Impact of non-apnea sleep disorders on diabetic control and metabolic outcome - A population-based cohort study

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ABSTRACT

Objective: There has been a growing recognition that obstructive sleep apnea (OSA) could increase the propensity for type 2 diabetes the metabolic syndrome. However, studies concerning about the impact of non-apnea sleep disorders (NSD) on diabetes control and metabolic outcomes are relatively scarce. Our aim is to investigate the impact of non-apnea sleep disorders (NSD) on diabetic control and associated metabolic outcomes in patients with type 2 diabetes.

Methods: The data were obtained from two nationwide population-based databases for a period 2007 to 2012. A total 66,992 patients with type 2 diabetes were enrolled and divided into two cohorts based on comorbidity with or without a NSD diagnosis, and were followed up four years. The primary outcomes were to compare rate of change in HbA1c and associated metabolic outcomes during follow-up visits between patients with or without NSD. The secondary outcome is to examine whether NSD were associated with poor glycemic control of the last clinical records while controlling for the baseline HbA1c value.

Results: Of the 66,992 patients with type 2 diabetes, 14.82% had comorbidity with a NSD. HbA1C decreases were significantly lower by 0.04% in the NSD group ($P < 0.05$), and triglyceride (TG) decreases remained significantly lower by 2.53% in the NSD group ($P < 0.05$). Furthermore, patients in the NSD group had an 8% higher risk of poor glycemic control (HbA1C > 9) (OR = 1.08; 95%CI, 1.01–1.16).

Conclusion: Our findings indicated patients with type 2 diabetes comorbid with NSD had a slower improvement in HbA1c compared with the comparison cohort. It may because there may exist potential floor effect given those with NSD having significantly lower HbA1c values at baseline. On the other hand, the poor diabetic control among those with NSD may be also affected by other confounders such as medical treatment or interventions. Nevertheless, given the rapidly increasing prevalence of metabolic diseases and subsequent complications, the results may highlight the importance of sleep in the clinical management of type 2 diabetes.

1. Introduction

Diabetes is a growing challenge in medical care and public health. An estimated 180 million people worldwide are affected and the prevalence continues to increase [1]. Long-term complications associated with type 2 diabetes may cause substantial burdens on morbidity and mortality. One half of patients with type 2 diabetes die of

cardiovascular cause and approximately 10% die of renal failure [2]. Effective diabetes management requires multidisciplinary health care professionals and interventions.

Over the past decade, there has been a growing recognition that sleep disturbances such as difficulty initiating sleep, difficulty maintaining sleep, short and long sleep durations, poor sleep quality, insomnia, obstructive sleep apnea (OSA), and restless legs syndrome are

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potential risk factors for glucose intolerance, insulin resistance, type 2 diabetes mellitus and metabolic syndrome (MetS) [3–7]. Among sleep disorders, OSA appears to have the strongest association with insulin resistance, glucose intolerance, type 2 diabetes and MetS, as supported by both epidemiologic surveys and laboratory studies [8,9]. Furthermore, there are emerging data suggesting an association between non-apnea sleep disorder (NSD) and a risk of type 2 diabetes [7,10]. A population-based cohort study in Taiwan showed that patients with NSD had an 11% higher risk of type 2 diabetes [11].

Several existing investigations have indicated an association between sleep disturbance and glycemic control [12–16]. However, some of studies were measured in limited study groups and in cross-sectional study designs. Besides, the assessment of sleep duration and complaints mainly relied on subjective questionnaire surveys [12,14,15], or subjective questionnaire surveys accompanied by wrist-actigraphy to evaluate sleep quality [13]. Moreover, previous studies did not control for sleep apnea and other potential confounders such as physical and mental comorbidities that could be associated with the outcome of type 2 diabetes [12,14,15]. Although there were emerging data suggesting that sleep disturbances were negatively associated with the diabetic control and metabolic outcomes, no longitudinal study was conducted to evaluate the long-term effect of NSD on the selected MetS parameters in patients with type 2 diabetes. There is a need to conduct further research for elucidating the impact of NSD on diabetic control and metabolic outcomes.

In the current study, we aimed to investigate the impact of NSD on diabetic control assessed by HbA1C and associated parameters of MetS in patients with type 2 diabetes by adopting 4-year longitudinal study design in a large population. Specifically, the primary outcomes were to compare rate of change in HbA1c and associated metabolic outcomes during follow-up visits between patients with type 2 diabetes comorbid with or without NSD. The secondary outcome is to examine whether NSD were associated with poor glycemic control of the last clinical records while controlling for the baseline HbA1c value.

2. Materials and methods

2.1. Study design and data source

The current study conducted a longitudinal cohort design using two nationwide population-based databases during the period from 2007 to 2012. One was a diabetes pay-for-performance (P4P) registry database from which we could obtain the clinical outcome metrics of diabetes patients, including glycosylated hemoglobin A1c (HbA1c), fasting plasma glucose, BMI, lipid profiles and blood pressures values. The other source was the Taiwan National Health Insurance (NHI) claims database from which we could obtain information on patient comorbidities and health provider characteristics. Data of same participants from both datasets were linking based on identifier. This study was approved by the Institutional Review Board at Kaohsiung Medical University Hospital.

2.2. Study cohort

This study first identified newly enrolled diabetes P4P patients between 2007 and 2008 (N = 78,694). A patient was defined as having diabetes if he or she had a primarily diabetes diagnosis (ICD-9-CM codes with 250.xx or A-code 181) in at least two outpatient visits or any diabetes diagnosis in at least one inpatient hospitalization during identification periods. The date of the patient's first enrollment into the program was defined as the index date. We excluded patients who had type 1 diabetes because they made up < 1% of the newly enrolled diabetes patients, were younger than 18 years old at the index date, had less than one follow-up visit after enrollment, or had specific exclusions (i.e., the gender variable was missing or with erroneous data, or the initial enrollment date was not recognizable). We followed Lai et al.

(2013)'s approach to define patients with NSD using diagnosis codes if they had at least one outpatient or inpatient service claim with ICD9-CM diagnosis codes 307.4× (specific disorders of sleep on nonorganic origin) or 780.5× (including sleep disturbance, insomnia, hypersomnia, disruptions of 24-h sleep-awake cycle, dysfunctions associated with sleep stages or arousal from sleep, sleep related movement disorder) within one year prior to the enrollment date of each patient, while patients with obstructive sleep apnea (OSA) diagnosis (ICD-9-CM code with 780.51, 780.53, or 780.57) were excluded [11,17]. Finally, total 66,992 diabetes patients were included in the analysis, including patients with NSD diagnosis (N = 9927) and without NSD diagnosis (N = 57,065).

2.3. Outcomes definition and measurement

A set of clinical outcome metrics were used as outcome variables, including physical examinations (e.g., systolic blood pressures (SBP), diastolic blood pressure (DBP), and BMI) and laboratory tests (e.g., HbA1c, fasting plasma glucose, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol (T-cho)). Each patient in both cohorts was followed for four years from the first date of enrollment, and was censored if he or she dropped out of the P4P program or had died.

We first derived the trends of clinical outcomes based on 14 follow-ups within four years. To further analyze data, we measured changes in clinical outcomes separately for each cohort using the patient's last clinical records during follow-up visits minus baseline clinical results at the date of the first enrollment. We then compared the adjusted and unadjusted difference in changes in clinical outcomes between patients with or without NSD. Given that HbA1c level was associated with a higher risk of cardiovascular disease(CVD) and higher risk of death [18], we also defined HbA1c > 9% as poor glycemic control of the last clinical records during follow-up visits while controlling for the baseline HbA1c value as well as associated variables.

2.4. Confounding variables

Several patient baseline characteristics that may affect patient outcomes were included as covariates, including age at the index date, gender, BMI, non-psychiatric comorbidities (e.g., a diabetes complication severity index (DCSI), and a chronic illness with complexity (CIC)) index within one year prior to the index date, and psychiatric comorbidities including anxiety and depression.

DCSI [19] and CIC [20] indexes are frequently used in studies on diabetes complexity. The DCSI contains 7 categories of complications, based on ICD-9-CM codes, including cardiovascular complications, nephropathy, retinopathy, peripheral vascular disease, stroke, neuropathy, and metabolic disorders. The DCSI has a total score of 13 points. A higher score indicates a more severe disease state. The CIC index was used to adjust for comorbidity of patients with multiple chronic diseases. This index contains non-diabetes physical illness complexity (including cancers, and gastrointestinal, musculoskeletal, and pulmonary diseases), diabetes-related complexity, and mental illness/substance abuse complexity. We excluded diabetes-related complexity when constructing the CIC index, to avoid the duplication of the comorbidity effect captured by the DCSI index, and we categorized both DCSI and CIC measures into three categories (0, 1, and ≥ 2). In addition, psychiatric comorbidities from anxiety and depression were also included and adjusted given the prevalence of comorbid anxiety and depression was significantly higher in diabetic patients [21] [22]. Besides, anxiety and depression have significant effects on the course and outcome of type 2 diabetes [23] [24].

The characteristics of health care institutions enrolling patients into the P4P programs may also affect outcomes. Health care institution characteristics included accreditation level (medical center, regional hospital, local hospital or clinic), ownership type (public, not-for-profit,