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Original Article

The prevalence of impaired glucose regulation in psychiatric patients with sleep disorders and its relationship with altered hypothalamopituitary–adrenal and hypothalamopituitary–thyroid axis activity

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ABSTRACT

Background: Sleep restriction, an important symptom of psychiatric diseases, is associated with adverse effects on glucose regulation, but few studies have examined its association with impaired glucose regulation and altered hypothalamic activity. Our study was designed to evaluate the sleep duration, fasting glucose, tolerance glucose, and concentration of plasma insulin; to assess the function of both the hypothalamopituitary–thyroid (HPT) and hypothalamopituitary–adrenal (HPA) axis; and to investigate the relationship of altered hypothalamic function with glucose metabolism in psychiatric patients with a sleep disorders.

Methods: From January 2010 to December 2011, 324 women (64.7%) and 177 men (35.32%) with a diagnosis of a sleep disorder participated in our cross-sectional study in the psychiatric outpatient department of the West China Hospital of Sichuan University. Results from 75-g glucose tolerance tests, insulin-releasing tests, morning (8:00 AM) serum cortisol, and thyroid-stimulating hormone (TSH) (TT_3, TT_4, FT_3, FT_4) were collected, as well as body mass index and waist–hip ratio to assess the prevalence of impaired glucose regulation and function of the HPA and HPT axis. Sleep quality was assessed through self-reported questionnaires.

Results: There were 301 patients previously diagnosed with an anxiety disorder (78%), and 200 patients previously diagnosed with depression and other psychiatric diseases (22%). Crude prevalence rates were 15.0% for diabetes mellitus (DM), 11.6% for impaired glucose tolerance, 15.8% for impaired fasting glucose, and 11.6% for impaired glucose regulation (impaired glucose tolerance [IGT] + impaired fasting glucose [IFG]). Total prevalence of impaired glucose regulation in patients with a sleep disorder was 48.8%. Mean cortisol level was 463.5 ± 178.8 nmol/L, and the cortisol concentration at 8:00 AM was significantly associated with a higher prevalence of impaired glucose regulation and insulin resistance. TSH values above 2.5 mU/L accounted for over 58% and were significantly associated with insulin resistance.

Conclusions: These results partially confirm that a high level of cortisol and an increased activity of the HPT axis are associated with impaired glucose regulation. Therefore, as a pathophysiologic event abnormal activity of the hypothalamic function of psychiatric patients with sleep disorders could be viewed as a potential risk factor for increasing incidence of DM.

1. Introduction

Insomnia, difficulties in initiating and maintaining sleep, and daytime sleepiness have been associated with elevated prevalence and incidence of type 2 diabetes mellitus (DM) in several cross-sectional and prospective studies [1–6]. Although these findings suggest that sleep disorders may induce an increased risk for type 2 DM, evidence has been scarce with respect to insulin resistance (IR) and insulin secretion, which are the two major features of type 2 DM.

A few studies have found that polysomnography-based sleep-disordered breathing was associated with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), a higher degree of IR [7,8], and decreased insulin sensitivity and pancreatic β cell function [9]. However, other studies have suggested that sleep apnea, habitual snoring, and daytime sleepiness do not increase the risk for IFG, IGT, or IR [10]. These laboratory studies only lasted 1 or 2 weeks, and the results may not have reflected the effects of habitual short sleep.

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Many recent studies have reported an elevated prevalence of DM among short sleepers [11–13]. Several prospective studies found higher rates of incident DM among individuals with shorter sleep durations. For example, a meta-analysis reported a pooled risk ratio of 1.28 (95% confidence interval [CI], 1.03–1.60) associated with sleep duration <6 h compared with 7 or 8 h per night [14]. Together, these studies suggested that short sleep duration and poor sleep quality may adversely affect glucose metabolism.

In addition, many studies have reported that short sleep affects the function of the human hypothalamopituitary–thyroid (HPT) axis. Acute sleep loss in humans is associated with increased thyroid-stimulating hormone (TSH), T4, and T3 [15]. Additionally, cortisol, which is a key hormone secreted during the stress response, often is associated with sleep disturbances and hypercortisolemia [16]. Some studies have confirmed that chronic insomnia without depression is associated with elevated cortisol levels [17–20]. Our study focused on whether or not long-term exposure to more severe prolonged sleep restriction can modify the function of the human hypothalamopituitary–adrenal (HPA) and HPT axis as well as the relationship between altered hypothalamic function and IGT, IFG, and IR.

2. Methods

Our study was a single-center cross-sectional study. We recruited Chinese adults ages 43.2 ± 13.9 years from the sleep disorder center of the West China Hospital of Sichuan University. Patients who were not pregnant were eligible to participate and 610 consented. Informed consent was obtained from all participants, and the study protocol was approved by the local institutional review board.

2.1. Physical examination and laboratory investigations

Trained staff gathered baseline information on sociodemographic variables during standard interviews. Patients' height and weight were measured and their body mass index was calculated. Information on sleep was obtained from a self-administered questionnaire. Sleep duration was assessed with the question "How long, on average, in hours and minutes do you normally sleep?" It was further categorized into fewer than 3 h, 3–3.5 h, 3.5–5 h, 5–6 h, and more than 6 h. Sleep disturbances were coded for answers to two questions: (1) "Do you have difficulties in initiating sleep?" and (2) "Do you use sleeping pills more than three times a week?"

The clinical examination results, fasting blood samples, and demographic variables were collected for each participant. Glucose and insulin levels were both assayed in a fasting state at 30, 60, and 120 min from a 75-g oral glucose tolerance test (OGTT) and an insulin-releasing test. TSH, FT4, FT3, TT4, TT3, adrenocorticotropic hormone (ACTH), and plasma total cortisol (PTC) (8:00 AM) were measured along with fasting glucose. Based on the most recent recommendations from the American Diabetes Association [21], IFG was defined when fasting plasma glucose (FPG) was >100 mg/dL and <126 mg/dL, and IGT was defined when OGTT was >140 mg/dL and <200 mg/dL.

2.2. Insulin resistance and secretion

The homeostasis model assessment of IR method (HOMA-IR), the area under the curve of insulin (AUCI), the AUC of glucose (AUCG), and the AUCI/AUCG were used as indices of IR and insulin secretion. Formulas that were used to calculate these variables were: HOMA-IR, (fasting plasma insulin [mU/L] three FPG level [mmol/L])/22.5; insulin sensitivity index (ISI), $10{,}000/\sqrt{}$(FPG [mmol/L]×fasting plasma insulin [mU/L])×[mean OGTT glucose [mmol/L]×mean OGTT insulin [mU/L]); corrected insulin response (CIR), (100 × insulin [mU/L] at 30 min/glucose [mmol/L] at 30 min × glucose [mmol/L] at 30 min–3.89 mmol/L); and DI (disposition index), CIR × ISI. AUCI and AUCG were calculated as follows: AUCI, (fasting plasma insulin [mU/L]/2 + insulin [mU/L] at 30 min + insulin [mU/L] at 60 min + insulin [mU/L] at 120 min)/2; and AUCG, (FPG [mmol/L]/2 + glucose [mmol/L] at 30 min + glucose [mmol/L] at 60 min + glucose [mmol/L] at 120 min/2)×18.

2.3. Statistic analysis

We used SPSS 18.0 software for statistical analysis. Differences in proportions were tested using Pearson χ^2 test. The t test was used for group comparisons involving numerical data. Linear regression models were used to examine the cross-sectional association between the sleep measures, PTC, ACTH, TSH, and FPG, fasting insulin, and IR (HOMA-IR), AUCI/AUCG, ISI, DI, and CIR. Values were considered significant at $P < .05$. We excluded 59 participants with positive thyroid antibodies tests, one of whom was diagnosed with Cushing syndrome, and three of whom were diagnosed with hypothyroidism for a final sample size of 501.

3. Results

The mean age of the subjects was 43.6 years (standard deviation, 13.47 y; range, 13–85 y), and 145 (33.3%) of the subjects were men. Mean body mass index was 22.77 ± 3.1 kg/m^2, and 77.11% of subjects were given a diagnosis of an anxiety disorder. Of the 501 subjects, 435 completed the OGTT. Average FPG was 5.45 ± 0.90 mmol/L, and average insulin was 8.22 ± 5.89 μU/mL. Two-hour glucose was 6.87 ± 3.06 mmol/L and insulin level was 43.41 ± 33.70 μU/mL. Results of the OGTT suggested that 32 subjects had occult DM (6.8%), 110 subjects had IFG (25.2%), 74 subjects had IGT (17.0%), and 175 subjects had impaired glucose regulation (39.5%). The average TSH level was 2.75 ± 1.77 mU/L, and 216 subjects had a TSH level above 2.5 mU/L (46.15%). The average ACTH was 26.11 ± 16.74 nmol/L, and the average cortisol level was 437.7 ± 167.45 nmol/L. We used age groups of ⩽34, 34 to 43, 43 to 53, and ⩾53 years, and each group consisted of 25% of the total subjects.

Table 1 presents the mean (standard deviation) key variables in the analysis, stratified by sleep duration. Subjects with severe sleep restriction were younger. Among subjects with severe sleep restriction, IR factors such as CIR, DI, INS-0 h, and AUCI were significantly higher than in those with normal sleep duration. In addition, subjects with sleep duration of fewer than 3 h demonstrated a greater increase in TSH, ACTH, and cortisol levels than those who slept more than 6 h.

The results of our cross-sectional analyses examining the association between the sleep-hour measures and fasting glucose, fasting insulin, HOMA-IR, and morning PTC are presented in Table 2. In subjects in the unadjusted models, shorter sleep duration was associated with higher insulin levels and higher HOMA values. However, these associations were no longer statistically significant in the fully adjusted models. Short sleep duration (<3 h) was associated with higher fasting glucose, higher AUCI, and higher AUCG, even in the fully adjusted models. Among subjects with shorter sleep duration, higher AUCG was associated with higher plasma levels of TSH.

4. Discussion

Our study suggests that sleep restriction and altered activity of HPA and HPT were associated with increased IR of different age