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Role of vitamin D in the association between pre-stroke sleep quality and post-stroke depression and anxiety

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Abstract

Purpose Poor sleep quality, mood disorders, and vitamin D deficiency are common in stroke. We investigated the association between serum vitamin D levels and pre-stroke sleep quality and the occurrence of poststroke depression (PSD) and poststroke anxiety (PSA) in acute ischemic stroke (AIS).

Methods This prospective cross-sectional study included hospitalized patients with AIS and age- and sex-matched controls. Vitamin D levels were measured within 24 h of admission. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) at admission. The severity of depression and anxiety symptoms was evaluated according to Beck Depression Inventory and Beck Anxiety Inventory scores, respectively, within 72 h after admission.

Results Comparing 214 AIS patients with 103 controls, patients had significantly higher scores of Beck Depression Inventory, Beck Anxiety Inventory, and PSQI and lower vitamin D levels ($p < 0.001$). Among AIS patients, Beck Depression Inventory ($p = 0.004$) and Beck Anxiety Inventory ($p = 0.018$) scores were significantly higher in bad sleepers (PSQI score ≥ 6) than in good sleepers (PSQI score ≤ 5). Correlation analysis revealed negative correlations between serum vitamin D levels and Beck Depression Inventory ($r = -0.234$; $p < 0.001$), Beck Anxiety Inventory ($r = -0.135$; $p = 0.016$), and PSQI ($r = -0.218$; $p < 0.001$) scores.

Conclusion Decreased serum vitamin D levels at admission are associated with a high risk for PSD and PSA in patients with poor pre-stroke sleep quality during the early stages of AIS.

Keywords Acute ischemic stroke · Anxiety · Depression · Sleep · Vitamin D

Introduction

Sleep and emotional disorders are commonly present in acute ischemic stroke (AIS) [1, 2]. Notably, poor sleep quality significantly affects daytime functional outcomes [3]. Approximately one-third of stroke survivors experience poststroke depression (PSD) and poststroke anxiety (PSA) [4]. These conditions are associated with poor prognoses in patients with AIS [5, 6]. Furthermore, preexisting sleep disturbance is a risk factor for patients with stroke and mood disorders. This risk can be exacerbated following an AIS [1, 7–9]. The complex association between sleep and mood disorders creates a vicious circle in AIS.

Vitamin D, a neuroactive steroid hormone, plays an essential role in brain development [10]. Its receptors are expressed widely in glial and neuronal cells [11]. Vitamin D is involved in various brain processes, such as neuroinflammation [12], immunomodulation [13], and neurotrophic signaling [14]. Multiple studies have demonstrated an association between vitamin D deficiency and AIS, which indicates its potential involvement in stroke development [15–19]. Furthermore, vitamin D deficiency can lead to atherosclerosis progression [20] and is associated with poor prognosis in AIS patients; in contrast, vitamin D supplementation improves functional outcomes [16]. In addition, multiple reports have indicated a substantial effect of vitamin D on sleep and mood disorders [21–26]. Vitamin D insufficiency is related to poor sleep quality, such as difficulty initiating and maintaining sleep, resulting in shorter sleep duration and nocturnal awakenings [21–23].

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We hypothesized that vitamin D deficiency may significantly affect the linkage between poor pre-stroke sleep quality and PSD and PSA in patients with AIS. We investigated the relationship between serum vitamin D levels and pre-stroke sleep quality and the occurrence of PSD and PSA in patients with early stroke in a Turkish cohort.

Methods

Hospitalized patients with AIS patients and age- and gender-matched controls diagnosed with cervical or lumbar discopathies were included in this prospective cross-sectional study. The study was conducted between January 2021 and April 2022 at Kirsehir Ahi Evran University Training and Research Hospital, Turkey, between 36° and 42° latitudes. The study was approved by the Kirsehir Ahi Evran University Local Research Ethics Committee (date of approval: 12/22/20; approval no. 2020–19/146), and all patients gave the informed consent for the participation.

Participants

AIS was diagnosed in harmony with the World Health Organization criteria, which involves a neurological examination performed by a neurologist. The diagnosis was confirmed by neuroimaging performed within 24 h of admission [27]. Computed tomography was performed to rule out hemorrhagic stroke, followed by diffusion-weighted magnetic resonance imaging [28]. In addition, patients underwent transthoracic echocardiography and carotid Doppler ultrasonography. Regarding the criteria of the Trial of ORG 10172 in Acute Stroke Treatment (TOAST), the subtypes of stroke were categorized as large artery atherosclerosis (atherothrombotic stroke), cardioembolic stroke, small vessel disease (lacunar stroke), and strokes of undetermined etiology [29]. Patients of age < 18 years, hemorrhagic stroke, transient ischemic attack, neurodegenerative disorders such as dementia or Parkinson disease, serious visual or auditory impairments that prevent assessments, severe cognitive dysfunction, decreased level of consciousness, aphasia, or dysarthria were excluded. Furthermore, patients with a history of malignancy, pregnancy, thyroid, or parathyroid disease, osteoporosis, psychiatric illnesses as posttraumatic stress disorder, depressive and/or anxiety disorders, sleep problems as insomnia, narcolepsy, obstructive and/or central sleep apnea, or vitamin D supplementation were excluded. The information for the exclusion criteria was collected through self-reported questionnaire and medical records.

Measures

Baseline data included age, gender, body mass index, systemic diseases, educational level, marital status, and residency. Standardized scales were used to conduct assessments within the first 3 days of admission to the stroke unit. Depression and anxiety severity were assessed by Beck Depression Inventory [30] and Beck Anxiety Inventory [31] scores, respectively. A score ≥ 10 on the Beck Depression Inventory and ≥ 8 on the Beck Anxiety Inventory indicated the presence of depression and anxiety symptoms, respectively [30, 31]. Sleep quality was evaluated according to the Pittsburgh Sleep Quality Index (PSQI), a self-reported questionary designed for measuring quality of sleep over the past month [32]. The PSQI has seven elements, containing subjective quality of sleep, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, medication usage, and daytime dysfunctioning. A cut-off score of 5 was used to differentiate patients with bad sleepers from good ones [32].

Blood collection

Fasting serum specimens were gathered in 5 mL tubes within 24 h of entrance. Routine laboratory analyses were conducted using standardized methods. Enzyme-linked immunosorbent assay kits were utilized to measure serum levels of vitamin D (EIA-5396, DRG, Marburg, Germany); the measurements were carried on a microplate reader (EL 9 800 TM, BioTek Instruments, Winooski, VT, USA) using appropriate wavelengths. Vitamin D insufficiency was set at ≤ 20 ng/mL [33].

Statistical analysis

Categorical and continuous variables are given as numbers (frequency or percentages) and means ± standard deviations, respectively. The Kolmogorov–Smirnov test was used to test the normality, and variance homogeneity was assessed using Levene's test. One-way analysis of variance, the Kruskal–Wallis test, or the Mann–Whitney *U* test were performed to compare quantitative data between groups. The Bonferroni post hoc tests were performed for pairwise comparisons. Chi-square (v2) analyses were used to determine the associations between categorical variables. Spearman's correlation coefficient was calculated to analyze the relationships between numerical variables. Scatterplots were generated to visualize the correlation analysis results between vitamin D levels and Beck Depression Inventory, Beck Anxiety Inventory, and PSQI scores. Analyses were conducted using SPSS ver. 21.0

(IBM, Armonk, NY, USA) with considering a $p < 0.05$ statistically significant.

Results

The baseline characteristics of 214 patients with AIS and 103 controls were shown in Table 1. With respect to age, gender, body mass index, systemic diseases, education level, and residency, no significant difference was found between the control group and AIS group ($p > 0.05$). Significantly, more patients (vs. controls) were single; such patients had considerably higher scores of Beck Depression Inventory, Beck Anxiety Inventory and PSQI, and lower vitamin D, vitamin B12, and folate levels ($p < 0.001$; Table 1).

Among patients with AIS, Beck Depression Inventory ($p = 0.004$) and Beck Anxiety Inventory ($p = 0.018$) scores were significantly higher in bad sleepers (PSQI score ≥ 6) than in good sleepers (PSQI score ≤ 5) (Table 2).

Table 2 Relationship between Pittsburgh Sleep Quality Index scores and the scores of Beck Depression Inventory and Beck Anxiety Inventory

Scores	Pittsburgh Sleep Quality Index scores		*p* value
	Good sleep (≤ 5)	Poor sleep (≥ 6)	
Beck Depression Inventory	8 [0–25]	10 [1–24]	**0.004**
Beck Anxiety Inventory	4 [0–19]	6 [0–30]	**0.018**

Values are expressed as median [min–max]

Bold values indicate statistically significant ($p < 0.05$)

Among 214 patients with AIS, 72 (33.6%) had an atherothrombotic stroke, 63 (29.5%) had a cardioembolic stroke, 72 (33.6%) had a lacunar stroke, and 7 (3.3%) had a stroke

Table 1 The baseline characteristics of the controls and patients with acute ischemic stroke

	Controls ($n = 103$)	Stroke ($n = 214$)	*p* value
Age (years)	66.4 ± 8.0	66.2 ± 10.5	0.842
Female gender	34 (33)	86 (40.2)	0.266
Body mass index (kg/m^2)	28.5 ± 3.8	28.2 ± 4.1	0.280
Systemic diseases			
Hypertension	66 (64.1)	145 (67.8)	0.527
Diabetes mellitus	41 (39.8)	99 (46.3)	0.334
Hyperlipidemia	32 (31.1)	66 (30.8)	0.999
Coronary artery disease	32 (31.1)	74 (34.6)	0.611
Education level			
Illiterate	14 (13.6)	48 (22.4)	0.078
Primary school	56 (54.4)	124 (57.9)	
Secondary school	10 (9.7)	17 (7.9)	
High school	15 (14.6)	16 (7.5)	
University	8 (7.8)	9 (4.2)	
Marital status			
Married	97 (94.2)	157 (73.4)	**< 0.001**
Single	6 (5.8)	57 (26.6)	
Area of residence			
Village	24 (23.3)	69 (32.2)	0.26
Town	18 (17.5)	32 (15)	
City	61 (59.2)	113 (52.8)	
Scale scores			
Beck Depression Inventory	4 [1–19]	9 [0–25]	< 0.001*
Beck Anxiety Inventory	3 [1–16]	5 [0–30]	
Pittsburgh Sleep Quality Index	4 [1–10]	6 [1–16]	
Blood parameters			
Vitamin D (ng/mL)	20 [6–43]	12 [1–44]	**< 0.001***
Vitamin B12 (pg/mL)	205 [69–680]	153 [23–1500]	
Folate (ng/mL)	8.5 [3.3–39]	7.5 [2.3–34]	**0.003***

Values are expressed as *n*(%), mean ± SD or median [min–max]

*Mann–Whitney *U* test

Bold values indicate statistically significant ($p < 0.05$)

Table 3 Scale scores and blood parameters across the stroke subgroups

Scores	Atherothrombotic stroke ($n=72$)	Cardioembolic stroke ($n=63$)	Lacunar stroke ($n=72$)	Otherstroke ($n=7$)	p value
Beck Depression Inventory	10 [1–25]	9 [0–24]	8 [1–24]	7 [2–9]	0.119**
Beck Anxiety Inventory	4.5 [0–17]	6 [0–20]	4.5 [0–30]	3 [1–15]	0.127**
Pittsburgh Sleep Quality Index	6 [2–16]	6 [2–12]	6 [1–15]	5 [3–8]	0.724**
Vitamin D (ng/mL)	13 [3–35]	12 [1–44]	10.5 [2–37]	8 [4–16]	0.076**
Vitamin B12 (pg/mL)	151.5 [23–1052]	155 [73–1500]	155 [42–504]	137 [73–222]	0.629**
Folate (ng/mL)	7.2 [3.7–34]	7.7 [2.9–23]	8 [2.3–25]	5.2 [3.4–9.7]	0.059**

Values are expressed as n(%) or median [min–max]

**Kruskal–Wallis test

of undetermined etiology (Table 3). Beck Depression Inventory, Beck Anxiety Inventory, and PSQI scores and vitamin D, vitamin B12, and folate levels demonstrated no significant differences across the stroke subgroups ($p>0.05$). Correlation analysis revealed negative correlations between vitamin D levels and Beck Depression Inventory ($r=-0.234$; $p<0.001$), Beck Anxiety Inventory ($r=-0.135$; $p=0.016$), and PSQI ($r=-0.218$; $p<0.001$) scores (Fig. 1).

In total, 105 patients (49.1%) had anterior circulation stroke, 87 (40.7%) had posterior circulation stroke, 13 (6.1%) had bihemispheric stroke, and 9 (4.2%) had one-sided anterior and posterior circulation stroke. Among patients with anterior circulation strokes, 99 had middle cerebral artery infarcts (54 [51.4%] had left-sided, and 45 [42.9%] had right-sided infarcts) and 6 (5.7%) had anterior cerebral artery infarcts (4 had left-sided and 2 had right-sided infarcts). Beck Depression Inventory, Beck Anxiety Inventory, and PSQI scores did not significantly differ according to infarct localization or the involved middle cerebral artery site ($p>0.05$; Table 4).

Discussion

Recent studies have revealed a significant link between stroke and sleep and mood disorders [34]. Patients who are poststroke are more prone to experience sleep problems, depression, and/or anxiety [7]. Fan et al. [7] revealed that 70.2% of patients experienced persistent poor sleep. These patients are at high risk of developing depression and anxiety 3 months after the stroke. Furthermore, a recent review demonstrated an increased prevalence of poststroke insomnia among patients with depression and anxiety [35]. However, limited data are available regarding the pre-stroke state. Shorter pre-stroke sleep duration is related to a high risk for anxiety and depression at 3 months after AIS [9, 36]. This association has been explained by neurobiological mechanisms, such as inflammation, hypoperfusion, and the inhibition of neurogenesis [9, 36]. The present study is the first to show a relationship between poor pre-stroke sleep quality and high depression and anxiety scores in the early stages of AIS. We found that 54% of the patients had poor sleep quality in the pre-stroke period, whereas 45% and 28% experienced PSD and PSA, respectively, consistent with previous studies [18, 36, 37]. Meta-analyses have revealed that sleep deprivation and mood disorders share common pathophysiological mechanisms, such as activation of neurotransmitter and neuroendocrine systems, oxidative stress, and inflammatory response [38, 39]. Furthermore, poor pre-stroke sleep can increase the levels of stress hormones, such as cortisol, thereby triggering the release of inflammatory cytokines that contribute to emotional dysfunction during the early stages of stroke [38, 39]. Gruber et al. [40] revealed that sleep problems can disrupt the connectivity between the pre-frontal cortex and amygdala, which leads to emotional dysregulation. Furthermore, functional brain magnetic resonance imaging by Wang et al. [41] demonstrated abnormal local activities in certain regions of the default-mode network in patients with poststroke insomnia during the subacute phase, which can contribute to emotional dysregulation, such as PSD and PSA [4]. These psychiatric symptoms are related to dysfunction of the brain network rather to lesion location caused by ischemic damage.

In accordance with previous studies, we showed that serum vitamin D levels were considerably lower in patients with AIS than in controls [19, 21, 28, 37]. Multiple studies have demonstrated that hypovitaminosis D is linked to an increased risk for poor outcomes and recurrent strokes in patients with AIS [42, 43, 44, 45]. The anti-inflammatory effect of vitamin D reduces systemic inflammation and atherogenesis and plays an important role in stroke pathogenesis [28, 46]. Furthermore, vitamin D can inhibit the production of inflammatory cells [47] that are easily triggered by AIS [48]. Chaudhuri et al. [28] revealed a significant association between hypovitaminosis D and large artery atherosclerosis and cardioembolic stroke; they explained this association through the anti-atherogenic effects of vitamin D on the vasculature, which provides protection against cerebral and myocardial infarctions [28]. We found negative correlations

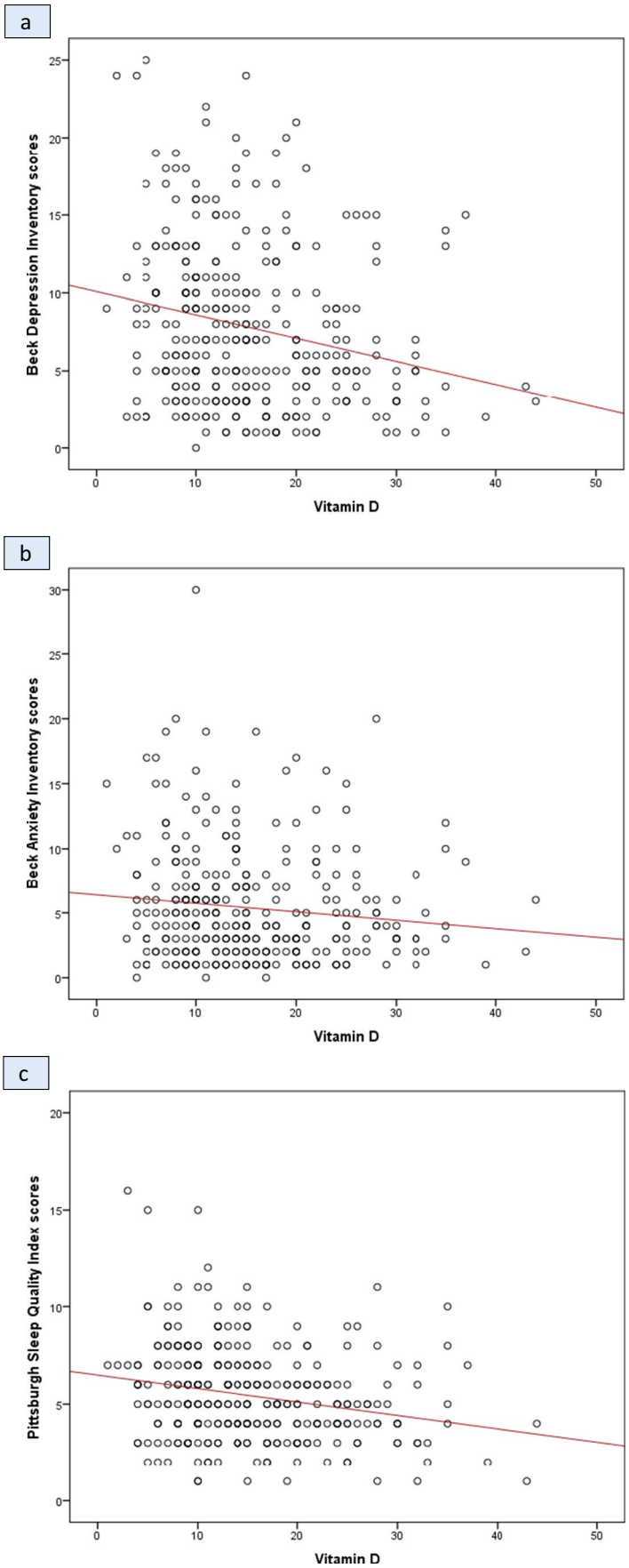

Fig. 1 Scatterplot for Vitamin D and Beck Depression Inventory (**a**), Beck Anxiety Inventory (**b**), and Pittsburgh Sleep Quality Index (**c**) scores

Table 4 Scale scores according to infarct localization or involved middle cerebral artery site

Scores	Infarct localization*				*p* value	Involved MCA**		*p* value
	Anterior circulation (*n* = 105)	Posterior circulation (*n* = 87)	Both circulation (*n* = 9)	Bihemisferic (*n* = 13)		Left (*n* = 54)	Right (*n* = 45)	
Beck Depression Inventory	10 [1–25]	8 [0–24]	9 [5–21]	7 [2–4]	0.384	10 [1–21]	10 [1–25]	0.385
Beck Anxiety Inventory	5 [0–9]	5 [0–30]	5 [0–20]	6 [1–19]	0.505	5 [0–19]	5 [1–17]	0.974
Pittsburgh Sleep Quality Index	6 [2–16]	6 [1–15]	5 [3–11]	6 [2–9]	0.872	6 [2–16]	6 [2–10]	0.251

MCA middle cerebral artery

*Kruskal–Wallis test

**Mann–Whitney *U* test

between vitamin D levels and the scores of PSQI, Beck Depression Inventory, and Beck Anxiety Inventory. In addition to its effects on inflammation [12], vitamin D may penetrate the blood–brain barrier and modulate the immune system through its receptors [11, 13]. These receptors are widely distributed throughout the brain, particularly in the cingulate cortex and hypothalamus, which are involved in sleep regulation and pleasure [21–25]. Moreover, vitamin D can affect sleep processing [21, 37]. The active form of vitamin D regulates neurotrophic signaling [14], which facilitates the synthesis of neurotransmitters, such as serotonin, norepinephrine, and dopamine [25, 49]. Consequently, vitamin D deficiency is associated with decreased production of these neurotransmitters in the brain, primarily involved in mood disorders, such as depression or anxiety [18, 19]. Furthermore, vitamin D deficiency can lead to sleep and mood disorders in the early stages of AIS. Serum levels of vitamin D show significant associations with stroke and sleep and mood disorders, primarily through the vitamin's involvement in neuroinflammation, immunomodulation, and the biosynthesis of monoamines. Poor self-care and decreased vitamin B12 and folate levels can lead to sleep and mood dysfunction in AIS patients [50].

There are certain limitations to our study. First, it was cross-sectional, thus not allowing causality. Second, it was performed at a single center on patients with a specific ethnic background, and thus, the findings cannot be generalized to other racial or ethnic groups. Third, the exclusion of aphasic or critically ill patients who could not cooperate may have led to selection bias. Fourth, there was a lack of information on daily diet and the level of physical activity, and these factors can influence vitamin D metabolism. Fifth, the lack of a follow-up period limited our ability to display the long-term association between vitamin D, sleep, and depression or anxiety. Future studies with 3–6 months of follow-up are necessary to explore the actual effect of vitamin D supplements on depression and anxiety scores in patients with AIS.

Conclusion

Decreased serum vitamin D levels at admission are associated with a high risk for PSD and PSA in patients with poor pre-stroke sleep quality during the early stages of AIS. Further longitudinal studies are needed to establish a definitive conclusion.

Data availability Researchers can apply for access to anonymized data from the present study for well-defined research questions that are in line with the overall research agenda for the cohort. Please contact the corresponding author.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of Kirsehir Ahi Evran University Faculty of Medicine research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interests.

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