Association of Diabetic Retinopathy and Sleep Quality

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Abstract- Sleep disorders are more common in diabetes mellitus (DM) cases rather than normal ones. In addition, this condition could be associated with diabetic retinopathy (DR) development with more inflammatory indices in circulation. In the present study, we have evaluated the association between DR and sleep quality. This cross-sectional study is a part of the second phase of the study of the elderly cohort of Amirkola City, which was conducted in 2015-2016 on all people aged 60 and higher. Of all diabetic cases, 44 cases had retinopathy and were selected as the case group. To compare two control groups, 135 diabetic patients without retinopathy and 135 people without diabetes were randomly selected. The presence and type of retinopathy were determined based on an eye physical examination by an ophthalmologist. In addition, sleep quality was evaluated based on the Pittsburgh Questionnaire. The obtained data were analyzed by ANOVA, t-test, and linear regression tests. In the present study, there was a significant difference in the score of the Pittsburgh questionnaire between people with DR (45.5±68.2) compared to diabetic people without retinopathy (76.5±48.2) and people without diabetes (95.4±36.2) (P=0.470), but diabetic people without retinopathy had significantly worse sleep quality than people without diabetes (P=0.019). Also, sleep quality in women with DR was worse than in men (P=014). In the linear regression analysis, it was observed that age, gender, diabetes, and history of depression significantly affect the sleep quality of the evaluated cases (P<0.05 for all). According to the results of the present study, DR does not negatively influence the quality of sleep, and DR is not related to sleep disorders.

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Keywords: Sleep latency; Sleep initiation and maintenance disorders; Daytime dysfunction; Diabetic retinopathy

Introduction

Diabetic retinopathy (DR), as the main etiology of population blindness, is a progressive and chronic disorder that may result in different levels of visual impairment (1). Even though DR in the early stages is an asymptomatic condition of retina involvement, abnormalities of electrophysiological in the inner layer function of the retina have been registered as soon as six months after diabetes mellitus diagnosis, even in the absence of visible DR (2). Other changes in electrophysiological condition are observed in the longer duration of diabetes mellitus (3). Furthermore, animal DR models show vascular and morphological changes and dysfunction of retinal cells, i.e., loss of retinal ganglion cells (RGCs) (4,5).

Some studies and documents mentioned poor sleep quality related to DR pathogenesis and proliferative DR development (6). Another attention is on the issue that sleep disorders have a negative effect on inflammation and the immune system, which has been observed in DR pathogenesis and is an aim for DR treatments based on pharmacological methods (7,8). Recent research by optical coherence tomography (OCT) performed on DR patients and animal models showed that the loss of RGC with severity enhancement of DR results in progressive

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loss of visual severity. An RGC subpopulation, photosensitive retinal ganglion cells (pRGCs), are influenced in patients with diabetes mellitus (9).

Therefore, it is difficult to determine whether sleep disorders are the result of DR or a risk factor for developing DR, or whether both occur independently of each other (9). Based on this, the importance of evaluating the correlation between sleep disorder and DR has been cleared, so the aim of the present study was to evaluate the association between DR and sleep quality.

Materials and Methods

Study setting and population

This cross-sectional study has been conducted on elderly cases of Amirkola City who participated in the second phase of the Amirkola Elderly Cohort Project in 2015-2016. In the Amirkola cohort project, a total of 44 patients with retinopathy were found. Also, a control group with diabetes mellitus without retinopathy and people without diabetes mellitus who had an eye physical examination (135 cases in each control group) were evaluated.

Clinicallyconfirmed patients and healthy individuals with ages equal to and above 60 years old were enrolled in this study. Also, the exclusion criteria included type I diabetes mellitus, severe kidney failure, and heart failure.

Measurements and examination

All included cases in the retinopathy and diabetic mellitus group have a confirmed history of diabetes and are being treated with diabetes medications, so diagnostic criteria are not necessary for the diagnosis of diabetes in cases who enter the study. On the other hand, patients who did not have a history of diabetes and had an FBS equal to or greater than 126 on two screening tests were considered to have diabetes mellitus.

Demographic information, including age, gender, history of other diseases, and medication taken, were collected from all cases. Also, information related to possible confounders of sleep quality, such as BMI, history of hypertension, smoking, lung diseases, and depression, was collected from the database related to the second phase of the Amirkola cohort project.

DR of patients was evaluated with a standard protocol and after pupil dilation by a retina specialist to diagnose DR. DR is considered based on the presence of any indicative lesion according to ETDRS criteria, which includes microaneurysms, hemorrhages, cotton wool spots, retinal microvascular defects, hard exudates, vitreous hemorrhages, and neovessels. The type of retinopathy was divided into non-proliferative and proliferative categories.

Pittsburgh Questionnaire was used to check sleep quality and related disorders. This questionnaire was done for the first time by Buysse *et al*., (10), which includes 19 questions that were answered by the patient per se, which evaluates the quality of the person's sleep during the last month. These 19 questions assess 7 aspects of sleep (sleep onset delay, sleep duration, effectiveness, quality, disturbances, medication use, and daytime dysfunction). Each of these items receives a score between 0-3, which, in total, any case has a score between 0-21, the higher score related to lower quality of sleep. It has also been determined that a score of >5 is a cutoff point for distinguishing between patients with and without insomnia. In Iran, its validity and reliability have been confirmed by Hassanzadeh *et al*., with Cronbach's alpha coefficient as 78.0 to 82.0 (11).

Ethical considerations

The study was performed by the research committee of the orthopedics department of the hospital and approved by the Research Ethics Board of Babol University of Medical Sciences. The study complied with the rules of the Helsinki Convention and was approved by the ethical code as IR.MUBABOL.HRI.REC.1400.051.

Statistical analysis

The data were obtained based on the mentioned questionnaire and checklist, then the data were entered into SPSS software (IBM, USA) version 22, and these data were analyzed by ANOVA, T-Test, Chi-square, and linear regression at the 95% confidence level.

Results

Demographic data

Out of 314 evaluated cases, 44 cases with DR as the case group, 135 cases with diabetes without retinopathy, and 135 cases without diabetes were included in this study. The mean±SD of the age of cases in retinopathy, diabetic without retinopathy, and without diabetes groups were 68.61±6.31, 68.79±6.21, and 68.78±6.71 years, respectively, which did not have a statistically significant difference (P=0.987). Also, the mean±SD of systolic blood pressure of cases in the retinopathy, diabetes without retinopathy, and without diabetes groups were 138.80±21.98, 143.69±20.85, and 143.60±22.48 mmHg, respectively (P=0.391). Also, in the retinopathy group, 26 cases (59.1%) were male, and 18 cases (40.9%) were female; in the diabetic group without retinopathy, 62

cases (45.9%) were male, and 73 cases (54.1%) were female; and in the group without diabetes, 74 cases (54.8%) were male, and 61 cases (45.2%) were female, which did not have a statistically significant difference (*P*=0.193). Also, there were 7 cases (15.9%) in the retinopathy group, 22 cases (16.3%) in the diabetic without retinopathy group, and 20 cases (14.8%) in the non-diabetic group that was positive about smoking (*P*=944.0) (Table 1).

Table 1. Comparison of Demographic and Basic Data in study groups

Variable		Groups			*P*
		Retinopathy	Diabetes without retinopathy	No diabetes	
Age (year; mean±SD)		68.61±6.31	68.79±6.21	68.78±6.71	0.987
Sleep Quality (Pittsburgh score; mean±SD)		5.45±2.68	5.76±2.48	4.95±2.36	0.025
BMI (kg/m^2; mean±SD)		28.31±4.16	29.52±4.71	42.4±0.28	0.019
Systolic blood pressure (mmHg; mean±SD)		138.80±21.98	143.69±20.85	143.60±22.48	0.391
Duration of diabetes (years; mean±SD)		7.50±5.22	9.63±7.88	-	0.15
Gender	Male [n (%)]	26 (59.1)	62 (45.9)	74 (54.8)	0.193
	Female [n (%)]	18 (40.9)	73 (54.1)	61 (45.2)	
Smoking	Positive [n (%)]	7 (15.9)	113 (83.7)	115 (85.2)	0.944
	Negative [n (%)]	37 (84.1)	22 (16.3)	20 (14.8)	

Sleep quality (pittsburgh questionnaire)

The mean±SD of Pittsburgh Questionnaire score of cases in the retinopathy, diabetic without retinopathy, and non-diabetic groups were 5.45±2.68, 5.76±2.48, and 4.95±2.36 respectively; these values were significantly different in the groups so that its rate was the lowest in the group without diabetes mellitus (*P*=0.025) (Table 2). Also, Post Hoc analysis showed that there is no significant difference in the Pittsburgh Questionnaire score between DR, diabetes without retinopathy, and without diabetes cases, but there is a significant difference in the Pittsburgh Questionnaire score between cases with diabetes, without retinopathy, and without diabetes (Table 3).

Table 2. Comparison of sleep quality in study groups

Groups	Sleep Quality (score; mean±SD)	*P*
Retinopathy	5.45±2.68	
Diabetes without retinopathy	5.76±2.48	0.025
No diabetes	4.95±2.36	

Table 3. Post hoc test analysis results related to the Pittsburgh sleep quality score in the study groups

Groups		Mean Difference	*P*
Diabetic retinopathy	Diabetes without retinopathy	-0.31	0.741
	No diabetes	0.49	0.470
Diabetes without retinopathy	Diabetic retinopathy	0.31	0.741
	No diabetes	0.81	0.019
No diabetes	Diabetic retinopathy	-0.49	0.470
	Diabetes without retinopathy	-81.0	0.019

Possibly study confounders

To evaluate possible confounders of the study, the linear regression statistical test was used based on the mean of the PSQI score. After adjusting for possible confounders, the used test excluded some variables, including smoking, retinopathy, BMI, history of hypertension, and history of pulmonary disease from the adjusted test. The variables of age, gender, diabetes, and history of depression remained in the adjusted analysis, which showed that the four mentioned indices had a statistically significant influence on the sleep quality score of patients (Table 4).

Table 4. Linear regression test to investigate possible confounders on the pittsburgh questionnaire score

Variable	Crude analysis		Adjusted analysis	
	Standardized coefficient B	*P*	Standardized coefficient B	*P*
Age	0.139	0.035	0.131	0.032
Gender	0.284	<0.001	0.297	<0.001
Smoking	0.018	0.787	-	-
Retinopathy	0.022	0.714	-	-
Diabetes	0.109	0.079	0.122	0.042
BMI	0.041	0.541	-	-
History of HTN	0.032	0.626	-	-
History of depression	0.205	0.001	0.214	<0.001
History of pulmonary disease	0.047	0.447	-	-

Discussion

Abnormal sleep conditions such as sleep disorders have a relation with diabetes risk (12). Nevertheless, the relation between sleep disorders and DR is not exactly clear. The present study has evaluated the influence of DR, and its different severity on sleep quality without preexisting disorders of sleep in comparison to control cases. Related research is very rare, and none of the four research conducted in this field have not evaluated whether cases with DR have worse sleep quality than control ones or whether there is a correlation between the severity of DR and sleep quality (8,13-15). In the present study, we have compared these indices and observed that there is no statistically significant relation between sleep quality and DR.

A literature review and meta-analysis study that evaluated the quality and quantity of sleep in diabetes mellitus have mentioned that any disorder of quality and quantity of sleep may be a risk factor for developing type II diabetes mellitus and poor quality of sleep, in addition, shorter duration of sleep is related to type I diabetes mellitus (16). In addition, reduced duration of sleep has been mentioned as a risk factor of resistance to insulin in type II diabetes mellitus and has been associated with abnormal metabolism of glucose and enhanced risk of diabetes mellitus. Disorders of sleep quantity and quality have been shown not only to predict the onset of diabetes mellitus but also to be more prevalent in diabetes mellitus cases (8,13-18). Anyway, retinal physical examination was not evaluated in any of the mentioned research, so it is not probable to be certain if the mentioned sleep disorders are because of pRGC involvement or other related factors.

Four related research evaluated the quality of sleep, specifically duration of sleep, in DR patients (8,13-15); of these, only two research were conducted on the severity of DR in sleep, but none of these researches excluded preexisting sleep conditions such as restless legs syndrome, obesity, enuresis, obstructive sleep apnea, and pain (8,13). So, the study conducted by Tan *et al*., mentioned that the severe group had excessive sleepiness during the daytime and longer duration of sleep time rather than normal ones, which can be because of some conditions that influence sleep conditions in comparison to DR (8).

They evaluated daytime sleep and sleep disorders in 1231 cases with diabetes mellitus (129 cases with DR and 77 cases with severe DR (macular edema, severe proliferative, and no proliferative). In addition, Jee *et al*., mentioned a relation between sleep duration and DR but observed only the presence of a long duration of sleep in severe DR and enhanced daytime sleepiness (13). Nevertheless, there is no comparison between their positive or negative DR and its severity, making it inconceivable to characterize whether enhancing and severity of DR is related to worsening sleep quality. In the present study, there is no statistical difference in sleep quality between cases with DR and controls, nor with enhancing the severity of DR. This mentioned that short and long sleep duration could be due to factors other than circadian rhythm dysfunction or RGC integrity. In addition, Meng *et al*., mentioned that there is no enhanced presence of sleep latency in cases with DR (15).

The potential variables are confounding in cases with DR who are older than the control ones. In addition, gender difference and age did not have an impact on sleep scores, and the quality of sleep was comparable (19). Although Bjorvatn reported an increased BMI may indicate sleep problems in the absence of sleep apnea (20), we have not observed an enhanced rate of poor sleep in the DR group compared to control ones. Lamond *et al*., mentioned that disorders of sleep quality in diabetes mellitus were related to diabetes complications; however, in our study, there are no differences in sleep disorders, in addition, there was no difference in pain scores between DR and control groups (21). However, based on the present study and in comparison to other results in this

field, sleep quality in diabetic patients with retinopathy is lower than in other cases. Therefore, as an effective strategy in reducing sleep disorders, we can reduce retinopathy in these cases, leading to better control of their condition.

According to the results of the present study and in comparison to the results of other studies, it is mentioned that in cases with good acuity of visual condition, DR does not have a negative influence on the quality of sleep and is not related to sleep disorder, but cases with diabetes mellitus without retinopathy have significantly lower sleep quality rather than cases without diabetes. Also, the sleep quality in the female gender was at a lower level than the male gender. However, the sleep quality was not reduced in cases with higher severity of DR.

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