ORIGINAL ARTICLE

Association Between Sleep Duration and Glycemic Control Among Patients with Type 2 Diabetes Mellitus in India

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Abstract

Context: An increasing prevalence of type 2 diabetes mellitus is a growing public health concern in India. The problem of chronic partial sleep loss due to changes in lifestyle is also rapidly increasing.

Aim: The aim of the present study was to examine the association between sleep duration and glycemic level (HbA_{1c}) in type 2 diabetic patients.

Settings and design: This was a tertiary care hospital based cross-sectional study in India.

Materials and methods: A total of 202 patients with type 2 diabetes mellitus aged 20 years and above attending an endocrinology outpatient clinic during the month of July 2013 were studied. Information on glycosylated haemoglobin (HbA_{1c}) value, sleep duration, age, gender, duration of diabetes, total energy intake, current smoking, current alcohol consumption, insulin use, depressive symptoms and Body Mass Index (BMI) were obtained.

Results: The adjusted mean (95% Confidence Interval (CI)) HbA_{1c} values for subjects who slept less than 4.5 hours (h) was 9.90% (8.76, 11.19), for subjects who slept 4.5 – 6.4 h was 8.42% (8.04, 8.81), for subjects who slept 6.5 – 8.4 h was 8.18% (7.77, 8.63) and for subjects who slept more than 8.5 h was 8.28% (7.04, 9.74). Log mean HbA_{1c} between those who slept less than 4.5 h was significantly higher compared to the subjects who slept 6.5-

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8.4 h (P = 0.011) and the subjects who slept 4.5-6.4 h (P = 0.013) . Significant interactions were observed between sleep duration and age (<50 years and e"50 years) (P for interaction = 0.026). On the other hand, there was no significant interaction between sleep duration and gender, the presence or absence of obesity and depressive symptoms. However a significant interaction was observed between sleep duration and use of insulin therapy (P for interaction = 0.001) in predicting HbA_{1c}.

Conclusion: This is the first epidemiological study in India to investigate the U-shaped associations of sleep duration with glycemic level in patients with type 2 diabetes mellitus. Our observations suggested that the patients with short sleep duration particularly among the elderly without insulin use should be considered high risk patients for poor glycemic control. Future studies can look into the optimal sleep duration required which may be considered as an important modifiable factor for the clinical management of patients with type 2 diabetes mellitus.

Keywords: Sleep duration, Glycemic level, Type 2 diabetes mellitus

Introduction

An increasing prevalence of type 2 diabetes and its macro and micro vascular complications is a growing public health problem in both developed and developing countries[1-3]. The projected diabetic population in India for 2025 is 69.9 million and for 2030 is 80 million with a current estimate of 40.9 million[4]. The prevalence of coronary artery disease was 21.4 percent and the prevalence of peripheral vascular disease (PVD) was 6.3 percent among diabetic patients in India[5,6]. The problem of chronic partial sleep loss due to changes in lifestyle is also rapidly increasing. Moreover, changes in social habits as exemplified by the increase in the number of shops and restaurants that stay open until late at night, coupled with the increase in the number of people who stay up late at night browsing the internet have resulted in a new lifestyle culture in urban cities of India. Hence, an increase in the prevalence of sleep disturbance has been recognized as a social problem in recent years[7]. Few community based epidemiological studies done in the other parts of the country had reported an association of short sleep duration with obesity, metabolic syndrome and poor glycemic control[8-10]. The negative impact of prolonged sleep duration on glycosylated haemoglobin (HbA_{1c}) has also been described[11-15] and suggested a U-shaped relationship.

However, very few studies were conducted among diabetes patients in Asian region investigating the association between sleep duration with HbA_{1c} values despite the fact that racial differences have been suggested[16,17]. To the extent of our knowledge, no study has been conducted in India to examine the association of sleep duration with HbA_{1c} among diabetic patients. Therefore the aim of the present study was to examine the association between sleep duration and glycemic control among patients with type 2 diabetes mellitus adjusting for the possible confounders that influence HbA_{1c}. The confounders considered were age, gender, duration of diabetes, current smoking status, current alcohol consumption, energy intake, energy expenditure, depressive symptoms, insulin use, obesity and sleep quality.

Materials and Methods

Sample Size

With an expected correlation r = 0.30[8] , of those having either lower or higher sleep duration with HbA_{1c} and α = 0.05, β = 0.10 the minimum sample size required was 115.

Study subjects

A total of 202 diabetic patients aged 20 years or older who attended the endocrinology outpatient (OP) clinic of PSG Institute of Medical Sciences and Research between 1st July 2013 to 7th August 2013 and who gave written informed consent to participate in this study were included. The exclusion criteria were 1) patients with type 1 diabetes mellitus; 2) patients with Gestational Diabetes Mellitus (GDM); 3) patients on renal replacement therapy; and 4) patients with malignancies and liver cirrhosis.

Clinical evaluation and laboratory measurements

The questionnaire covered information on sleep duration, duration of diabetes, current smoking status, alcohol consumption, diet, depressive symptoms and physical activities. The validated Pittsburg Sleep Quality Index (PSQI)[18] questionnaire was used to measure the sleep quality which covers seven components include subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, uses of sleep medication and daytime dysfunction. Alcohol consumption and smoking habits were classified as either current user or not. The individual dietary intake was obtained by 24-hour dietary recall method. Standard containers were shown to obtain their quantity of food intake. Physical activity was assessed by International Physical Activity Questionnaire (IPAQ- short form) [19]. The questions were about the time spent being physically active in the last 7 days. The questionnaire includes questions about activities done at work, as part of house and yard work, to get from place to place, and in spare time for recreation, exercise or sports. Each of the physical activity was marked in frequency per week and number of hours per session. The metabolic equivalents for each physical activity were obtained from compendium of physical activity by Ainsworth et al[20]. The presence of depressive symptoms was assessed using the Center for Epidemiologic Studies Depression scale (CES-D)[21].The subjects were categorized as either taking insulin therapy or not. Alcohol consumption and smoking habits were classified as either current user or not. BMI was calculated from height and weight and blood samples were collected by veni-puncture. The HbA_{1c} values were determined by high-performance liquid chromatography (BIO-RAD, D-10)

Statistical analysis

Calorie intake was computed using standard reference from Nutritive Value of Indian Foods[22]. The total energy expenditure during physical activity was calculated using the metabolic equivalents (MET values). Energy expenditure (EE) was calculated using the following formula

EE = MET * Duration of activity (hours) *Body weight (kilograms)[23].

Subjects who scored more than 16 out of 60 points in the CES-D score were classified as elevated depressive symptom. Obesity was defined as BMI e" 30 kg/m^2 [24]. As this is the first reported study in India, we have categorized HbA1c similar to other studies reported in Asia to have an idea on pattern of HbA1c according to sleep duration[25] .The differences in the mean values or proportion of the characteristics of the studied subjects across various sleep duration were then tested using ANOVA or X^2 test as appropriate. Post hoc comparisons were done using least significance difference method. The quadratic trend for the marginal means of HbA_1C values across various sleep duration categories was then tested using quadratic regression analysis. The HbA_1C values were log-transformed for statistical analysis due to their skewed distribution. Multivariate and obesity, energy intake adjusted mean values of the HbA_1C were calculated by an ANCOVA using General Linear Model (GLM) analysis, back-transformed, and reported as adjusted means and their 95% confidence interval. The effect of interaction of sleep duration with other confounding factors on the HbA_1C was examined by adding additional interaction term of sleep duration with the covariates to the statistical model in the multivariate regression analysis with log transformed HbA_1C as the dependant variable. All statistical analysis were performed using SPSS (Statistical Package for Social Science version 19.0). Values of $p<0.05$ was considered to be statistically significant in all analyses.

Results

Table 1 shows the characteristics of the participants. Mean duration of sleep among the elderly were shorter compared to younger subjects (P = 0.002). Current smokers, current alcohol consumers and duration of diabetes had no statistically significant differences between sleep duration categories. BMI and the proportion of obese subjects had no statistically significant differences between sleep duration categories.

Table 2 shows HbA_{1c} levels with sleep duration category. In general, we observed a U-shaped relationship (P for quadratic trend P = 0.032). The shape remains the same after adjusting for age, gender, duration of diabetes, current smoking status, current alcohol consumption status, energy expenditure, insulin use, status of elevated depressive symptoms and sleep quality, (though P for quadratic trend was not statistically significant) and remains the same even after adjusting total energy intake and obesity status along with them. Figure 1 presents the multivariate adjusted mean values

of HbA_{1c} according to sleep duration with mean levels of 9.90% (95% CI: 8.76, 11.19) for subjects who slept less than 4.5 h, 8.42% (8.04, 8.81) for 4.5-6.4 h, 8.18% (7.77, 8.63) for 6.5-8.4 h and 8.28% (7.04, 9.74) for those who slept more than 8.5 h. Log mean HbA_{1c} between those who slept less than 4.5 h was significantly higher compared to those who slept 6.5- 8.4 h ($P = 0.011$) and even with those who slept 4.5-6.4 h ($P = 0.013$). In addition, the interaction analysis between sleep duration and possible confounding factors on the HbA_{1c} levels were conducted in Table 3. Significant interactions were observed between sleep duration and age (<50 years and e"50 years) (P for interaction = 0.026). On the other hand, there was no significant interaction between sleep duration and gender, the presence or absence of obesity and depressive symptoms. However a significant interaction was observed between sleep duration and use of insulin therapy (P for interaction = 0.001) in predicting HbA_{1c}.

Table 1: Clinical characteristics of the studied subjects according to sleep duration

	Sleep duration					
	All	≤4.4	4.5-6.4	6.5-8.4	≥8.5	P value
N	202	22	89	83	8	
Age (years)	54±11	57±10	54±11	54±10	41±9	0.002*
Male (%)	61	55	69	53	75	0.145
Duration of diabetes (years)	8±8	11±7	9±8	8±7	5±4	0.125
Total energy intake (kcal/day)	2137±316	2086±268	2134±309	2121±321	2461±355	0.026*
Current smoker (%)	6	9	7	4	13	0.591
Current drinker (%)	6	14	6	5	13	0.417
Energy expenditure MET (kcal/day)	2066±364	1977±242	2065±376	2052±363	2460±318	0.012*
Depressive symptoms (%)	67	82	67	63	75	0.371
Insulin user (%)	35	59	32	35	13	0.049*
BMI (kg/m^2)	26±4	26±4	26±5	27±4	28±6	0.508
Obese (%)	18	23	18	17	25	0.885
PSQI score	5.76 ± 3.49	11.95±2.66	6.19±2.56	3.92±2.40	2.87±2.64	0.000*

* P < 0.05

Values are expressed as means ± SD or the percentages. Obesity is defined as a BMI e" 30 kg/m^2

Table 2: Marginal means (95% CI) of the HbA_{1c} according to sleep duration

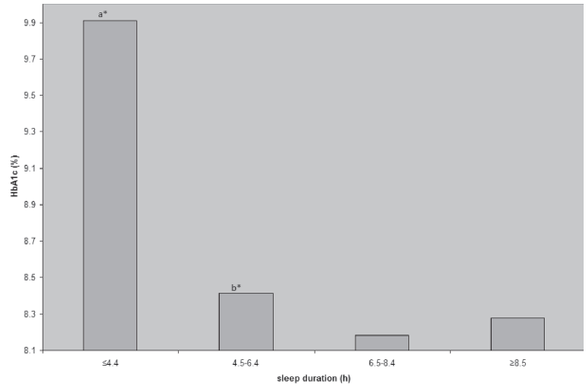
Sleep Duration (hours)	Mean HbA_{1c} (%)
≤4.4	9.698 (8.802-10.676)
4.5-6.4	8.364 (7.973-8.776)
6.5-8.4	8.256 (7.854-8.679)
≥8.5	8.568 (7.301-10.054)

P value for quadratic trend = 0.032

Table 3: P values for interaction of sleep duration with obesity, age, sex, insulin use and depressive symptoms

Interaction of sleep duration with	P value
Obesity. (Yes, No)	0.243
Age. (<50 years, e" 50 years)	0.026*
Sex (Male, Female)	0.815
Insulin use. (Yes, No)	0.001*
Depressive symptoms. (Yes, No)	0.154

* P < 0.05



Multivariate adjustment was made for age, gender, duration of diabetes, current smoking, current drinking, energy expenditure (MET), insulin use, depressive symptoms and PSQI

a* $P = 0.011$ for sleep duration d" 4.4 h with 6.5-8.4 h per day

b* $P = 0.013$ for sleep duration d" 4.4 h with 4.5-6.4 h per day

P for quadratic trend = 0.079

Discussion

The present study demonstrated that short duration of sleep relative to the intermediate duration was statistically associated with higher HbA_{1c} levels. This association remained significant after adjusting the confounding factors. Though several studies have investigated the association between the sleep duration and higher risk for diabetes, this was the first study in India to indicate that a U-shaped relationship between sleep duration and glycemic level among type 2 diabetic patients.

There are several potential mechanisms through which the relationship between sleep duration and glycemic level may be explained. Sleep curtailment decreases the satiety hormone leptin and increases the appetite – stimulating hormone ghrelin[12,26] which may lead to increase in appetite[26], hunger[26,27] and energy intake[27] thereby increases glycemic level and consequently lead to obesity. However in our analysis, even after adjusting obesity status and total energy intake the association between less sleep duration and higher HbA_{1c} was statistically significant. A similar finding was reported by Toshiaki Ohkuma et al and suggested other possible explanations which may include changes in counter regulatory hormones and proinflammatory cytokines. Another possible mechanism include sleep duration has reported to be significantly associated with increase in cortisol[28], interleukin 6 and tumor necrosis factor-á [28]. These changes may contribute to insulin resistance. Future studies can look more into these mechanisms which may play a role in the association between less sleep duration and higher HbA_{1c} values.

In our study, the long sleep duration was also found to have higher HbA_{1c} though the difference with intermediate sleep duration was not statistically significant. This may be due to the small number of patients who had longer duration of sleep that we could enroll during the period of study. Several studies in other countries have reported a significant association between longer sleep duration and higher HbA_{1c} [30-34]. The mechanisms underlying the association between a long sleep duration and higher glycemic level are not clear. However it was reported in a previous study that the depression and physical inactivity were associated with long sleep duration and may have confounded the association[35].

The current study indicated no interactions between various confounding factors and sleep duration on HbA_{1c} levels with the exceptions of age and use of insulin. On further sub data analysis, we observed that the association of short sleep duration and higher HbA_{1c} levels were attenuated in subjects 50 years and younger and in those with insulin therapy. A similar finding was observed by Toshiaki Ohkuma et.al[25].

Recently many studies have reported U-shaped associations between sleep duration and mortality risks of diabetes[36-39]. Studies had also reported U-shaped associations between sleep duration and the morbidity risks of diabetes and obesity[40,41]. It is also well known that diabetes and obesity are the main risk factors of Coronary Heart disease (CHD)[42]. Further prospective studies can look more in detail whether the U-shaped associations exist between these pathological conditions and sleep duration will explain the such association between the mortality risk of CHD and sleep duration.

The present study has the following strengths. First, we considered many covariates that may contribute to the association of interest. Second, we used validated questionnaire for measuring sleep quality, energy intake and depression in the analysis while exploring the relationship between sleep duration and HbA_{1c} values. Our study has several limitations. First, sleep duration was self-reported. However some studies have shown that self-reported data on sleep duration are concurrent to a certain extent, with physiological data[43,44]. Second, with cross sectional study we were not able to interpret whether short or long duration of sleep induces impaired glucose tolerance and consequently diabetes mellitus or in contrast whether impaired glucose tolerance induces sleep disturbances. Third, the questionnaire did not include all terms known to affect sleep and glucose metabolism. Employment status, noise and home environment may also affect sleep and glucose metabolism[42]. Finally, this was only a pilot study and sample size is small for those who sleep more than 8.5 hours per day. However, the results of this study will motivate for future large scale multicentre studies in Asia region to generalize the results.

Conclusion

This is the first epidemiological study in India to investigate the U-shaped association of sleep duration with glycemic level in patients with type 2 diabetes mellitus. Our findings suggested that the patients with short sleep duration particularly elderly people aged 50

duration required which may be considered as an important modifiable factor for the clinical management of patients with type 2 diabetes mellitus.

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