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Research paper

Lower nocturnal urinary 6-sulfatoxymelatonin is associated with more severe insulin resistance in patients with prediabetes

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ABSTRACT

Objective: Melatonin, a neurohormone secreted by the pineal gland, controls circadian rhythmicity, modulates sleep and plays a role in glucose metabolism. Low secretion of nocturnal urinary 6-sulfatoxymelatonin (aMT6S) was associated with incident diabetes. Sleep disturbances have also been shown to be risk factors for diabetes. In this study, we explored the relationship between nocturnal urinary aMT6s and markers of glucose metabolism in prediabetes patients, considering sleep related factors.

Methods: Sixty two non-shift working patients with prediabetes [hemoglobin A1c (HbA1c) 5.7–6.49%] who were not on beta-blockers participated. Sleep duration and efficiency was recorded using 7-day actigraphy. Obstructive sleep apnea was evaluated using an overnight in-home monitoring device. Nocturnal urinary aMT6s/creatinine ratio was measured from an overnight urine sample. Oral glucose tolerance test (OGTT, 75-grams glucose) was performed, with measurements of insulin and glucose levels.

Results: Mean (SD) age was 55.3 (8.2) years and mean HbA1c level was 6.01 (0.2)%. Mean (SD) sleep duration 6.0 (0.9) h, sleep efficiency was 83.4 (6.6)% and a median (interquartile rage) apnea hypopnea index was 10.3 (3.6, 16.4). Median nocturnal urinary aMT6s was 17.4 (9.4, 28.2) ng/mg creatinine. Higher nocturnal urinary aMT6s significantly correlated with lower fasting insulin ($p = 0.004$), lower insulin response to OGTT ($p = 0.027$), and lower fasting and whole body insulin resistance as indicated by lower HOMA-IR and higher Matsuda insulin sensitivity index ($p = 0.006$ and $p = 0.011$, respectively), but it was not correlated with fasting glucose, glucose response to OGTT, or HbA1c. Sleep duration inversely correlated with HbA1c but no other correlations were found between other sleep variables and markers of glucose metabolism or nocturnal urinary aMT6s. After adjusting for body mass index, higher nocturnal urinary aMT6s significantly correlated with lower HOMA-IR ($p = 0.025$) and fasting insulin levels ($p = 0.014$).

Conclusion: Nocturnal urinary aMT6s inversely correlated with fasting insulin resistance and insulin levels in patients with prediabetes. These results support the role of melatonin in glucose metabolism.

1. Introduction

The circadian system, controlled by the master circadian clock located in the suprachiasmatic nucleus (SCN) in the hypothalamus, plays a major role in regulating daily rhythms of sleep/wake cycle, central and peripheral tissue metabolism, and hormonal secretions (Huang et al., 2011). The central clock is entrained by the light-dark cycle and other environmental factors, and relays the information via various pathways to the peripheral organs, leading to coordinated rhythms. In humans, it was estimated that ~ 15% of all identified metabolites in plasma and saliva were under circadian control, especially plasma fatty acids and salivary amino acids (Dallmann et al., 2012). Growing evidence has confirmed the detrimental effects of the disruption of circadian organization on metabolism. Experimental circadian misalignment in healthy human volunteers led to increased glucose levels, reduced insulin sensitivity, increased mean arterial blood pressure, reversal of daily cortisol rhythm, impaired autonomic function and elevated inflammatory markers (i.e. interleukin-10, interleukin-6, tumor necrosis factor-α, C-reactive protein) (Buxton et al., 2012; Leproult et al., 2014; Scheer et al., 2009;

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Wright et al., 2015; Morris et al., 2015; Morris et al., 2016). Cohort studies have also confirmed an association between shift work, usually associated with circadian misalignment, to an increase risk of incident diabetes (Morikawa et al., 2005; Suwazono et al., 2006), with longer duration of shift work being associated with higher risk (Pan et al., 2011).

Melatonin is a neurohormone secreted by a pineal gland during the biological night under the control of the central clock, and inhibited by light exposure (Brzezinski, 1997). Two G-protein coupled receptors, MT1 and MT2 (found in the SCN, brain tissues and peripheral tissues including pancreatic β-cells), mediate the effects of melatonin (Peschke and Muhlbauer, 2010). The 24 h rhythm of melatonin acts as an internal synchronizer of the circadian system (Morris et al., 2012). In addition, melatonin has potent anti-oxidant and anti-inflammatory effects (Mauriz et al., 2013). Data suggested that melatonin plays a role in glucose regulation. In a nested case control study within the Nurses' Health Study Cohort, women with the lowest tertile of nocturnal urinary 6-sulfatoxymelatonin (aMT6s, a major urine melatonin metabolite) to creatinine ratio had a significantly increased risk of diabetes development compared to those in the highest tertile (odds ratio 2.17) (McMullan et al., 2013b). A cross sectional study of 513 elderly Japanese also found that high nocturnal urinary aMT6S (75th percentile vs 25th percentile) was associated with a 32% decrease in prevalent diabetes (Obayashi et al., 2014). In addition, variants in the melatonin receptor type 1B (MTNR1B) have been shown to be associated with impaired fasting glucose and type 2 diabetes (Sparso et al., 2009; Bonnefond et al., 2012). Moreover, 8–10 weeks of melatonin administration in diabetic rats resulted in reduction in glucose levels along with an improvement in insulin resistance (Agil et al., 2012; de Oliveira et al., 2012). These data support the possible beneficial effect of melatonin on glucose metabolism. However, administrations of immediate release melatonin in healthy women, both in the morning and evening, resulted in an increase in glucose response following glucose challenge, as compared to placebo (Rubio-Sastre et al., 2014). This was related to decreased insulin secretion in the morning, and decreased insulin sensitivity in the evening. In another study of 14 postmenopausal women, 1 mg melatonin administered at 0800 h resulted in reduced glucose tolerance and insulin sensitivity as assessed by oral glucose challenge 45 min later (Cagnacci et al., 2001). These conflicting data highlight further research needed to clarify the role of melatonin in human's glucose metabolism.

The prevalence of diabetes is increasing in the U.S. and worldwide. Alarming statistics revealed that additional significant number of population have prediabetes, a state of abnormal glucose levels not yet meeting the criteria for diabetes (Centers for Disease Control and Prevention, 2014). These individuals, estimated at 86 million adults in the U.S. in 2012, are at high risk of developing diabetes (Centers for Disease Control and Prevention, 2014). Whether melatonin secretion is related to glucose metabolism in this population has not been studied. Besides traditional risk factors for diabetes, sleep disturbances [i.e. insufficient sleep duration, poor sleep quality and obstructive sleep apnea (OSA)] have been shown to be associated with metabolic dysfunction and increased risk of incident diabetes (Anothaisintawee et al., 2015). Some of these sleep disturbances were also found to be related to lower nocturnal aMT6S levels (Saksvik-Lehouillier et al., 2015). Therefore, this study was conducted with the aim to explore the relationship between nocturnal aMT6s and markers of glucose metabolism in patients with prediabetes, taken into consideration sleep related factors.

2. Material and methods

A cross-sectional study was conducted in non-shift working adults attending the outpatient department at the Faculty of Medicine Ramathibodi Hospital with a previous diagnosis of prediabetes defined as hemoglobin A1c (HbA1c) ≥ 5.70 to < 6.50% (American Diabetes Association: Standars of Medical Care in Diabetes, 2017). Exclusion criteria included beta blocker use (known to affect melatonin secretion), being currently pregnant, a history of congestive heart failure or low ejection fraction, chronic obstructive pulmonary disease, end stage renal disease or severe chronic liver disease such as cirrhosis, stroke, permanent pacemaker placement, and use of certain medications (opioids/ narcotics, alpha adrenergic blockers, clonidine, methyldopa, nitroglycerin). The data utilized in this study were a part of those obtained from a larger cross-sectional study exploring the role of sleep duration and markers of glucose metabolism (clinicaltrials.gov, NCT02108197). All participants gave written informed consent. The protocol was approved by the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

After obtaining informed consent, weight and height were measured. Body mass index (BMI) was calculated as weight (kg)/height^2 (m)^2. The participants then underwent the following assessments, all performed within a two-week period.

2.1. Sleep duration and efficiency measurement

Participants wore an Actiwatch 2 wrist activity monitor (Philips Respironics, Bend, Oregon) for 7 days. These monitors use highly sensitive omnidirectional accelerometers to count the number of wrist movements in 30-s epochs. The software scores each 30-s epoch as sleep or wake based on a threshold of activity counts that is estimated using activity within the epoch being scored as well as the epochs 2 min before and after that epoch. The participants were instructed to press the event marker button upon going to bed and awakening. Bedtime and wake time are set by the researcher using the event markers, a sleep log data as well as an in-person review of sleep timing with the participants upon return of the watch. Sleep duration was defined as the amount of actual sleep obtained at night, and sleep efficiency (a measure of sleep quality) was defined as percentage of time in bed spent sleeping. These two variables were calculated using Actiware 6.0 software, supplied by the manufacturer. Mid sleep time was defined as a midpoint between sleep start and sleep end. For each participant, the mean across all available nights was used. For 95% of participants in these analyses, at least 6 days of actigraphy recording were available and the remaining 5% had 5 days of actigraphy recording.

2.2. Assessment of OSA

OSA was diagnosed using an FDA-approved portable diagnostic device, WatchPAT 200 (Itamar Medical, Israel), which has been validated against PSG in populations with and without diabetes (Zou et al., 2006; Yuceege et al., 2013). This non-invasive device is shaped similar to a large watch, worn on the non-dominant wrist immediately before bedtime and removed upon awakening in the morning. The device has two probes connecting to the participants' fingers to measure changes in peripheral arterial tone (PAT) and oxygen saturation, along with a built-in actigraphy to measure sleep time. The severity of OSA is assessed by PAT Apnea Hypopnea Index (AHI) which is automatically generated by the software, using changes in the peripheral arterial tonometry. OSA is considered present if AHI ≥ 5. OSA is considered mild if AHI ≥ 5 but < 15, moderate if AHI ≥15- 30, and severe if AHI > 30.

Because this device relies on changes in peripheral arterial tone, use of certain medications including alpha-blockers and short acting nitrates, as well as permanent pacemaker, was not allowed according to the device's operation manual. In addition, it cannot differentiate obstructive from central apnea events. Therefore, we also excluded patients with certain conditions which may pose a higher risk for central apnea. These were described in the exclusion criteria.