Original Article

The prevalence of restless legs syndrome and comorbid condition among patient with type 2 diabetic mellitus visiting primary healthcare

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Abstract

Aim: The aim of this study was to determine the prevalence of restless legs syndrome (RLS) and Pittsburgh Sleep Quality Index (PSQI) in patients with type 2 diabetes mellitus (T2DM) attending primary healthcare. **Subjects and Methods:** This is a cross-sectional study and participants were between 25 and 70 years old who visited the diabetes and endocrinology department of Mega Medipol University Teaching Hospital, Istanbul. The diagnosis of RLS was performed according to the International Restless Legs Syndrome Study Group consensus criteria. The RLS and PSQI instruments were conducted on 871 patients with T2DM. Good sleep quality was defined as PSQI score <5. RLS severity was assessed by the Restless Legs Syndrome-6 Scales (RLS-6). The scale development and validation was carried out using Rasch measurement model. **Results:** The prevalence of RLS was 22.8% including 60.3% of females and 39.7% of males. This study showed significant differences between RLS and no RLS patients with respect to their age (years), body mass index (BMI) (kg/m^2), physical activity, smoking habit, sheesha smoking, income, and sleeping quality with PSQI. Also, the analysis presented that statistically significant differences between both RLS and no RLS reported sleep complaints including difficulty falling asleep, inadequate sleep, anytime fatigue, and leg discomfort. There were statistically significant differences between RLS and no RLS patients regarding hypoglycemia, numbness in legs, retinopathy, neuropathy, nephropathy high blood pressure, depression, stroke, anemia, diabetic foot, ulcer, arthritis, respiratory disease, metabolic syndrome, and coronary heart disease. Furthermore, there were statistically significant differences between RLS and no RLS concerning the number of sleeping hours, wake-up time (AM), sleeping time (PM), BMI (kg/m^2), HbA1c, vitamin D, calcium, creatinine, fasting blood glucose, low-density lipoprotein, triglyceride, uric acid, and systolic and diastolic blood pressure (mmHg). **Conclusion:** This study confirms positive relation and high prevalence of RLS among patients with T2DM visiting primary healthcare. The results suggest that physical activity is associated with a better perception of functional capacity and pain in diabetic patients with RLS, and thus a more active lifestyle should be encouraged.

Keywords: Pittsburgh Sleep Quality Index, restless leg syndrome, risk factors, sleeping disturbances, type 2 diabetes mellitus

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Introduction

Restless legs syndrome (RLS) is a chronic neurosensorimotor disease characterized by an urge to move the legs which is usually accompanied by unpleasant or uncomfortable often painful

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sensations in the legs.[1-3] RLS is a burdensome sleep disorder affecting 10%–15% of the general population and over 20% of primary care patients.[4-6] RLS can have profound negative effects on the quality of life and daily activities and is associated with significant economic, social, and healthcare burdens.[7-10] RLS has been significantly associated with diabetes, hypertension, obesity, and metabolic syndrome;[5,6] meanwhile, the situation and role of these relationships remain unclear.

At present, many experimental and epidemiological studies have reported that poor sleep quantity and quality are related to greater prevalence of high fasting plasma glucose and high HbA1c level.[11-14] Most recently, studies have been reported that long durations of sleep are associated with severity of diabetes.[15-18] Many studies provided evidence that sleep quality influences the glycemic control among patients with type 2 diabetes mellitus (T2DM) and approximately 37%–50% of patients with T2DM have sleep problems, which is higher than the general population.[19]

The aim of this study was to determine the prevalence of RLS and Pittsburgh Sleep Quality Index (PSQI) in patients with T2DM attending primary healthcare. The ethical approval obtained from The Committee as Institutional Review Board (IRB) of Istanbul Medipol University, (Research Protocol and IRB# 10840098-604.01.01-E.20326 Dated: 26/02/2016 and IRB# 10840098-604.01.01-E.40791 Date: 26/10/2017).

Subjects and Methods

This is a cross-sectional study and participants were patients age 25–70 years who visited the diabetes and endocrinology unit of Mega Medipol University Teaching Hospital, Istanbul, and Primary Health Care Clinics. Data used in this report were used to investigate the relationship between RLS, sleep, and glycemic control in people with T2DM.[20] A systematic random sample of 1000 patients administered in the endocrinology unit in four general hospitals were recruited between January 2016 and April 2018, and 871 agreed and gave their consent to take part in this study, thus giving a response rate of 87.1%. The inclusion criteria were as follows: (1) diagnosed with T2DM for over 3 years, additionally verified by the medical record; (2) age 25 years or over; and (3) able to communicate in Turkish. Participants were excluded if they had gestational diabetes, severe heart, lung, and cerebral disease and mental illness or disorders.

Laboratory measurements

People living with T2DM were considered as "case" patients if they had a history of DM and were taking any oral diabetes medications for at least a period of 3 years.[20] These "case' subjects were investigated for their lipid profile [total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein, triglyceride (TG)], glycosylated hemoglobin (HbA1c), postprandial glucose, blood pressure, serum creatinine, thyroid and presence related medical comorbidities. On the other hand, "control" subjects were not taking any DM medications and their HbA1c was less than 6.5% and their fasting blood glucose (FBG) was less than 7.0 mmol/L (126 mg/dL), which were confirmed by their medical records.[20]

This study was based on questionnaire, which assessed participant sociodemographics, physiological parameters, clinical and biochemistry parameters, blood pressure, and HbA1C. The level of HbA1C ≤7% was defined as good glycemic control based on the American Diabetes Association 2010 Guidelines, whereas a level of HbA1C >7% was considered poor glycemic control.[20]

Pittsburgh Sleep Quality Index

The PSQI was developed by Buysse *et al.*[21] to evaluate subjective sleep disturbance over the past month. The questionnaire measures seven groups for sleep difficulty including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each component is scored on a 4-point Likert scale from 0 to 3; the sum of the seven components results in a global PSQI score between 0 and 21. Based on the total PSQI score, the patients were divided into three groups: the "good sleep quality group" with PSQI score of ≤5, "average sleep quality group" with PSQI 6–8, and "poor sleep quality group" with PSQI ≥9.[16,17] The internal consistency Cronbach's alpha was 0.84, the split-half reliability was 0.87, and the 2-week test–retest reliability was 0.81; meanwhile, the sensitivity was 98.3% and specificity was 90.2% with a cut-off point set at 8.[21,22]

Restless Legs Syndrome-6 Scales

The RLS-6 includes six items, each one scoring on a 0–10 scale from 0 (no symptoms) to 10 (very severe). RLS severity was classified into mild (0–10), moderate (11–20), severe (21–30), and very severe (31–40) according to total International RLS Study Group Rating Scale scores.[23,24]

Statistical analysis and Rasch measurement

To determine the internal validity of the scale, we conducted a Rasch analysis.[25-27] The Rasch method is used to examine a participant's response to an item that is a function of the difference between an individual's ability and the characteristics of the item. Rasch measurement determines the relationship between the difficulty of an item and the ability of an individual. It is expected there is a higher probability in answering easier items correctly and a lower probability in answering more difficult items incorrectly.[25-27] According to the model, the probability of an individual n responding in category x to item i is given by

$$P_{xni} = \frac{exp\sum_{j=0}^{x}[\beta_n - (\delta_i + \tau_j)]}{\sum_{k=0}^{m} exp\sum_{j=0}^{k}[\beta_n - (\delta_i + \tau_j)]} \quad x = 0,1,\ldots,m$$

where $\tau_0 = 0$, so that

$$exp\sum_{j=0}^{0}[\beta_n - (\delta_i + \tau_j)] = 1.$$

β_n is the individual's position on the variable, δ_i is the scale value (difficulty to endorse) estimated for each item i, and $\tau_1, \tau_2, \ldots, \tau_3$ are the m response thresholds estimated for the $m + 1$ rating categories.[25-27]

Measuring goodness of fit for the Rasch model

Testing the normality of residuals is the most frequently used goodness-of-fit measure for the Rasch model.[25-27] The Rasch analysis tests how well the observed data fit the model. Misfits statistics consist of the infit and outfit test statistics which are based on the standardized residuals. The most commonly used misfit statistics for Rasch analysis are the mean-square (MNSQ) misfit statistics and z-standardized misfit statistics. The z-standardized misfit statistics are usually used when the MNSQ statistics fail.[27]

Data were analyzed using the Statistical Package for the Social Sciences (SPSS Statistics for Windows, Version 22.0; IBM Corp, Armonk, NY, USA). Student's *t*-test was conducted to reveal whether any significant difference exists between mean values of two continuous variables. Fisher's exact test (two-tailed) and Chi-square were used to display differences in proportions of categorical variables between two or more groups. The scale development and validation was carried out using Rasch measurement model. The level of statistical significance was considered as $P < 0.05$ for all tests.

Results

The prevalence of RLS was 22.8% including 60.3% of females and 39.7% of males. Age in years was 49.30 ± 13.67 years with RLS and without RLS was 50.63 ± 14.47. Table 1 shows significant differences between RLS and no RLS patients with respect to their age in years, physical activity, smoking habit, sheesha smoking, income, and sleeping quality with PSQI. Also, the analysis presented that statistically significant differences between both RLS and no RLS reported sleep complaints including difficulty falling asleep, inadequate sleep, anytime fatigue, leg discomfort, number of sleeping hours, wake-up time (AM), and sleeping time (PM). Table 2 presents the clinical characteristics and comorbid condition by RLS among patients with T2DM. There were statistically significant differences between RLS and no RLS patients regarding hypoglycemia, numbness in legs, retinopathy, neuropathy, nephropathy high blood pressure, depression, stroke, anemia, diabetic foot, ulcer, arthritis, respiratory disease, metabolic syndrome, and coronary heart disease (CHD).

Table 3 reports the baseline values of biochemical indices by RLS and no RLS among patients with T2DM. Significant differences were reported between RLS and no RLS concerning body mass index (kg/m^2), HbA1c, vitamin D (mmol/L), calcium (mmol/L), creatinine (mmol/L), FBG (mmol/L), LDL (mmol/L), TG (mmol/L), uric acid (mmol/L), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and vitamin D deficiency.

Table 1: Sociodemographic characteristics of sleeping disorder studied by RLS among patients with T2DM (*n*=871)

Variables	RLS=199 *n* (%)	No RLS=672 *n* (%)	*P*
Age groups (years)			
<40	51 (25.6)	183 (24.6)	0.019
40-49	63 (31.7)	147 (21.9)	
50-59	37 (18.6)	162 (24.1)	
>60 and above	48 (24.6)	200 (29.8)	
Gender			
Male	79 (39.7)	251 (37.4)	0.549
Female	120 (60.3)	421 (62.6)	
Married			
Single	20 (10.1)	101 (15.0)	0.128
Married	29 (78.9)	515 (76.7)	
Divorce/widow	22 (11.0)	56 (8.3)	
BMI (kg/m^2)			
Normal (<25 kg/m^2)	50 (25.1)	195 (29.0)	0.347
Overweight (29-30 kg/m^2)	80 (45.3)	309 (46.0)	
Obese (>30 kg/m^2)	59 (29.6)	168 (29.0)	
Physical activity 30 min/day			
Yes	74 (37.2)	161 (24.0)	0.001
No	125 (62.8	511 (76.0)	0.007
Household income	88 (44.2)	376 (56.0)	0.008
Low	72 (36.2)	174 (25.9)	
Medium	39 (19.6)	122 (18.1)	
High	35 (17.6)	71 (10.6)	
Sheesha smoking	164 (82.4)	601 (88.4)	
Yes			
No			
Cigarette smoking			
Never	154 (77.4)	577 (85.9)	0.007
Current smoker	33 (16.6)	60 (8.9)	
Past smoker	12 (6.0)	35 (5.2)	
Reported sleep complaints			
Difficulty falling asleep	49 (24.6)	75 (11.2)	0.001
Inadequate sleep	31 (15.6)	56 (8.3)	0.003
Daytime fatigue	43 (21.6)	71 (10.6)	0.001
Leg discomfort	66 (33.2)	82 (12.2)	0.001
PSQI sleep quality			
Good (PSQI <5)	40 (20.1)	199 (29.6)	0.024
Average (6 <PSQI ≤8)	73 (36.7)	203 (30.2)	
Poor (PSQI >8)	86 (43.2)	270 (40.2)	
Number of sleeping hours	5.36±1.12	6.12±1.31	0.008
Wake-up time (AM)	6.60±0.81	6,73±0.86	0.016
Sleeping time (PM)	11.50±0.72	11.39±0.72	0.001

RLS=restless legs syndrome; T2DM=type 2 diabetes mellitus; BMI=body mass index; PSQI=Pittsburgh Sleep Quality Index

In Figure 1, Rasch analysis was performed in Winsteps 4.0.1. Each "#" symbol indicates eight people and each "." indicates one to seven people in the left-hand column. Each entry symbolizes a scale item in the right column. The items at the top are the most difficult items, while the people at the top are the

Table 2: Clinical characteristics and comorbid condition by RLS among patients with T2DM (*n*=871)

Variables	RLS *n*=199 *n* (%)	No RLS *n*=672 *n* (%)	OR and 95% confidence interval	*P*
Hypoglycemia	72 (28)	94 (14.0)	1.95 (1.32-2.89)	0.001
Numbness in legs	36 (18.1)	77 (11.9)	1.70 (1.08-2.62)	0.014
Retinopathy	48 (24.1)	106 (15.8)	1.69 (1.15-2.49)	0.007
Neuropathy	29 (14.6)	45 (6.7)	1.37 (1.44-3.90)	0.001
Nephropathy	26 (13.1)	43 (6.4)	2.19 (1.31-3.68)	0.002
High blood pressure	49 (24.6)	105 (15.6)	1.76 (1.20-2.59)	0.003
Depression	41 (20.6)	67 (10.0)	2.34 (1.53-3.61)	0.001
Stroke	25 (12.6)	42 (6.3)	2.15 (1.27-2.63)	0.003
Iron deficiency	45 (22.6)	57 (8.5)	3.27 (2.12-5.05)	0.001
Diabetic foot	34 (17.1)	53 (7.9)	2.40 (1.51-3.82)	0.001
Ulcer	18 (9.0)	56 (8.3)	1.09 (0.62-1.90)	0.752
Arthritis	34 (17.1)	71 (10.6)	1.74 (1.11-2.71)	0.013
Respiratory disease	17 (8.9)	26 (3.9)	2.32 (1.32-4.37)	0.008
Metabolic syndrome	53 (26.6)	126 (18.8)	1.57 (1.10-2.27)	0.016
Coronary heart disease	72 (28)	72 (28)	1.95 (1.32-2.89)	0.002

RLS=restless legs syndrome; T2DM=type 2 diabetes mellitus; OR=odds ratio

Table 3: Clinical biochemistry baseline value by RLS among patients with T2DM (*n*=871)

Variables	RLS *n*=199 Mean±SD	No RLS *n*=672 Mean±SD	*P*
BMI (kg/m^2)	28.30±4.89	27.35±4.31	0.006
Hemoglobin (g/dL)	12.21±1.49	12.95±1.62	0.001
HbA1c	7.89±0.80	7.48±0.88	0.001
Vitamin D (mmol/L)	19.11±8.94	21.63±9.46	0.002
Calcium (mmol/L)	1.59±0.69	1.71±0.52	0.010
Creatinine (mmol/L)	65.18±27.49	63.18±22.87	0.387
Fasting blood glucose (mmol/L)	7.45±0.95	7.15±0.89	0.024
Cholesterol (mmol/L)	4.83±1.18	4.67±1.20	0.959
HDL (mmol/L)	1.14±0.35	1.36±0.31	0.590
LDL (mmol/L)	1.45±0.72	1.89±0.99	0.001
Triglyceride (mmol/L)	1.82±0.72	1.75±0.66	0.258
Uric acid (mmol/L)	294.22±62.17	273.26±60.10	0.001
TSH	2.73±1.00	2.67±0.99	0.363
Systolic blood pressure (mmHg)	131.86±14.84	128.07±13.78	0.001
Diastolic blood pressure (mmHg)	80.09±9.70	79.10±9.97	0.037
Vitamin D	***n* (%)**	***n* (%)**	
Deficiency<20 ng/mL	122 (61.3)	289 (43)	
Insufficiency 20-29 ng/mL	43 (21.6)	214/31.8)	0.001
Sufficiency>30 ng/mL	34 (17.1)	169 (25.1)	

RLS=restless legs syndrome; T2DM=type 2 diabetes mellitus; SD=standard deviation; BMI=body mass index; HDL=high-density lipoprotein; LDL=low-density lipoprotein; TSH= Thyroid stimulating hormone

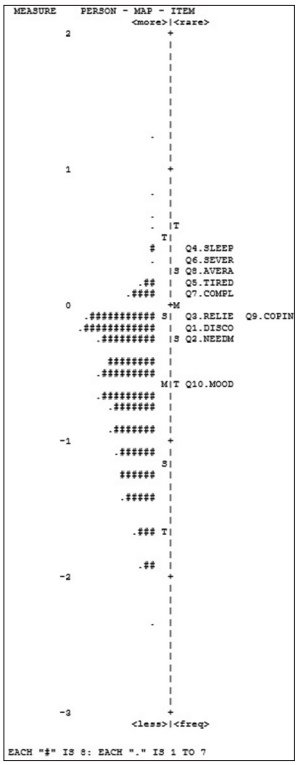

Figure 1: Person-item map for Restless Leg Scale (*N* = 871)

highest scorers and versa vice. Items 4, 6, and 8 are difficult for people to endorse. The vertical line between the two columns represents the scale for parameter estimates measured in logits. Along the vertical line, M shows the mean, S shows one standard deviation above or below the mean, and T indicates two standard deviations above or below the mean.

In Table 4, the person and item reliability indexes were 0.43 and 0.98, respectively, by Rasch analysis. Reliability ranged from 0 to 1.0. If a reliability coefficient is 0, there is no reliability, and if the coefficient is 1.0, it indicates perfect reliability. Furthermore, the person and item separation indexes were 0.87 and 6.78, respectively. Table 4 demonstrates that the restless leg scale has acceptable characteristics because the model fit MNSQ values range from 0.99 to 1.02, outfit MNSQ is 1.02, and infit MNSQ is 1.02. The values of infit and outfit MNSQs are in the acceptable range of 0.5–1.5 for these statistics.[25,26]

In Figure 2, each "#" symbol indicates 27 people and each "." indicates 1 to 7 people in the left-hand column. Items 5-I, 11, 8, 9, 5-B, and 5-H are difficult for people to endorse.

Table 4: Fit statistics for Restless Leg scale (*n*=871, # item of scale=10)

Person	871 Input		871 Measured		Infit		Outfit	
	Total	Count	Measure	RealSe	IMNSQ	ZSTD	OMNSQ	ZSTD
Mean	10.8	10.0	−0.59	0.40	0.99	−0.1	1.02	0.0
P.Sd	3.9	0.0	0.54	0.07	0.43	1.2	0.47	1.2
Real RMSE 0.41 true Sd			0.35	Separation	0.87	Person reliability		0.43
Item	**10 Input**		**10 Measured**		**Infit**		**Outfit**	
	Total	Count	Measure	RealSe	IMNSQ	ZSTD	OMNSQ	ZSTD
Mean	942.8	871	0.00	0.04	1.01	−0.03	1.02	−0.3
P.Sd	191.8	0.0	0.29	0.00	0.28	6.8	0.31	6.8
Real RMSE 0.04 true Sd			0.28	Separation	6.78	Item reliability		0.98

Table 5: Fit statistics for Pittsburgh Sleep Scale (*n*=871, # item of scale=25)

Person	871 Input		871 Measured		Infit		Outfit	
	Total	Count	Measure	RealSe	IMNSQ	ZSTD	OMNSQ	ZSTD
Mean	78.3	25.0	−4.32	0.17	0.93	−0.1	0.83	−0.6
P.Sd	11.1	0.0	0.29	0.04	0.64	0.9	0.31	1.1
Real RMSE 0.18 true Sd			0.23	Separation	1.31	Person reliability		0.63
Item	**25 Input**		**25 Measured**		**Infit**		**Outfit**	
	Total	Count	Measure	RealSe	IMNSQ	ZSTD	OMNSQ	ZSTD
Mean	2726.6	871	0.00	0.03	0.84	−3.5	0.83	−3.7
P.Sd	4856.7	0.0	1.67	0.01	0.25	4.8	0.25	4.7
Real RMSE 0.04 true Sd			1.67	Separation	46.69	Item reliability		1.00

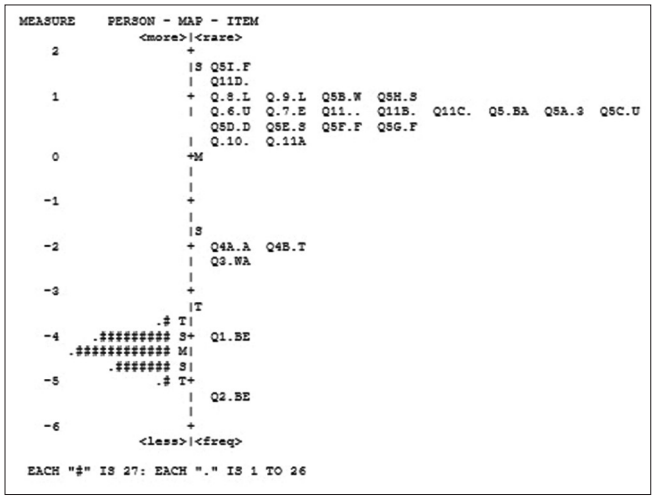

Figure 2: Person-item map for Pittsburgh Sleep Scale (*N* = 871)

In Table 5, the person and item reliability indexes were 0.63 and 1.00, respectively, by Rasch analysis. The person and item separation indexes were 1.31 and 46.69, respectively. Table 5 demonstrates that the Pittsburgh Sleep Scale has acceptable characteristics because the model fit MNSQ values range from 0.83 to 0.93, outfit MNSQ is 0.83, and infit MNSQ is 0.84.

Discussion

RLS is a common comorbidity in patients with diabetes which can be considered a significant burden on the quality of sleep and quality of life of patients, although this condition is frequently underdiagnosed. The prevalence of RLS in diabetics in Italy was 17.7%, significantly higher than that reported in the general population, ranging from 5% to 10%.[7] The prevalence of RLS was 22.8%, observed to be high in this population compared with the study done in Italy. In the Italian study,[7] there was a significantly higher prevalence of women with diabetes with RLS than in the diabetic no RLS group (64% vs 30%), and this is consistent with the current Turkish population (females 60.3% vs males 39. 7%).

The RLS was diagnosed with diabetes; the participants had a variety of comorbid health conditions including hypoglycemia, numbness in legs, retinopathy, neuropathy, nephropathy, high blood pressure, depression, stroke, anemia, diabetic foot, ulcer, arthritis, respiratory disease, metabolic syndrome, and CHD.

The RLS was diagnosed in 22.6% of the women with iron deficiency anemia. Iron deficiency is a well-known condition correlating with several forms of symptomatic RLS in the diabetic population; our study was in consistent with a previously reported study that showed an association between RLS and iron status in diabetic patients.[19] The association between RLS and hypertension and heart diseases could be due to the effects of a prolonged sleep loss in increasing the probability of developing hypertension and diabetes,[13,14,16-18] which may lead to vascular diseases.

More recently, study and data suggest that poor sleep quality as measured by the PSQI contributes to suboptimal diabetes control.[12] Sleep disturbances have effect and increase HbA1c level. In fact, the mechanism for the relationship between sleep

disturbances and HbA1c was presented very clearly in the current study and it is consistent with previously reported studies.[11,17,18,22]

In this study, diabetic patients reported high prevalence of RLS (22.8%), and this is confirmative with other studies conducted in Iran (19.5%),[8] Bosnia and Herzegovina (21%),[13] the United States (24.5%),[5] Brazil (27%),[11] and Turkey (28.3%).[6] This result supports the study findings of other studies[13,14,16-18] that sleep disorders correlate highly with hypertension and diabetic population in the present study.

In patients affected by RLS, the unpleasant sensations may lead to a severe difficulty in initiating and maintaining sleep, disrupting sleep situation, and cause an important sleep disorder.[7] A chronic sleep debt, as observed in RLS patients, has been shown to be a predictor of morbidity or mortality. Patients with restless legs appear to have a significantly higher risk of ischemic stroke and hypertension than do subjects without this sleep disorder. The association between RLS and cerebrovascular diseases could be due to the effects of a prolonged sleep loss in increasing the probability of developing hypertension and diabetes[3,7,9,28] which are known to be the predictors of vascular diseases. Therefore, in the diabetic population, RLS and diabetes can interact in a vicious circle. Hence, RLS symptoms should be adequately treated to help with the management of the endocrine disease and, consequently, to reduce the risks of mortality caused by vascular diseases.[28]

This study is not without limitations. First, this is a cross-sectional design of the study which did not identify the causal relationship between the presence of sleep disturbance/insomnia symptoms and T2DM. Second, the sample of T2DM individuals was recruited from different hospitals, and there may be sampling bias. Third, some patients might be affected with T2DM or associated with other diseases. Fourth, participants who had subjective sleep disturbance have not been clinically diagnosed but have been assessed by higher score of the PSQI.

Conclusion

This study confirms positive relationship and high prevalence of RLS among patients with T2DM visiting primary healthcare. The results suggest that physical activity is associated with a better perception of functional capacity and pain in diabetic patients with RLS, and thus a more active lifestyle should be encouraged.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest.

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