Protocol Title: The Relationship between Sleep and Glucose Tolerance in Prediabetes: the Role of GLP-1 in Short Sleepers

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Protocol and Planned Statistical Analysis

Background and Rationale

Humans spend approximately a third of their lifetime sleeping. Sleep is viewed as a state of energy conservation and replenishment of energy storage. Human behaviors and certain pathological conditions may affect this important physiological process, resulting in sleep disturbances, including insufficient sleep, poor sleep quality and obstructive sleep apnea (OSA). There is a large body of evidence from human experimental as well as observational studies linking sleep disturbances to abnormal glucose metabolism and diabetes risk.

Insufficient sleep has been linked to reduced insulin sensitivity and increased risk of type 2 diabetes, both in laboratory studies in healthy humans and in epidemiologic studies. A causative role of partial sleep restriction in promoting alterations in glucose metabolism was first established in 1999(1). Intravenous glucose tolerance testing (IVGTT) following sleep restriction to 4 hours per night(h/night) for 5 nights resulted in a 24% decrease in insulin sensitivity as well as a 30% decrease in the acute insulin response to intravenous glucose(1,2). Multiple cross sectional epidemiologic studies have indicated that short sleep duration (usually < 6 h/night) is associated with increased impaired glucose tolerance and diabetes risk(3). A recent meta-analysis including 7 of these 10 studies (total 107,756 participants concluded that short sleep (5-6 h/night) predicts the development of type 2 diabetes with a pooled relative risk (RR) of 1.28(4). There are only a few studies examining the impact of insufficient sleep on glycemic control in patients with established type 2 diabetes. A questionnaire survey study of 161 African Americans with type 2 diabetes found that 3 hours of perceived sleep debt per day (i.e. a self-report of insufficient sleep duration) predicted a HbA1c level of 1.1% above the median(5). The magnitude of this difference is comparable to the effect size of several FDA-approved diabetes medications. Recently, a large cross sectional study of 4,870 Japanese participants revealed a U-shaped relationship between sleep duration and glycemic control, with higher HbA1c levels in patients with self-reported sleep duration <5.5 h/night and 8.5 h/night compared to those with 6.5-7.4 h/night (6). These data support a role of sleep duration on glycemic control in patients with type 2 diabetes. However, the assessments of sleep duration in these studies were done subjectively i.e. by questionnaires. The only study which assessed the relationship between glycemic control (HbA1c) utilizing objective sleep measurement by actigraphy revealed that only sleep fragmentation, but not sleep duration, was associated with higher HbA1c level (7).

In addition, other aspects of sleep disturbances have also been shown to affect glucose control in patients with type 2 diabetes, including poor sleep quality(8) and the severity of untreated OSA (9). Therefore, the independent role of sleep duration and glycemic control requires further investigation. Whether the relationship extends to those with prediabetes is unknown. We hypothesized that prediabetes patients with short sleep duration, as measured objectively, will have worse glucose tolerance than those with normal sleep duration.

GLP-1 is an important incretin hormone which plays a role in regulating postprandial glucose excursion and appetite regulation. The role of sleep in GLP-1 regulation was explored in a few experimental studies in healthy human. Sleep restriction to 4 hours per night in healthy participants resulted in lower GLP-1 levels in the afternoon in women (10). In addition, total sleep deprivation in healthy participants resulted in a delayed GLP-1 response to breakfast (11). Sitagliptin treatment for 12 months in patients with type 2 diabetes resulted in 0.6% decrease in HbA1c as well as improved sleep quality as assessed by questionnaire (12). The role of GLP-1 response in patients with prediabetes who are short sleepers has not been explored. We hypothesize that those with chronic short sleep will have a lower or delayed GLP-1 response to meal compare to those with normal sleep duration. If this is proven, GLP-1 therapy may especially be effective in improving glycemic control in patients with abnormal sleep. Since the current proposed study is exploratory in nature by means of association, future interventional trial will be needed to show the causal relationship between GLP-1 and sleep.

Therefore, the aims of the current study are to explore the relationship of sleep duration and glucose tolerance in patients with prediabetes, as well as the effects of chronic short sleep duration on GLP-1 response to meals in these patients

Objectives & Hypotheses:

1. To determine the independent role of sleep duration on glucose tolerance in patients with prediabetes.
2. To determine if patients with prediabetes with short sleep have delayed or reduced GLP-1 response to meal

Hypothesis

1. Prediabetes patients who have insufficient sleep will have worse glucose tolerance than those with normal sleep duration.
2. Prediabetes patients with short sleep will have a delayed or reduced GLP-1 response to a standardized meal

Study Design/Population/Method

The study has three components;

Step 1: Questionnaire study of 600 patients with prediabetes. The questionnaires will capture subjective sleep measurements and eating habits.
Step 2: Participants ages 40-65 reporting short sleep duration (≤6 h/night) and normal sleep duration (7-8 h/night) will undergo objective sleep measurements including sleep duration, sleep quality and obstructive sleep apnea. This step will serve as a screening for step 3 (expected N= 80).
Step 3: Study to compare GLP-1 response to standard mixed meal test in patients with chronic short sleep and those with normal sleep duration. (n= 31 in each group).

STEP 1:
Inclusion Criteria:

1. Patients with prediabetes (HbA1c 5.7-6.4% or history of fasting plasma glucose 100-125 mg/dl) who receive medical care at Ramathibodi Hospital
2. Age 18 or older
3. Can understand Thai (speaking, listening and reading)
4. Agree to participate by written informed consent

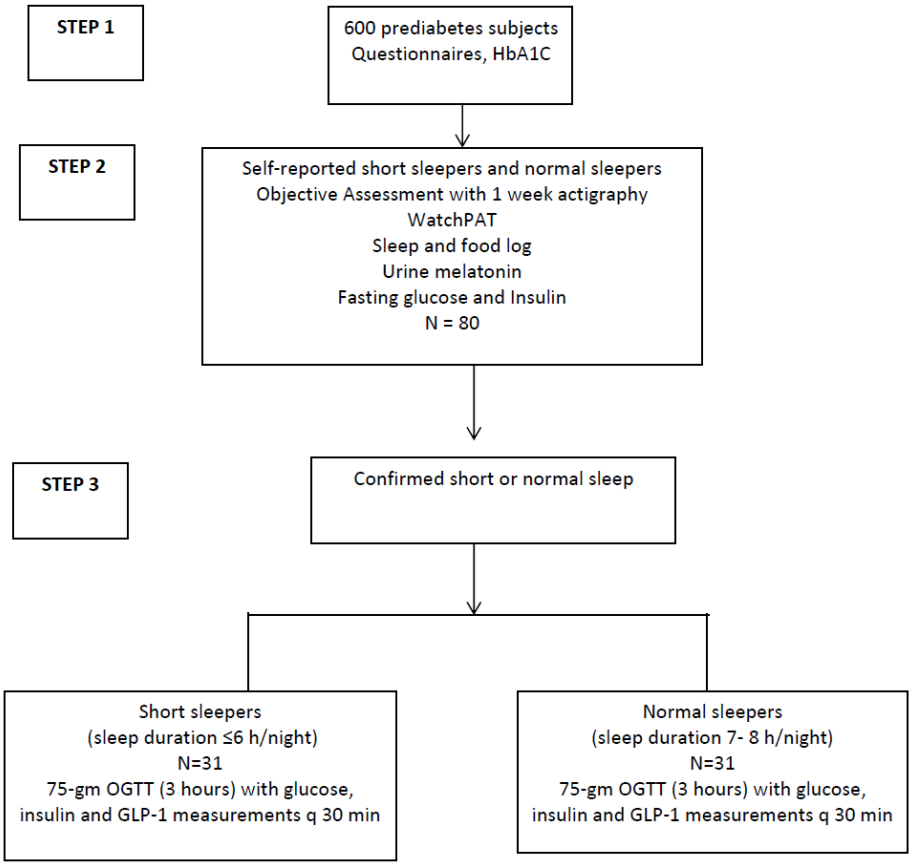
Exclusion criteria:

1. Those who depend on others for feeding (such as stroke patients)
2. Shift workers
3. History of congestive heart failure or low ejection fraction
4. Chronic obstructive pulmonary disease, end stage renal disease or chronic liver disease (AST or ALT > 3 times the upper limit of normal)
5. Use of medications: opioids/ narcotics , alpha blockers (prazosin, doxazosin, terazosin), clonidine, methyldopa, nitroglycerin
6. Patients with permanent pacemaker
7. History of previous stroke

STEP 2:
Participants age 40-65 who completed step 1 and were not taking diabetes medications will be invited to participate if they reported sleep duration <6 h/day, or normal sleep duration (7-8 h/day). They will undergo objective sleep assessments

STEP 3:
Participants who complete step 2 and are confirmed to have short sleep duration and normal sleep duration by objective assessments will undergo a mixed meal test with measurements of GLP-1, glucose and insulin.

Study Procedures/Study Flowchart



STEP 1

After informed consents are obtained, the participants will be interviewed regarding their medical history and sleep schedules on weekdays and weekends, as well as other aspects of sleep, mood and dietary habits. Standardized questionnaires will be utilized, including Morningness-Eveningness questionnaire (13) Pittsburg Sleep Quality Index to assess sleep quality (14), Berlin Questionnaire to assess risk of sleep apnea(15), depressive symptoms (CES-D)(16), Epworth Sleepiness Scale to assess daytime sleepiness (17), and review of dietary intake in the past 24 hours (24 hour food recall).
Medical records will be reviewed to collect data regarding medication use.
Weight, height, hip and waist circumference as well as neck circumference will be measured.
Blood sample will be obtained for hemoglobin A1c levels within 6 months of an interview if not done in the prior 6 months. Additionally, blood sample will be saved for possible further genetic and metabolic analyses.

STEP 2

Those between ages 40-65 years who reported short sleep (≤6h/day) and normal sleep (7-8 h/day) will undergo objective sleep measurements as follow. Expected participants = 80
Participants will wear Actiwatch (Respironics, USA) at home for 1 week. Actiwatch is a small, watch-like device which can measure sleep timing and quality, daytime activities as well as light exposure.

Participants will wear the device on their non-dominant wrist and instructed not to wear clothes which sleeves may cover the watch. The device is water resistant.
During this week, the participants will keep a record of their sleep schedules and dietary intake.
On the last morning of actiwatch wearing, participants will collect overnight urine for urine melatonin measurements. They will fast after midnight and return to the hospital to have blood sample taken for fasting glucose and insulin, as well as return the actiwatch device.
The participants will bring the device, Watch PAT 200(18), to wear overnight at home. This device will assess the presence and the severity of sleep apnea (Apnea Hypopnea Index). This non-invasive device is shaped similar to a large watch which the participants will wear on their non-dominant wrist. There will be two probes connecting the device to their fingers to measure peripheral arterial tone and oxygen saturation. The participants will wear the device before going to bed, remove it upon awakening and return the device to the investigators in the morning.

STEP 3
After confirming the sleep duration by Actiwatch, both short and normal sleepers will undergo a 75-gram OGTT after an overnight fasting. Serum glucose, insulin and GLP-1 will be collected every 30 minutes for 3 hours. Expected participants in each group = 31

Statistical Methods

STEP 1 and 2:

Sleep variables from questionnaires (subjective) and actigrapgy/WatchPAT (objective) including sleep duration, sleep quality and sleep apnea will be analyzed to explore their relationship with HbA1c, and when available, fasting glucose and insulin levels. Bivariate analysis will be used. To identify the independent sleep predictor of glucose tolerance status, multivariate regression analysis will be employed.

STEP 3:

Area under the curve of GLP-1 and its peak response will be compared between short and normal sleepers.

Power/Sample Size:

STEP 1: The sample size of 600 was selected to follow a rule of 10 participants for each variable in the multivariate regression analysis. Predictors of HbA1c include age, sex and BMI. Sleep predictors will include sleep duration, quality and sleep apnea risk. In addition, the sample size was chosen to ensure adequate recruitment of short sleepers (based on prevalence of 20-25%) into STEP 2 and 3.

STEP 2: The sample size of 80 in step 2 was chosen to ensure adequate recruitment for STEP 3 which requires 62 participants, with a 75% concordance rate of self-reported and objectively measured sleep duration

STEP 3: Based upon a sample size of n=31 patients per group, this study has 80% power to detect a 35% difference in the peak time of GLP-1 between groups GLP-1 level with a 10% drop out rate. This calculation is based on data of a previous study of acute sleep deprivation and GLP-1 response (11).

2.8 References

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