional and translational feedback loops (TTFLs) generate circadian rhythms and regulate biochemical processes. Central and peripheral circadian clocks are affected by circulating levels of hormones which vary over the course of a 24-hour circadian cycle. Melatonin affects the SCN and the sleep-wake cycle, glucocorticoids affect the SCN and body temperature regulation with regard to the exogenous light-dark cycle, and glucose affects the SCN and insulin secretion rhythms. Together the hormones and circadian clocks regulate energy homeostasis.

Circadian Misalignment

The circadian clock is endogenous; it functions even if there are no environmental cues. According to Flynn-Evans, Barger, Kubey, Sullivan, and Czeisler (2016), "In the absence of exposure to light of sufficient intensity, timing, duration, and spectral composition, human

circadian pacemakers will revert to oscillating at their intrinsic period, which is slightly longer than 24 hours for most individuals” (para 3). The circadian clock is also entrainable, meaning it can be reset by exposure to exogenous stimuli. Exogenous stimuli that affect the circadian clock are called zeitgebers. Zeitgebers help synchronize the internal circadian clock located in the SCN to the external light-dark cycle of the environment. Light exposure is the most potent zeitgeber (Fuhr et al., 2015) and consequently is the primary synchronizer of human circadian rhythms. Melatonin, food, exercise, noise, and temperature are also zeitgebers. The timing of these zeitgebers is highly significant, in that they will have a different effect on the circadian rhythm depending on the time of exposure. For example, morning light will advance (move earlier) whereas evening light will delay (move later) the circadian rhythm. Excessive light exposure at night leads to perturbations in the melatonin rhythm and disruption of the circadian system (Flynn-Evans et al., 2016).

Circadian disruption is a biological timing disturbance, a misalignment of behavior with environmental cues. When behaviors such as sleep timing and meal intake occur at inappropriate times relative to the SCN (the master circadian clock) and the external environment’s light-dark cycle desynchrony occurs which results in circadian misalignment. Changes in the established circadian rhythm result in clock lesions, which lead to circadian dysregulation (desynchronization between the central and peripheral circadian clock systems), irregular sleep patterns, and abnormal eating schedules, all of which are associated with obesity, insulin resistance, and cardiac arrhythmias (Lin et al., 2015).

Prevalence of Circadian Rhythm Disruption in the United States

Because many behaviors lead to circadian misalignment - social jet lag (changes in sleep schedule between work and weekend days), chronotype preference (an individual’s natural

inclination to sleep early in the evening or stay up later), daylight savings time, trans-meridian travel and shift work - it is difficult to assess the actual prevalence of circadian disruption.

However, two of the leading contributors are workdays spent indoors coupled with excessive nighttime light exposure due to electronic devices and shift work, which together encompass a clear majority of the nation's workforce. Modern technology has altered the conventional solar day by increasing exposure to artificial lighting at night disrupting endogenous circadian rhythms. Compelling evidence that the risk for developing cardiometabolic disorders due to circadian rhythm disruption is observed by researchers conducting experiments simulating rotating shift work.

Studies indicate, according to Forsyth, Voigt, Burgess, Swanson, and Keshavarzian (2015), that shift workers, who constitute approximately 15 to 20 % of the United States workforce, are impacted by chronic circadian misalignment. Shift work has no universal definition, but encompasses any work schedule that requires an individual to be awake at a time that the endogenous circadian rhythm anticipates sleep. Leproult, Holmbäck, and Van Cauter, (2014) indicated that roughly 20 % of adults in industrialized countries worldwide are shift workers and are affected by circadian misalignment. Takahashi (2014) stated that 28.7% of the US population is either night or shift workers. Qian and Scheer (2016) are of the opinion that at least 80% of the population in the US is exposed to artificial light during the night, and between 50 and 70 million people in the US have a chronic sleep disorder.

Impacts of Circadian Misalignment

The Circadian System and Cardiovascular Diseases

Circadian rhythmicity affects both the myocardium and central and peripheral vasculature. Cardiomyocytes contain a circadian clock that regulates energy metabolism,

contractile rate, electrophysiology, and injury response in the myocardium (Zang, Sabeh, & Jain, 2014). Cells in the vascular smooth muscle have a similar intrinsic clock that governs diurnal blood pressure variations. To ensure a proper response to predictable daily changes in the external environment, these peripheral molecular clocks must be synchronized with the central circadian clock. Desynchronization between the central and peripheral clocks occurs when the normal day-night or light-dark cycle is disrupted by excessive nighttime light exposure, jet lag, or shift work; per Chen and Yang (2015) this desynchronization causes a domino effect of disrupted biochemical and physiological processes, potentially leading to cardiovascular disease.

Studies have shown that shift workers have impaired glucose tolerance, higher total cholesterol, lower high-density lipoprotein, worse beta-cell function, and a higher incidence of metabolic syndrome than their counterparts, who work only during the day (Reutrakul & Knutson 2015). These are all risk factors for cardiovascular disease. During a ten-day trial, Scheer, Hilton, Mantzoros, and Shea (2009) forced circadian disruption in ten healthy adult subjects by using a 28-hour sleep-wake cycle while maintaining the usual 1:2 sleep-wake ratio, and controlling for glycemic changes by using four isocaloric meals during each wake cycle. To separate the effects of behavior from endogenous circadian rhythm effects, they uniformly distributed the behavioral cycle throughout all phases of the circadian cycle. Via hourly samples of plasma insulin, glucose, and cortisol, they found that the circadian rhythm itself influenced blood glucose levels (change in glucose throughout the day: $p = 0.018$, peak to trough 4 %) independent of behavior, and that postprandial plasma insulin levels increased by 22 % and glucose by 6 % during circadian misalignment; confirming their hypothesis that insulin resistance and poor pancreatic beta-cell response result during circadian misalignment. Additionally, they measured blood pressure frequently and found a three mmHg increase in

mean arterial blood pressure during the wake cycle. While this trial controlled for environmental and behavioral conditions the sample size was rather small and the trial did not mimic real life in that the subjects spent the entire ten days in the laboratory and did not go about their normal daily routine.

Martino et al. (2007) induced circadian rhythm disturbance by exposing mice to a twenty-hour day – ten hours of light/ten hours of dark – and found that these conditions altered expression of cardiac remodeling genes and adversely affected cardiac structure and function. They also found that resynchronization of the circadian rhythm resulted in a reversal of the abnormal cardiac pathophysiology. Human trials inducing circadian rhythm disturbance via a 28-hour day while limiting sleep to 5.6 hours per cycle for three weeks were conducted by Buxton et al. (2013). They, like Scheer et al. (2009), conducted their study in a laboratory that controlled environmental and behavioral factors but did not mimic a subject's normal daily routine. 24 subjects stayed in a temperature controlled laboratory free of external circadian cues and received isocaloric meals (55-60 % carbohydrate, 15-20 % protein, and 15-30 % fat). They found that pancreatic beta cells did not respond adequately during circadian disruption accompanied by sleep deprivation because glucose levels increased 8 % above baseline while subjects were fasting ($p = 0.0019$) and by 14 % above baseline postprandially ($p = 0.0004$). Buxton et al. allowed for a nine-day recovery period where the endogenous circadian rhythm was followed, and subjects were allowed to sleep up to ten hours per 24-hour cycle; at the end of the nine-day recovery period, fasting and postprandial glucose levels had returned to normal, and pancreatic beta-cells were functioning adequately. These findings suggest that cardiovascular health relies at least in part on the synchronization of the central circadian clock with the peripheral circadian clocks.

The Circadian System and Metabolic Disease

Increasingly obvious is that circadian alignment is necessary for metabolic homeostasis and that environmental cues affecting circadian rhythms play essential roles in maintaining metabolic homeostasis. Modern 24-hour lifestyles promote the development of obesity and type 2 diabetes because they create disharmony between external cues and internal circadian timing, compromising metabolic homeostasis. Night shift workers have a higher incidence of obesity compared to their day shift worker counterparts, and chronic shift work is associated with a higher body mass index (BMI). (Pan, Schernhammer, Sun, & Hu, 2011). In a long-term study that followed 177,184 female nurses who worked at least three night shifts per month plus several day and evening shifts in the same month, Pan et al. (2011) found that the risk of developing diabetes increased with the duration of years that rotating night shift hours were part of the subject's work schedule. Using females who never worked night shift hours as the control group the researchers found that "the pooled hazard ratios [for developing diabetes] (95% confidence intervals) for participants with 1–2, 3–9, 10–19, and ≥ 20 years of shift work were 1.05 (1.00-1.11), 1.20 (1.14-1.26), 1.40 (1.30-1.51), and 1.58 (1.43-1.74, p-value for trend < 0.001), respectively" (Pan et al., 2011, p. 2) and that body mass index further attenuated the association of shift work with diabetes.

Desynchronization between meal timing, the endogenous circadian rhythm, and external light/dark cues causes a decrease in glucose tolerance and an increase in insulin resistance (Buxton et al., 2013). Glucose tolerance decreases as the day progresses regardless of eating behaviors per Morris et al. (2015). They found that glucose tolerance was reduced by circadian misalignment, indicating that circadian rhythmicity contributed to glucose tolerance and insulin

response. They identified and investigated three separate contributors to glucose tolerance: the behavioral cycle (normal meal timing, meaning breakfast after waking and dinner a few hours before sleeping), normal circadian phase versus circadian phase inversion (sleep during the light phase and wakefulness during the dark phase), and endogenous circadian misalignment defined as meal timing adverse to the exogenous light/dark cycle that guides the SCN (causing desynchronization between the SCN and the peripheral circadian clocks). The behavior cycle showed no effect on fasting glucose. However, postprandial glucose was 8 % ($P < 0.0001$) higher after dinner than after breakfast (Figure 1) regardless of whether breakfast was eaten in the biological morning or biological evening, indicating the behavior cycle has an independent influence on glucose tolerance separate from that of the circadian system. The circadian system did not affect fasting glucose either, but postprandial glucose was 12 % higher in the biological evening versus the biological morning ($P < 0.0001$) (Figure 1) regardless of whether the subject slept during the dark phase or light phase of the solar day. Interestingly, though the circadian system did not affect fasting glucose, fasting insulin was 21 % lower in the biological evening versus the biological morning ($P = 0.024$) regardless of whether the subject slept during the light or dark cycle. So, both systems contribute to glucose intolerance; the behavioral cycle shows a deterioration of glucose tolerance from breakfast to dinner and the circadian phase shows a deterioration of glucose tolerance from the biological morning to the biological evening. During circadian misalignment, independent of circadian phase or behavioral effects, postprandial glucose increased 6 % ($P = 0.0003$) and insulin sensitivity was reduced, but fasting glucose was not affected, indicating that circadian misalignment itself lowers glucose tolerance. Because Morris et al. controlled for variables that allowed them to separate the effects of the behavioral

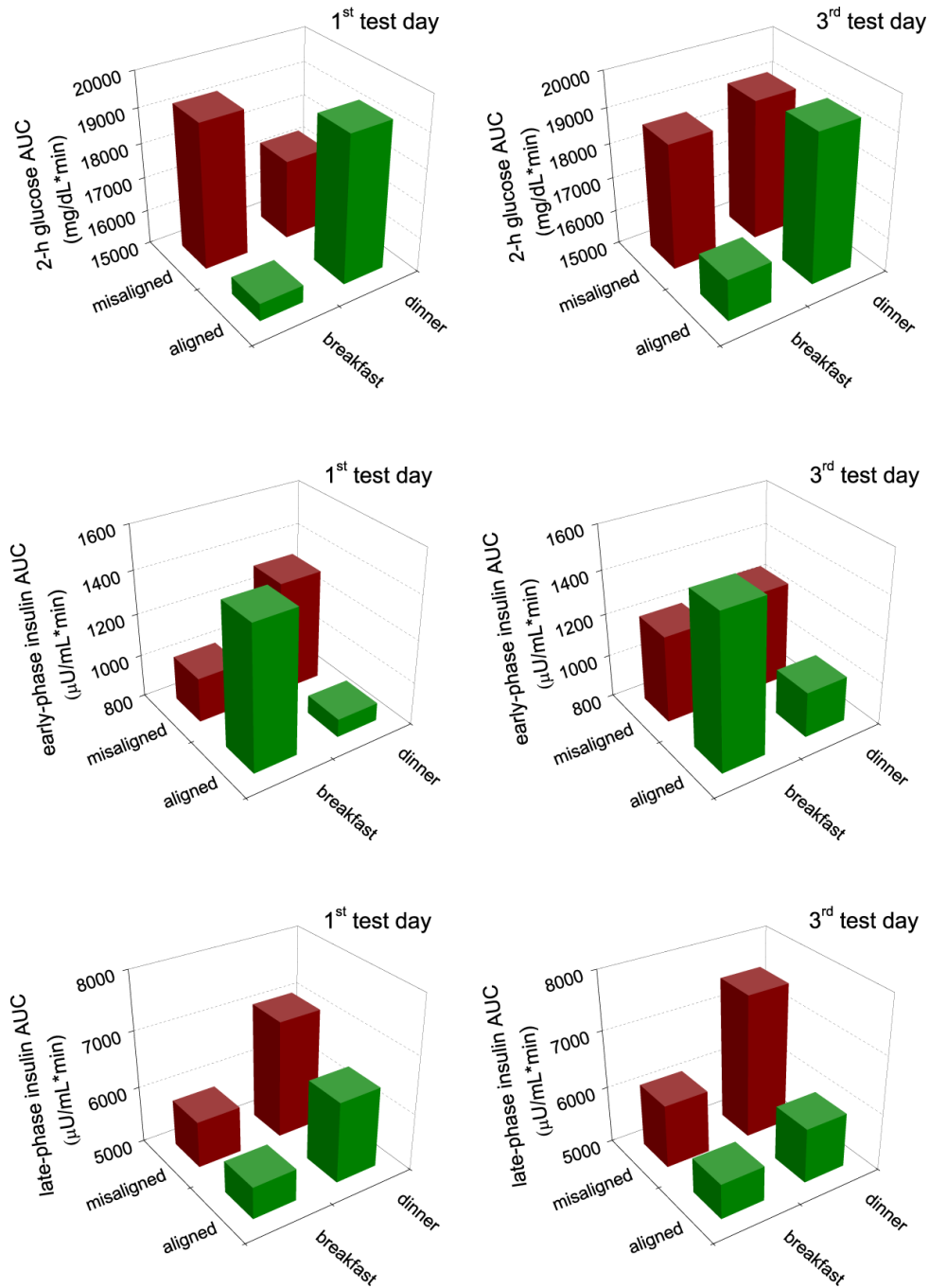


Figure 1. Three-dimensional plot displaying the effect of the behavioral cycle (breakfast versus dinner) and circadian misalignment compared to circadian alignment on postprandial glucose and early- and late-phase insulin area under the curves (AUC). Adapted from “Endogenous circadian system and circadian misalignment impact glucose tolerance via separate mechanisms in humans,” by C. J. Morris, J. N. Yanga, J. I. Garcia, S. Myers, I. Bozzi, W. Wang, ... F. Scheer, 2015, *Proceedings of the National Academy of Sciences of the United States of America*, 112, p. 5 in the supplemental information appendix. Copyright 2015 by the National Academy of Sciences. Reprinted with permission.

cycle, circadian misalignment and circadian phase they were not able to assess the relative/cumulative contributions of each on glucose metabolism. The trial was small, only 14 participants, and lasted only a few days so they did not assess the effect of prolonged circadian misalignment and behavioral habits on glucose metabolism.

The Circadian System and Sleep Schedule

It is widely accepted that circadian misalignment results in chronic sleep loss, but according to Gonnissen et al. (2013), it might also affect sleep architecture. They state that sleep is divided into several stages, rapid eye movement (REM) sleep and non-REM sleep which is sub-divided into four stages of progressively deeper sleep with stages three and four being referred to as slow-wave sleep (SWS). It is believed that REM sleep is experienced during the second half of the sleep cycle due to circadian rhythmicity and that SWS experienced at the beginning of the sleep cycle is a reflection of how long the subject has been awake (homeostatic process); from this information Gonnissen et al. hypothesized that circadian rhythm affected the distribution of REM sleep and SWS. Their study examined the metabolic consequences of circadian phase changes on sleep architecture. In order to do this, they conducted a random, single, blind, crossover study of 13 subjects for whom they shifted the circadian cycle forward three hours and backward three hours during two different trials conducted four weeks apart. Researchers preserved the 1:2 ratio of the sleep-wake cycle during both trials. Using the endogenous 24- hour melatonin cycle to confirm circadian misalignment they measured total sleep time, sleep period time, wake after sleep onset, amount of sleep in all stages (REM, and non-REM stages one through four), sleep efficiency, sleep latency, and REM sleep latency. REM was decreased when sleep duration was shortened regardless of whether there was a circadian shift; SWS was unchanged. Also, independent of circadian shift, longer sleep time showed an

increase in REM sleep and SWS. A decrease in REM was associated with higher cortisol ($p = 0.021$), fasting glucose ($p = 0.024$) and insulin levels ($p = 0.026$). This study did not control for the contribution of behavioral habits to circadian misalignment.

Often circadian misalignment is accompanied by sleep deprivation when studying the risk of increased diabetes in shift workers and it is well known that sleep deprivation itself promotes insulin resistance. To differentiate between sleep deprivation as a cause for glucose intolerance in shift workers and circadian misalignment as the cause, Leproult et al. (2014) examined 26 subjects in a parallel study involving circadian alignment with and without sleep restriction and circadian misalignment with and without sleep restriction. They determined circadian phase via a measurement of melatonin in saliva samples, measured insulin sensitivity to predict beta-cell function (a major contributor to diabetes risk) and measured high-sensitivity C-reactive protein to indicate inflammatory status (predictive of cardiovascular disease risk). Glucose intolerance increased during sleep restriction with circadian alignment, and both glucose intolerance and inflammatory markers increased during sleep restriction coupled with circadian misalignment. In male subjects, the decrease in insulin sensitivity doubled when circadian misalignment and sleep restriction existed concomitantly. Additionally, Leproult et al. noted that the caloric intake of the two groups (circadian alignment and circadian misalignment) was nearly identical, but the misalignment subjects consumed less protein and more carbohydrates and fat than did the alignment subjects. Also, the misalignment subjects consumed 21 % of their calories after 7 p.m. compared with their alignment counterparts who consumed only 7 % of their calories after 7 p.m., though weight gain between the two groups was nearly identical. Sleep architecture was measured during these trials and Leproult et al. found that SWS did not change regardless of sleep restriction or circadian alignment/misalignment and that REM sleep was

suppressed to a similar degree in both groups. The sample size was small and this 11-day trial was conducted entirely in a laboratory, potentially altering a subject's normal sleep pattern.

Sleep as a Countermeasure for Circadian Misalignment

After providing background information about circadian misalignment and its effect on cardiometabolic health in the previous subtopics, this section focuses on sleep as a lifestyle change proposed by various researchers to be effective in addressing circadian misalignment. Several small studies have examined the effect of everyday sleep extension and catch up sleep on insulin sensitivity, fasting glucose, and obesity. Killick et al. (2015) studied the effects of weekend catch up sleep on nineteen male subjects who were chronically sleep deprived throughout the workweek via a random order, two-period crossover design with a three-week washout period between trials. Each subject slept six hours on weeknights and 10 hours on weekend nights. Fasting blood glucose samples were obtained on Friday, Saturday, Sunday, and Monday mornings during each trial, and on Monday morning each subject underwent a two-hour oral glucose tolerance test to determine insulin sensitivity. Dietary intake was standardized during the weekend but not during the work week. They found that three nights of catch up sleep resulted in a 45 % increase in insulin sensitivity ($p = 0.03$). From this information Killick et al. (2015) hypothesized that "Over a prolonged period of time (years or decades), this improvement in insulin sensitivity could be highly relevant in delaying or even preventing prediabetes or type 2 diabetes mellitus in a relatively healthy young individual" (p. 505). Their study was limited by the fact that all subjects were male and by their small sample size.

Leprout, Deliens, Gilson, and Peigneux (2015) believe that habitual sleep restriction is a factor that contributes to the development of type 2 diabetes and cardiovascular disease. They investigated the hypothesis that increasing sleep time in subjects with chronic sleep deprivation

would be metabolically beneficial. Sixteen young, healthy, chronically sleep deprived subjects with a history of using the weekends for catch up sleep completed a sleep log and wore an activity monitor on their wrist during this eight-week trial. The first two weeks of the trial consisted of the subjects following their regular sleep routine at the end of this period the subject's weight was measured a fasting blood sample was obtained. The second part of the trial consisted of the subjects increasing their time in bed by one hour per week-night while following the sleep hygiene recommendations of the American Academy of Sleep Medicine; once again at the end of this period the subject's weight was measured, and a fasting blood sample was obtained. The wrist actinograph measured how much of the extra hour spent in bed resulted in extra sleep. Results showed that on weekdays subjects increased their sleep time by just under one hour, 54 ± 33 minutes during the first two weeks of the intervention, 48 ± 31 minutes during the middle two weeks of the intervention, and 44 ± 34 minutes during the last two weeks of the intervention. Glucose and insulin levels were measured from the fasting blood samples. Leproult et al. found that while there was no statistical significance between fasting glucose, insulin levels and weight pre- and post-intervention, there was a statistical significance between glucose to insulin ratio pre- and post-intervention ($p = 0.019$) indicating insulin resistance decreased as sleep time increased. This study was relatively small, included only non-obese, young, healthy participants, measured fasting glucose metabolism only, and did not control for caloric intake.

A pilot study of 22 otherwise healthy, hypertensive or pre-hypertensive, and chronically sleep deprived subjects found that extending sleep time by 60 minutes each night for six weeks lowered both systolic and diastolic blood pressure (Haak et al., 2013). Researchers defined hypertension as a systolic blood pressure of 140-159 mmHg with a diastolic of 90-99 mmHg and prehypertension as a systolic blood pressure of 120-139 mmHg with a diastolic of 80-89 mmHg.

At the end of a two-week baseline assessment period, each subject's blood pressure was continuously measured for a 24-hour period; subjects were then randomized to either the control group (continuation of habitual sleep habits) or the intervention group (sleep extended one hour each night). For six weeks subjects followed their assigned protocol, at the end of the six weeks their blood pressure was again assessed continuously for 24 hours. No change was noted in the control group's blood pressure but the intervention group's systolic blood pressure decreased by 14 ± 3 mmHg ($p < 0.001$). Though the sample sizes of the previous two studies were rather small, only 16 and 22 subjects respectively, and the subjects were young and healthy other than hypertension, these preliminary studies indicate that sleep extension as a behavioral intervention may be effective in curbing the development and progression of cardiometabolic disease risk factors.

To reduce circadian misalignment and promote sleep, a study was performed by Vetter, Fischer, Matera, and Roenneberg (2015) on shift workers at a factory. Each worker's chronotype and habitual sleep cycles were assessed using the Munich chronotype questionnaire for shift workers. Work schedules were then based around a worker's preferred chronotype. They found that overall when a work shift is matched to worker's preferred chronotype, social jetlag decreased by over an hour; indicating that circadian disruption can be reduced resulting in less sleep deprivation.

Discussion

Preliminary studies have provided significant data supporting the utilization of sleep hygiene as a modifiable risk factor for the prevention and treatment of cardiometabolic diseases. Weight loss, physical activity, and nutritional modification are all lifestyle changes currently recommended for improving cardiometabolic health; however, sleep hygiene is rarely addressed.

Most individuals experience social jet lag by artificially curtailing their weekday sleep via the use of alarm clocks and by using artificial light during the biological night; some suffer chronic sleep deprivation due to the demands of work and family obligations; still others experience circadian misalignment when they work a shift adverse to the natural light/dark solar circadian cycle. Morris et al. (2015) demonstrated that glucose tolerance was influenced heavily by circadian control independent of behavioral influences. When the normal circadian light/dark cycle is disrupted, desynchronization between the central and peripheral clocks occurs per Chen and Yang (2015) leading to disrupted biochemical and physiological processes ending in cardiometabolic disease. Leproult et al. (2014) found that glucose intolerance increases during sleep restriction with circadian alignment, and both glucose intolerance and inflammatory markers increase during sleep restriction coupled with circadian misalignment. The finding of insulin insensitivity and glucose intolerance has been consistently replicated in individuals who experience circadian misalignment, with or without chronic sleep loss, indicating a close relationship between sleep and cardiometabolic health.

Does Adequate Sleep at the Appropriate Time have the Potential to Halt Pathological Progression and Improve Cardiometabolic Health Before Overt Disease Ensues?

Loss of synchronization between external stimuli and the internal circadian clock can induce cardiovascular damage per Chen and Yang (2015). Recent progress in studying the mechanism and function of the circadian clock helped form the idea that intrinsic circadian rhythms are closely related to cardiovascular pathology. Physiological functions of cardiovascular organs such as heart rate, blood pressure, and cardiac remodeling show diurnal variations (Zang et al., 2014). Martino et al. (2007) found that in mice, circadian rhythm disturbances caused the expression of cardiac remodeling genes to alter which adversely affected

cardiac structure and function. But more importantly, they found that if a normal 24-hour circadian rhythm was reinstated, the adverse effects on cardiac structure and function were reversible.

Several human studies have been conducted that indicate circadian misalignment causes poor beta-cell response and increases insulin resistance. Scheer et al. (2009) found that postprandial plasma insulin levels increased by 22 % and glucose by 6 % when the circadian rhythm was disrupted; though they did not account for sleep restriction or adequacy during their study. Additionally, they found a three mmHg increase in mean arterial blood pressure during the wake cycle of subjects whose circadian rhythm had been disrupted. Buxton et al. (2013), like Scheer et al., found that pancreatic beta cells did not respond adequately when the circadian rhythm was misaligned because glucose levels were increased both when subjects were fasting and postprandially during circadian disruption. Unlike Scheer et al., Buxton et al. accounted for sleep deprivation and found that sleep deprivation with concomitant circadian disruption caused an even greater increase in plasma glucose levels. During their trial, Buxton et al. allowed for a 9-day recovery period where the endogenous circadian rhythm was followed, at the end of which they found that fasting and postprandial glucose levels had returned to normal and pancreatic beta-cells were functioning adequately.

Extending sleep time by less than one hour each weeknight for six weeks in habitually sleep restricted subjects improved insulin sensitivity (Leproult et al., 2015) and lowered both systolic and diastolic blood pressure (Haak et al., 2013). Though the sample sizes were small, only 16 and 22 subjects respectively, these studies indicate that sleep extension as a behavioral intervention effectively curbs the development and progression of cardiometabolic disease risk

factors. When sleep extension every night is not possible, Killick et al. (2015) found that three nights of catch up sleep on the weekend results in a 45 % increase in insulin sensitivity.

Glucose tolerance varies throughout the day; in fact, glucose is tolerated better in the biological morning than the biological evening as demonstrated by Morris et al. (2015). Morris et al. used a within-participant cross-over design to separate the effects of circadian phase on glucose tolerance from the effects of circadian misalignment on glucose tolerance. By controlling for caloric intake, meal timing and sleep schedule relative to the exogenous circadian phase they assessed for glucose tolerance during circadian alignment vs misalignment and behavioral alignment/misalignment with regard to the exogenous circadian rhythm. They also tested whether glucose tolerance would subside or become amplified with repeated daily exposure to circadian misalignment by measuring the change in glucose tolerance from day one of the trial versus day three of the trial. A behavioral effect independent of circadian effect was noted— postprandial glucose was 8 % higher after dinner versus after breakfast regardless of whether dinner was eaten in the biological morning or night – as was a circadian phase effect independent of behavioral effects – postprandial glucose was 12 % higher in the biological evening than in the biological morning – and a circadian misalignment effect was also noted – postprandial glucose increased by 6 %. There was no effect on fasting glucose by circadian phase, circadian misalignment or behavior. This is an adverse finding to that of Scheer et al. (2009) who found that circadian misalignment increases fasting glucose levels. This adverse finding could be easily discounted if Scheer et al. had neglected to account for behavioral effects; however, they did account for behavioral effects in their study.

The data indicates that circadian misalignment and sleep deprivation impede cardiovascular function and cause a decrease in glucose tolerance and insulin sensitivity

Therefore, every effort should be made to reduce the health impact of sleep deprivation by focusing on sleep hygiene and circadian realignment as a means of reducing cardiometabolic disease risk factors.

Glucose metabolism is influenced by the circadian clock, but it is unclear exactly how sleep cycles, behavioral habits, and environmental cues interact with the circadian clock to produce optimal insulin sensitivity and glucose tolerance. Future studies should focus on separating these influences and understanding the underlying mechanism that contributes to glucose tolerance so that sleep hygiene recommendations can be optimized for shift workers and the general populace.

Should Adjusting One's Chronotype to Reduce Sleep Debt, Social Jet Lag, and Circadian Misalignment be Included in Lifestyle Modification Recommendations?

Sleep is a biological imperative. According to Buxton et al. (2013), sleep of sufficient depth and duration without circadian disruption is necessary to prevent physiological changes that may predispose one to adverse health outcomes. The evidence linking habitually shortened sleep duration and circadian desynchrony to cardiometabolic diseases has accumulated over the past decade. To differentiate between sleep deprivation and circadian misalignment as the cause of glucose intolerance, Leproult et al. (2014) designed a study that examined circadian alignment with and without sleep restriction and circadian misalignment with and without sleep restriction. They found that glucose intolerance increased during sleep restriction with circadian alignment, and both glucose intolerance and inflammatory markers increased during sleep restriction coupled with circadian misalignment. Interestingly, in male subjects, the decrease in insulin sensitivity doubled when circadian misalignment and sleep restriction existed concomitantly. They also found that, though weight gain and caloric intake between the two groups was nearly

identical, the circadian misalignment subjects consumed 21 % of their calories after 7 p.m. and consumed less protein and more carbohydrates and fat than did the alignment subjects who consumed only 7 % of their calories after 7 p.m.; indicating that caloric intake itself was not responsible for insulin resistance. Leproult et al. also accounted for sleep architecture in their study; they noted that REM sleep was suppressed when sleep was restricted both during circadian alignment and circadian misalignment, and that SWS did not change regardless of sleep restriction or circadian alignment/misalignment.

Gonnissen et al. (2013) hypothesized that circadian misalignment affects sleep architecture, specifically the distribution of REM sleep and SWS. It is believed that SWS, which is a reflection of how long the subject has been awake (homeostatic process), is experienced at the beginning of the sleep cycle and REM is experienced during the second half of the sleep cycle. They found that when sleep duration was shortened, regardless of circadian alignment/misalignment, SWS remained constant while REM decreased. Accompanying the decrease in REM were higher cortisol, fasting glucose and insulin levels all of which are associated with obesity and type 2 diabetes. Vetter et al. (2015) found that when a work shift is matched to a worker's preferred chronotype, social jetlag decreases by over an hour; indicating that circadian disruption can be reduced and sleep debt can be improved by a chronotype based schedule.

Though the sample sizes were small, a link between circadian misalignment and the risk for developing cardiometabolic disorders has repeatedly been established providing the proof of concept that one way to mitigate the risk factors may be to impose a regular sleep schedule. Therefore, sleep should be considered when recommending lifestyle interventions that decrease cardiometabolic risk factors.

Clinical Application

The aim of this study was to evaluate the efficacy of including sleep in lifestyle changes recommended for mitigating cardiometabolic damage. As the world advances, lifestyles may not change in the near future; therefore, it is important to address the problem of circadian misalignment in order to slow the ever-increasing prevalence of cardiometabolic diseases. Leproult et al. (2015) showed that extending sleep time by less than one hour each weeknight for six weeks in habitually sleep restricted subjects improved insulin sensitivity lessening the risk for obesity, type 2 diabetes, and cardiac disease. Haak et al. (2013) found that extending sleep time by about 60 minutes each night for six weeks lowered both systolic and diastolic blood pressure. These studies show that sleep extension as a behavioral intervention is effective in curbing the development and progression of cardiometabolic disease risk factors, and so should be recommended to patients wishing to reduce their cardiometabolic risk profile.

When daily sleep extension is not possible then day off, catch up sleep could help mitigate the adverse consequences of sleep deprivation. Killick et al. (2015) found that three nights of catch up sleep resulted in a 45 % increase in insulin sensitivity. Interpreting these results, they suggested that “Over a prolonged period of time (years or decades), this improvement in insulin sensitivity could be highly relevant in delaying or even preventing prediabetes or type 2 diabetes mellitus in a relatively healthy young individual” (Killick et al., 2015, p. 505).

Often shift work is unavoidable for patients; if this is the case, then abrupt schedule inversion should be avoided, and work schedules in line with the patient’s preferred chronotype should be sought. Vetter et al. (2015) found that when a work shift is matched to worker’s

preferred chronotype, social jetlag decreases by over an hour, reducing circadian disruption and improving cardiometabolic health.

Exploiting the connection between circadian alignment, sleep, glucose tolerance, insulin sensitivity, blood pressure, and inflammatory markers by recommending sleep hygiene as a corrective measure is an important step toward curbing the worldwide epidemic of cardiometabolic disorders. Therefore, sleep hygiene should be considered when recommending lifestyle interventions for circadian misalignment and chronic sleep deprivation.

References

- Baron, K. G. & Reid, K. J. (2014). Circadian misalignment and health. *International Review of Psychiatry (Abingdon, England)*, 26(2), 139–154.
<https://doi.org/10.3109/09540261.2014.911149>
- Buxton, O. M., Cain, S. W., O'Connor, S. P., Porter, J. H., Duffy, J. F., Wang, W. ... Sheal, S. A. (2013) Metabolic consequences in humans of prolonged sleep restriction combined with circadian disruption. *Science Translational Medicine*, 4(129), 129ra43.
<https://doi.org/10.1126/scitranslmed.3003200>
- Chen, L., & Yang, G. (2015). Recent advances in circadian rhythms in cardiovascular system. *Frontiers in Pharmacology*, 6, 71. <https://doi.org/10.3389/fphar.2015.00071>
- Flynn-Evans, E. E., Barger, L. K., Kubey, A. A., Sullivan, J. P., & Czeisler, C. A. (2016). Circadian misalignment affects sleep and medication use before and during spaceflight. *NPJ Microgravity*, 2, 15019. <https://doi.org/10.1038/npjmgrav.2015.19>
- Forsyth, C. B., Voigt, R. M., Burgess, H. J., Swanson, G. R., & Keshavarzian, A. (2015). Circadian rhythms, alcohol and gut interactions. *Alcohol (Fayetteville, N.Y.)*, 49(4), 389–398. <https://doi.org/10.1016/j.alcohol.2014.07.021>
- Fuhr, L., Abreu, M., Pett, P., & Relógio, A. (2015). Circadian systems biology: When time matters. *Computational and Structural Biotechnology Journal*, 13, 417–426.
<https://doi.org/10.1016/j.csbj.2015.07.001>.
- Gonissen, H., Mazuy, C., Rutters, F., Martens, E., Adam, T., & Westerterp-Plantenga, M. (2013). Sleep Architecture When Sleeping at an Unusual Circadian Time and Associations with Insulin Sensitivity. *PLoS One*, 8(8), e72877.
<https://doi.org/10.1371/journal.pone.0072877>

Haak, M., Serrador, J., Cohen, D., Simpson, N., Meier-Ewert, H., & Mullington, J. M. (2013).

Increasing sleep duration to lower beat-to-beat blood pressure – a pilot study. *Journal of Sleep Research*, 22(3), 295–304. <https://doi.org/10.1111/jsr.12011>

Killick, R., Hoyos, C. M., Melehan, K. L., Dungan, G. C., Poh, J., & Liu, P. Y., (2015).

Metabolic and hormonal effects of ‘catch-up’ sleep in men with chronic, repetitive, lifestyle-driven sleep restriction. *Clinical Endocrinology*, 83(4), 498–507.
<https://doi.org/10.1111/cen.12747>

Krishnan, H. C., & Lyons, L. C. (2015). Synchrony and desynchrony in circadian clocks:

impacts on learning and memory. *Learning & Memory*, 22(9), 426–437.
<https://doi.org/10.1101/lm.038877.115>

Leproult, R., Deliens, G., Gilson, M., & Peigneux, P. (2015). Beneficial impact of sleep

extension on fasting insulin sensitivity in adults with habitual sleep restriction. *Sleep*, 38(5), 707–715. <https://doi.org/10.5665/sleep.4660>

Leproult, R., Holmbäck, U., & Van Cauter, E. (2014). Circadian misalignment augments

markers of insulin resistance and inflammation, independently of sleep loss. *Diabetes*, 63(6), 1860–1869. <https://doi.org/10.2337/db13-1546>.

Lin, L. L., Huang, H. C., & Juan, H. F. (2015). Circadian systems biology in Metazoan. *Briefings*

in Bioinformatics, 16(6), 1008–1024. <https://doi.org/10.1093/bib/bbv00>

Martino T. A., Tata N., Belsham D. D., Chalmers J., Straume M., Lee P. ... Sole, M. J. (2007).

Disturbed diurnal rhythm alters gene expression and exacerbates cardiovascular disease with rescue by resynchronization. *Hypertension*, 49, 1104–1113.

<https://doi.org/10.1161/HYPERTENSIONAHA.106.083568>

Morris, C. J., Yanga, J. N., Garcia, J. I., Myers, S., Bozzi, I., Wang, W. ... Scheer, F. (2015).

Endogenous circadian system and circadian misalignment impact glucose tolerance via separate mechanisms in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *112*(17), E2225–E2234.

<https://doi.org/10.1073/pnas.1418955112>

Pan, A., Schernhammer, E. S., Sun, Q., & Hu, F. B. (2011). Rotating night shift work and risk of type 2 diabetes: Two prospective cohort studies in women. *PLoS One*, *8*(12), e1001141.

<https://doi.org/10.1371/journal.pmed.1001141>

Paschos, G. K. (2015). Circadian clocks, feeding time, and metabolic homeostasis. *Frontiers in Pharmacology*, *6*, 112. <https://doi.org/10.3389/fphar.2015.00112>

Qian, J., & Scheer, F. A. (2016). Circadian system and glucose metabolism: implications for physiology and disease. *Trends in Endocrinology and Metabolism*, *27*(5), 282–293.

<https://doi.org/10.1016/j.tem.2016.03.005>

Reutrakul, S., & Knutson, K. L. (2015). Consequences of circadian disruption on cardiometabolic health. *Sleep Medicine Clinics*, *10*(4), 455–468.

<https://doi.org/10.1016/j.jsmc.2015.07.005>

Scheer, F. A., Hilton, M. F., Mantzoros, C. S., & Shea, S. A. (2009). Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proceedings of the National Academy of Science U.S.A.*, *106*, 4453–4458. <https://doi.org/10.1073/pnas.0808180106>

Takahashi, M. (2014). Assisting shift workers through sleep and circadian research. *Sleep & Biological Rhythms*, *12*(2), 85-95. <https://doi.org/10.1111/sbr.12065>

Vetter, C., Fischer, D., Matera, J. L., & Roenneberg, T. (2015). Aligning work and circadian time in shift workers improves sleep and reduces circadian disruption. *Current Biology*, 25(7), 907-911. <http://dx.doi.org/10.1016/j.cub.2015.01.064>

Zhang, L., Sabeh, M., & Jain, M. (2014). Circadian rhythm and cardiovascular disorders. *Chronophysiology and Therapy*, 2014(4), 27-40. <https://doi.org/10.2147/CPT.S44805>