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Sleep disorders in type 2 diabetes mellitus. Does vitamin D have roles on sleep disorders and metabolic parameters?

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Abstract

Aim: The aim of this study is to determine the frequency of Vitamin D (VD) insufficiency, and sleep disorders and to determine the effects of VD on diabetic parameters (fasting blood glucose, HbA1c, lipid parameters) with sleep disorders in a diabetic population.

Materials and methods: This study was performed on data gathered from patients with type 2 Diabetes Mellitus (DM) referred to outpatient clinics of family medicine between May and October 2014. Obstructive Sleep Apnea Berlin Questionnaire, the Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index were used to determine the frequency of sleep disorders and 25OH VD levels were obtained.

Results: A total of 452 subjects (148 males, 304 females and mean age of 56.19 ± 11.98 y) with type 2 diabetes mellitus were admitted to study. Patients who were having insulin therapy had significantly lower 25VD levels, in comparison with other diabetic patients. 25VD levels were significantly low in the group, in which HbA1C levels were over the target value of 6.5%. We found negative and significant correlations between 25VD levels and Epworth Sleepiness Scale and Pittsburgh sleep quality index scores. According to BQ results, 25VD levels were significantly low in "high risk" group.

Conclusion: Vitamin D plays an important role in metabolic control of type 2 DM and effects sleep quality in such population. Having vitamin D deficiency or sleep disorder can negatively affect the metabolic control of DM and when such disorders come together in diabetic population. Its negative effect can be more powerful than expected.

Keywords: 25OH vitamin D, Sleep disorders, Type 2 diabetes mellitus.

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Introduction

The main role of Vitamin D (VD) is to maintain calcium and phosphorus homeostasis and induce bone mineralization, and 25-hydroxy vitamin D (25 (OH) D) is accepted as the main indicator of vitamin D status [1].

Low VD levels are associated with beta cell dysfunction. Vitamin D deficiency was found to be associated with the development of insulin resistance, obesity and also type 2 diabetes mellitus. Insulin secretion is affected by vitamin D and it was found that vitamin D deficiency induces impaired secretion of insulin, which causes glucose intolerance [2]. Vitamin D levels appeared to be low in diabetes mellitus type 2 patients and seems to be related to poor glycaemic control in patients with diabetes mellitus type 2 [2-4].

Systematic reviews and meta-analyses confirm that low levels of 25 (OH) D are associated with cardiovascular risk factors (e.g. diabetes mellitus, dyslipidaemia and arterial hypertension) and predict cardiovascular events [5]. Vitamin D deficiency is commonly seen in patients with DM and is associated with dysregulation of metabolic parameters, especially HbA1C. In non-diabetic populations, vitamin D deficiency has been shown to be associated with sleep disorders and mental health disturbances, especially depression [6-8]. As low vitamin D is

found to be related to symptoms of sleepiness and wake impairment, chronically low vitamin D levels may be a risk factor for the development of obstructive sleep apnoea and associated cardiovascular diseases [6,9]. There has been an increasing awareness that sleep disturbances are frequently accompanied with diabetes and sleep disturbances are associated with decreased diabetes self-management in patients with T2DM [10].

We could not find any report on the effects of vitamin D on sleep quality in patients with DM. In this study we have evaluated the association of vitamin D levels with sleep quality and with HbA1c and other metabolic parameters in type 2 diabetic patients.

Materials and Methods

Patients and settings

This study was performed on data gathered from patients with type 2 Diabetes Mellitus (DM) referred to outpatient clinics of family medicine between May and October 2014. Inclusion criteria were: (a) the diagnosis of type 2 Diabetes Mellitus; (b) age between 18 and 65 y.

Assessments

Demographic characteristics of the patients (age, sex, weight, height, smoking, drugs used) were recorded. HbA1c, fasting blood glucose, lipid profile analyses were obtained, sleep quality was assessed. Serum 25-(OH)-vitamin D (25VD) levels were obtained from their files in a 3 month period and patients were selected as they were not taking any vitamin D supplementation or were not under vitamin D treatment. Vitamin D insufficiency was defined as serum 25-hydroxyvitamin D level of <30 ng/ml [11].

Demographic form, used for demographic characteristics of patients; the Pittsburgh Sleep Quality Index (PSQI), used to measure the quality and patterns of sleep; Berlin Sleep Questionnaire (BQ), used to identify sleep apnoea and risk categorization; and the Epworth Sleepiness Scale (ESS), used to measure sleepiness and to ask qualitative and quantitative information, were used for data collection [12,13].

Statistical analysis

Continuous data were given as mean ± standard deviation and categorical data were given as percentages (%).

Shapiro Wilk's test was used to investigate the data normality. For the comparison of groups which do not fit a normal distribution, Mann-Whitney U-test was used in situations with two groups and Kruskal-Wallis H was used in situations with three or more groups. For variables which do not fit a normal distribution, Spearman correlation coefficients were calculated to determine the direction and magnitude of the relation between variables (correlation). Pearson chi-square analysis was used in the analysis of cross tables. Odds Ratio was used to determine the risk factors. IBM SPSS Statistics 21.0 program was used for data analysis. A p value of <0.05 was considered as statistically significant.

Results

A total of 452 subjects (148 males, 304 females and mean age of 56.19 ± 11.98 y) with type 2 diabetes mellitus were admitted to study. Among patients, 17.70% were smokers, 51.90% were obese (mean BMI value 30.47 ± 5.42 kg/m^2). The mean disease duration was 8.61 ± 6.72 y, 129 patients (28.5%) were receiving insulin therapy. Average HbA1c values of patients was 7.37 ± 1.69, 37.70 percent of patients were under the target value of 6.5%. The mean LDL level was 126.30 ± 36.06 mg/dL and mean TG level was 169.40 ± 103.91 mg/dL.

Patients who were having insulin therapy had significantly lower 25VD levels, in comparison with other diabetic patients (with non-drug therapy and with oral anti-diabetic agents) 16.38 ± 14.75 *vs.* 21.41 ± 13.52 and 21.75 ± 10.95, respectively; p<0.001). 25VD insufficiency was found in 78.50 % of our study population. Age, BMI, waist/hip ratio, LDL, triglyceride, DM duration parameters were not significantly different between the VD insufficient group and VD normal group. There were significant differences between the VD insufficient group and VD normal group according to HbA1C and fasting plasma glucose values (statistical analyses were shown in Table 1).

25VD levels were significantly low in the group, in which HbA1C levels were over the target value of 6.5% (17.46 ± 13.84 *vs.* 24.02 ± 12.82, respectively; p<0.001). According to ESS scores, 25VD levels were significantly low in "very sleepy" group 18.79 ± 14.53 *vs.* 21.06 ± 13.23 and p=0.007.

According to Epworth Sleepiness Scale (ESS), 49.70% of the patients had excessive daytime sleepiness, whereas according to Pittsburgh Sleep Quality Index (PSQI), 67.90% of the patients had poor sleep quality. According to obstructive sleep apnoea Berlin questionnaire (BQ) results, 49.40% of patients were considered to have high risk for obstructive sleep apnoea. According to PSQI scores; 25VD levels were significantly low in "poor sleep quality" group 19.27 ± 14.54 *vs.* 21.13 ± 12.42; p=0.020). According to BQ results; 25VD levels were significantly low in "high risk" group 18.75 ± 14.19 *vs.* 21.09 ± 13.59; p=0.012.

Fasting blood glucose levels were significantly high in the group having low 25VD levels 166 ± 81.71 *vs.* 132.90 ± 56.64; p<0.001). We found positive and significant correlations between fasting blood glucose levels and ESS and PSQI scores (r=0.21, p<0.001; r=0.157, p<0.001 respectively). We did not find any correlation between 25VD level and lipid parameters (triglyceride, low density lipoprotein).

We found negative and significant correlations between 25VD levels and ESS and PSQI scores (r=-0.10, p=0.035; r=-0.093, p=0.049, respectively). There were significant and positive correlations between ESS scores and HbA1c, BMI and DM duration (r=0.228, p<0.001; r=0.109, p=0.009; r=0.101, p=0.016, respectively). There were significant and positive

correlations between PSQI scores and HbA1c, BMI and DM duration (r=0.137, p=0.001; r=0.167, p<0.001; r=0.142, p=0.001, respectively).

Table 1. *Statistical analyses of VD insufficient group and VD normal group.*

	Vitamin D insufficient	Vitamin D normal	Total	Test statistics	P value
Age[a]	56.65 ± 11.47	54.52 ± 13.62	46.19 ± 11.98	1.546	0.123
	57.50 (50.00-65.00)	54.50 (45.00-61.00)	58.00 (50.00-64.00)		
BMI[b]	30.60 ± 5.49	30.00 ± 5.13	30.47 ± 5.42	-1.232	0.218
	30.37 (27.04-33.81)	29.05 (26.74-33.07)	30.11 (27.05-33.98)		
Waist/Hip Ratio[b]	0.90 ± 0.79	0.89 ± 0.08	0.90 ± 0.08	-0.999	0.318
	0.91 (0.85-0.96)	0.92 (0.88-0.96)	0.91 (0.86-0.96)		
HbA1C[b]	7.50 ± 1.74	6.86 ± 1.37	7.36 ± 1.69	-3.657	<0.001
	7.20 (6.29-8.43)	6.30 (5.90-7.10)	6.90 (6.12-8.27)		
LDL[a]	125.57 ± 35.50	128.95 ± 38.09	126.29 ± 36.05	-0.812	0.417
	128.00 (107.00-149.00)	136.50 (101.25-149.00)	128.00 (105.00-149.00)		
Trig[b]	172.60 ± 107.24	157.69 ± 90.18	169.40 ± 103.91	-1.191	0.234
	152.00 (121.00-199.25)	148.50 (110.50-171.50)	148.00 (115.00-194.00)		
DM duration[b]	8.81 ± 6.98	7.87 ± 5.62	8.61 ± 6.72	-0.685	0.493
	8.00 (3.00-14.25)	5.00 (2.00-10.00)	7.00 (3.00-13.00)		
FPG[b]	166.35 ± 81.70	132.90 ± 56.64	161.05 ± 79.16	-3.974	<0.001
	146.00 (118.75-198.00)	122.00 (107.50-142.00)	139.00 (111.00-182.00)		

[a]Independent t-test; [b]Mann Whitney U-test; LDL: Low Density Lipoprotein, Trig: Triglyceride DM: Type 2 Diabetes Mellitus, FPG: Fasting Plasma Glucose (mg/dl).

The risk of not achieving target HbA1c was 1.81 times more in high risk group according to BQ than low-risk group (OR: 1.81, CI: 1.224-2.679, p=0.003). The risk of not achieving target HbA1c in patients with excessive daytime sleepiness according to the ESS results was 2.07 times more than the other group (OR: 2.07, CI: 1.39-3.07, p<0.001).

The risk of not achieving target HbA1c in patients with poor sleep quality according to the PSQI results was 1.83 times more than the other group (OR=1.83, CI: 1.21-2.76, p=0.004).

The risk of having 25VD insufficiency was found to be 1.62 times increased in patients, who have high risk of OSAS according to BQ results (OR: 1.62, CI: 1.02- 2.57, p=0.038). According to other scales we could not find any other such relationship.

We compared the patients (n=181) having both 25VD insufficiency and having high risk according to BQ result (Group-H) with the patients (53 patients) without 25VD insufficiency and with low risk (Group-L). We found that the risk of not achieving target HbA1c in Group-H was 3.51 times more than the Group-L (OR: 3.51, CI: 1.87-6.58, p<0.001).

We compared the patients (176 patients) having both 25VD insufficiency and detected to be "very sleepy" according to ESS results (Group-S) with the patients (48 patients) without 25VD insufficiency and having normal-average sleep (Group-N) and we found that the risk of not achieving target HbA1c in Group-S was 3.74 times more than the Group-N (OR: 3.74, CI: 1.93-7.25, p<0.001).

We compared the patients (239 patients) having both 25VD insufficiency and detected to have "poor sleep quality" according to PSQI results (Group-P) with the patients (32 patients) without 25VD insufficiency and having good sleep quality (Group-G) and we found that the risk of not achieving target HbA1c in Group-P was 2.43 times more than the Group-G (OR: 2.43, CI: 1.07-4.78, p=0.003).

Discussion

Vitamin D deficiency is common worldwide and has been shown to be related with sleep quality and psychological health in non-diabetic populations [14,15]. We could not find any study searching the role of vitamin D in sleep quality of patients with type 2 diabetes mellitus. Our study showed that vitamin D deficiency has negative effect in sleep quality of diabetes patients and increases the risk of OSAS. 25VD deficiency in patients with DM was associated with poorer sleep quality independently of demographic factors, smoking

and disease duration. Relationship between VD deficiency and sleep disorders seems to be unclear and thought to be multifactorial. Pain, worsening of metabolic control of chronic diseases and psychological effects, are all associated with vitamin D deficiency and can be the causes of such relationship [8,14-17].

We found negative and significant correlations between 25VD levels and ESS and PSQI scores (r=-0.10, p=0.035; r=-0.093, p=0.049, respectively). According to PSQI scores, 25VD levels were significantly low in "poor sleep quality" group, in high risk OSAS group and in "very sleepy" group.

Vitamin D is a hormone which interacts with the receptors of gut, bone, breast, prostate, brain, skeletal muscle, and the immune system. Vitamin D deficiency is more common in diabetic population and can cause pain and non-inflammatory skeletal myopathy, which may result in sleep disruption and daytime impairment [6,9,18].

It is known that sleep quality has a modulator effect on glycaemic control of diabetes through hormones. Sleep disorders are thought to be risk factors that can negatively affect the control of diabetes mellitus, resulting in high levels of fasting plasma glucose and HbA1C [19,20].

According our results, 49.70% of patients had excessive daytime sleepiness, 67.90% of the patients had poor sleep quality and 49.40% of patients were considered to have high risk for obstructive sleep apnoea. According to the results of BQ, the risk of the patient's not achieving target HbA1c, identified as high risk group, was 1.81 times more than low-risk group. The risk of not achieving target HbA1c in patients with excessive daytime sleepiness and in the patients with poor sleep quality were 2.07 and 1.83 times greater, respectively.

It is well known that vitamin D deficiency is a risk factor for impaired glucose tolerance. Vitamin D levels in patients with type 2 DM were found to be significantly lower than non-diabetics. Some studies revealed that, a positive relationship between 25VD levels and insulin sensitivity was found in subjects with normal glucose tolerance and normal body weight. It also concluded that, in large populations, low levels of 25V D is an independent risk factor for metabolic syndrome [21].

Patients 'at risk' for DM have lower levels of 25 (OH) Vitamin D than those who are 'not at risk'. Vitamin D insufficiency is associated with impaired insulin secretion, and this is a high risk factor for diabetes [22].

In another study, a positive correlation of 25VD levels with insulin sensitivity and negative effects of Vitamin D deficiency on the β-cell function were shown. Vitamin D reduces insulin resistance in peripheral tissues, thereby reducing excessive insulin secretion that occurs in response to increased blood glucose levels due to insulin resistance and enhances the insulin sensitivity. Therefore, vitamin D deficiency is a risk factor for metabolic syndrome and type 2 DM, and its relationship with insulin resistance and β cell dysfunction were shown [21,22]. In human and animal experiments, vitamin D deficiency is shown to be associated with impaired insulin secretion, which is normalized with use of VD supplementation [23]. Vitamin D increases both β cell production capacity and accelerates pro-insulin to insulin conversion [24]. In a recent study, with increase of 25VD levels from 10 ng/ml to 30 ng/ml, an insulin sensitivity improvement of 60% was observed [21,25].

In a study which is performed in adult patients, vitamin D deficiency was found to be related with increased prevalence of metabolic syndrome. Also, it was shown that increased body fat content plays a role in decreased vitamin D levels and insulin resistance; thus, 25VD level was found to be inversely correlated with body fat content [26-28].

Even if vitamin D deficiency is not the only factor in pathogenesis of diseases, it is stated to be an auxiliary agent for type 2 DM and/or metabolic syndrome [21]. In recent years, there has been more focusing on relationship between vitamin D deficiency and type 2 DM. Vitamin D levels were found significantly lower in type 2 DM patients either receiving OAD or insulin. This shows that vitamin D deficiency is related with diabetes and glucose intolerance [29].

Interesting results of our study were; having both 25VD insufficiency and high risk according to BQ result, or having both 25VD insufficiency and being detected to be "very sleepy" according to ESS results; or having both 25VD insufficiency and being detected to have "poor sleep quality" according to PSQI results were all found to be important risk factors for not achieving target HbA1C levels in comparison with other groups.

Conclusion

Vitamin D plays an important role in metabolic control of type 2 DM and effects sleep quality in such population. Having vitamin D deficiency or sleep disorder can negatively affect the metabolic control of DM and when such disorders come together in diabetic population; its negative effect can be more powerful than expected. Every diabetic patient should be screened for both vitamin D deficiency and sleep disorders.

Conflict of Interest

None declared.

Ethical Statement

The original study was approved by the Local University Ethics Committee in Malatya İnönü University.

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