

The Decreased Serum Level of Vitamin D3 is Correlated with Impaired Sleep and Cognition in Patients with Chronic Insomnia Disorder

Ting-Ting Qian, Ying-Xue Li, Yi-Jun Ge, Ping Zhang, Xue-Yan Li, Xiao-Yi Kong and Gui-Hai Chen*

Department of Neurology (Sleep Disorders), The Affiliated Chaohu Hospital of Anhui Medical University, Hefei (Chaohu), China

*Corresponding Author: Gui-Hai Chen, Department of Sleep Disorders, The Affiliated Chaohu Hospital of Anhui Medical University, Hefei (Chaohu), China.

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Abstract

Objectives: To explore serum level of 25-hydroxy vitamin D3 [25(OH)D3] and its correlations with sleep quality and cognitive function in the patients with chronic insomnia disorder (CID).

Methods: Fifty CID patients and forty healthy controls were enrolled. Pittsburgh Sleep Quality Index (PSQI), Montreal Cognitive Assessment scale (MoCA) and Nine-Box Maze Test were used to assess insomnia severity, general cognitive function and the special memories, including object/spatial reference memories, object/spatial working memories and object recognition memory, with the objective sleep status being assessed using polysomnography overnight in 26 patients. The serum level of 25(OH)D3 was detected using ELISA.

Results: Compared to the controls, the CID patients had significantly higher PSQI score ($P < 0.001$) and lower MoCA score ($P < 0.001$). The CID patients had significantly more errors in object working ($Z = -2.304$, $P = 0.021$), spatial working ($Z = -4.927$, $P < 0.001$) and object recognition memories ($Z = -3.770$, $P < 0.001$) in Nine-Box Maze Test than the controls, with lower serum level of 25(OH)D3 ($P < 0.001$). The partial correlation analysis showed that in the CID patients, the level of 25(OH)D3 correlated negatively with PSQI score ($r = -0.320$, $P = 0.030$), number of errors in spatial working memory ($r = -0.300$, $P = 0.043$) and duration of illness ($r = -0.360$, $P = 0.014$), and positively with total sleep time ($r = 0.515$, $P = 0.014$) and MoCA score ($r = 0.422$, $P = 0.003$).

Conclusion: The level of 25(OH)D3 decreased in the CID patients, which was correlated with insomnia severity and illness duration, and might affect the general cognitive function and spatial working memory.

Keywords: Cognition; Insomnia; Polysomnography; Serum; Vitamin D

Introduction

Chronic insomnia (CID) refers to frequent and persistent difficulties that occur in the initiation and maintenance of sleep, leading to an individual's dissatisfaction with its time and quality, with impaired daytime functions, such as mild cognition dysfunction [1,2]. However, the mechanisms of insomnia and related cognitive impairment is currently unclear.

As a steroid derivative, vitamin D exerts physiological functions through binding with vitamin D receptors (VDR), including calcium and phosphorus metabolism regulation, neuronal development and differentiation, neurotrophic factor expression control, neurotransmitter synthesis and immune regulation, etc. [3-6]. Studies have proven that in adult brain tissues, widespread VDRs are mainly distributed in the area like cerebral cortex, hippocampus, hypothalamus, striatum, amygdala, substantia nigra, and pontine reticulum, and are mainly located in the nucleus of neurons and glial cells [7-9]. Vitamin D can orientate and promote the growth, development, and differentiation

of the neurons, such as by means of VDRs expressed in the nucleus of dopaminergic neurons in the substantia nigra of the midbrain [10-12]. The activation of VDRs can boost the synthesis of multiple neurotransmitters (such as dopamine, norepinephrine, glutamic acid, serotonin, γ -aminobutyric acid), hence affecting cognition, mood and sleep-wake cycles [13-16].

According to the growing researches, vitamin D could play an important role in sleep regulation and its deficiency is related to cognitive impairment of various neurodegenerative diseases (such as Parkinson's disease, Alzheimer's disease, etc.) [17-20]. In a general population (n = 6139, aged 16 and above, 19.4% people complaining of sleep problems to doctors) from an early United States National Health and Nutrition Examination Surveys (NHANES, 2005 - 2006), a negative association had been found between serum 25(OH)D concentrations and minutes to fall asleep [21]. The hypothesis of vitamin D deficiency in sleep disorders, including insomnia [18,22], has been put forward. It has been emphasized that adequate levels of vitamin D are necessary for the maintenance of sleep, reducing the number of nocturnal awakenings [18]. So far, only few studies have found a declined level of serum 25(OH)D3 in patients with CID, but these studies do not explore the relationship between this condition and the insomniac severity and cognitive impairment [23].

Therefore, it is necessary to complete extensive exploration in this field. In this study, we measured the serum concentration of 25(OH)D3 in the patients with CID and assessed the sleep quality and cognitive function, with analyzing the correlations between serum 25(OH)D3 levels and insomniac severity and cognitive function.

Data and Methods

Subjects

The patients come from the Clinic of Sleep Disorder, the Affiliated Chaohu Hospital of Anhui Medical University, from October 1, 2016 to September 1, 2018. Total Fifty CID patients were collected, and their illness met the diagnostic criteria of the International Classification of Sleep Disorders (the third edition) [24]. The inclusion criteria were as follows: a. The illness duration was more than or equal to 6 months; b. Ages ranged from 18 to 65 years; c. Educated years was at least seven without comprehension problems; d. The score of Pittsburgh Sleep Quality Index (PSQI) was more than 7 points, and that of 17 items on the Hamilton Depression Scale (HAMD-17) was less than 17 points. The exclusion criteria consisted of: a. People who did not cooperate with the test; b. Persons who had damaged vision or hearing; c. Individuals who had suffered from liver and kidney dysfunction, chronic pain, malignant tumors, thyroid disease, diabetes mellitus and other serious medical/physical disease, mental diseases or other sleep disorders; d. Subjects who were taking vitamin D drugs and calcium; e. Women who were under pregnancy or lactating stage; f. Who did not take any sedative drugs within two weeks of consultation. At the same time, forty healthy subjects (the score of both PSQI and HAMD-17 was less than 7) without insomnia complaints and related medical history during the same period were selected as controls. The study obtained the review and approval of the Affiliated Chaohu Hospital of Anhui Medical University Ethics Committee (N. 201805-kyxm-01), and all subjects have signed informed consent.

Methods

General data collections

The collections of general information was completed, mainly including the gender, age, education level, illness history, life history, family history, etc. of the subjects. The depressive level was assessed with HAMD-17 [25]. A higher score means more severe depressive mood (the score less than 7 proves a normal status, and the score within the range of 7-17 means mild, 18 - 24 means moderate, and greater than 24 suggest severe depression). At the same time, the MINI-International Neuropsychiatric Interview was used to exclude the patients with clear symptoms of depression.

Sleep quality evaluation

The subjective sleep quality in all subjects was assessed on the basis of PSQI [26], a 4-point rating scale to reflect the sleep status during the past month, which range from 0 (not) to 3 (three or more times per week) that measures seven components, including subjective sleep

quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. These sleep-component scores are summed to yield a total score ranging from 0 to 21, with higher score corresponding to poorer sleep quality. The commonly used delimitation score of sleep disorders in China is the total score of PSQI greater than 7.

The objective sleep quality also was assessed in 26 patients with CID using standard overnight polysomnography (PSG, Compumedics Grael v2, Australia). The installation of the electrodes was coupled with the basic sleep diagnosis montage, and pressure and heat-sensing dual sensors were for the monitoring of oral and nasal airflow. The rules from the AASM Manual for the Scoring of Sleep and Associated Events (2007) was referenced to analyze sleep and related breathing, blood oxygen and ECG events, including the total sleep time (TST), sleep onset latency (SOL), sleep efficiency (SE), the numbers of awaking (NA) and time of awaking after sleep onset (WASO), time in the stages of 1, 2 and 3 (N1, N2, N3) of non-rapid eye movement (NREM) sleep period and their percent in total time (N1%, N2%, N3%), the time in rapid eye movement (REM) period and its percentage in total time (REM%).

Cognition evaluation

General cognition

The overall cognitive function was assessed using the Chinese-Beijing Version of Montreal Cognitive Assessment Scale (MoCA-C) [27], which involves 7 cognitive domains (visual space and executive function, naming, attention, language, abstraction, delayed recall, and orientation), being widely used for rapid screening of mild cognitive abnormalities, with a total score of 30 (the score greater than 26 means a normal condition). The higher the score is, the better the cognitive function is.

Special memories

The modified Nine-Box Maze was employed to evaluate the memory functions of subjects, covering spatial working (SWM), spatial reference (SRM), object working (OWM), object reference (ORM), object recognition (ORcM) memories [9,28]. The protocol has been described else-where [28,29]. Briefly, in a bright room, a 120-cm-diameter table was put in the center with a picture on one inside-wall as a place cue. Nine identical opaque containers (height 9 cm and diameter 8 cm) were equidistantly located along the table border. This test consisted of training and testing phases with a preceded object-familiarization phase. In the object-familiarization phase, the subject was shown 10 common objects (namely, button, key, coin, battery, watch, pencil sharpener, nail clipper, shears, scotch tape and clothespin), and asked to name each object. In the training phase (the performance was not recorded), the subject was respectively shown 2 random containers and objects familiarized and told to remember these objects and containers hid them. Then, the subject was required to move around the table twice clockwise and counterclockwise in sequence. Then the subject was required to recognize the objects from a photograph of the 10-common objects and the their containers. If the response was incorrect, the subject should continue to pointing out the objects or/and containers until correct response. In the testing phase, the subject was requested to remember the 2 objects and their positions in the training phase, which would not be moved and tested at the end of the test to form SRM and ORM, meanwhile, remember other 2 objects from the object-familiarization phase and corresponding containers hid the 2 object every trial, to form SWM and OWM. After 4 trials, subject was requested to recognize the objects in the training phase from a photograph that contained corresponding similar objects that had been used in the test, to obtain ORcM. The performance of these memories was reflected with wrong numbers. The more errors were, the worse the memory performed.

Serum 25(OH)D3 detection

At about 8:00 the next day after PSG monitoring was completed, the venous blood of subjects was taken (fasting and avoidance of strenuous exercise and excessive tension before collection) and centrifuged to extract serum after being kept for 30 minutes. The serum was stored frozen in a refrigerator at -80°C. Then ELISA was used to detect the serum 25(OH)D3 content of the subjects. Specific experimental steps were in accordance with the kit operation process (Wuhan USCN).

Statistical methods

Data analysis was performed based on SPSS16.0 statistical software. Means ± standard deviation was used to represent the data with normal distribution, and the t test was used to compare differences between both groups. The interquartile range [P50 (P25, P75)] was shown to represent the data of abnormal distribution, and the differences between groups were analyzed with rank-sum test on the footing of two samples with complete random design (Mann-Whitney U). The chi-square test was used to compare the classified data. Partial correlation analysis offered a guidance to analyze the correlation between serum 25(OH)D3 and sleep parameters (PSQI scores, PSG parameters), cognitive parameters (MoCA scores, numbers of memory errors) and illness duration with test level equivalent to 0.05 and two-sided test.

Results

General data

There was no statistical difference in gender, age, and education between the two groups (Ps > 0.05, see table 1). The CID sufferers had higher HAMD-17 (7.9 ± 3.3 scores) than the controls (3.0 (3.0, 4.0) scores), suggesting a status of mild depression, and meeting the feature of chronic insomniac condition.

Categories	Terms	Cironic insomnia	Controls	Statistics	P values
General data	Number of cases	50	40		
	Male/female (ex)	14/36	13/27	$\chi^2 = 0.214$	0.643
	Age (years)	47.2 ± 12.3	43.4 ± 10.4	t = 1.545	0.126
	Education (years)	9.4 ± 4.9	9.9 ± 4.7	t = -0.483	0.630
	HAMD-17 (scores)	7.9 ± 3.3*	3.0 (3.0, 4.0)	Z = -6.424	< 0.001
Serology	25 (OH)D3 (ng/ml)	38.0 ± 9.8*	61.5 ± 13.9	t = -9.367	<0.001
Subjective sleep	PSQI (scores)	13.4 ± 2.1*	4.0 (3.0, 4.0)	Z = -8.186	<0.001
Objective sleep (n = 26)	Total sleep time (min)	379.71 ± 72.84			
	Sleep onset latency (min)	60 (29.5, 124)			
	Sleep efficiency (%)	74.2 (66.5, 84.1)			
	Numbers of awaking	21 (15, 36)			
	Awaking after sleep onset (min)	151 (115, 183)			
	N1%	21 (13.2, 26.2)			
	N2%	63.1 (52.8, 71.7)			
	N3%	21.5 (14.7, 53.6)			
REM%	14.3 (10, 20.1)				

Table 1: General data, serological and sleep parameters in both groups.

*Compared to the controls, P < 0.05.

Sleep quality

The parameters of subjective and objective sleep quality are exhibited in the table. The CID patients had significantly higher PSQI score (13.4 ± 2.1) than the good sleepers (4.0(3.0,4.0), P < 0.001). The PSG results showed that compared to the norm, the sufferers had short TST, decreased SE, obviously increased NA, WASO and N1%. These suggested our CID patients had an average moderate insomnia.

Cognitive function

Compared to the control group, the score of MoCA-C in the CID group was significantly lower ($Z = -3.876, P < 0.001$). The CID group had significantly increased numbers of errors in SWM ($Z = -4.927, P < 0.001$), OWM ($Z = -2.304, P = 0.021$) and ORcM ($Z = -3.770, P < 0.001$) than the controls (See table 2).

Groups	N	MoCA-C (score)	ORM (error)	SRM (error)	OWM (error)	SWM (error)	ORcM (error)
CID	50	24.5 ± 3.2*	0.0 (0.0, 0.0)	0.0 (0.0, 0.3)	0.5 (0.0, 1.0)*	2.0 (2.0, 3.0)*	0.0 (0.0, 1.0)*
Controls	40	26.0 (26.0, 27.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	1.0 (1.0, 2.0)	0.0 (0.0, 0.0)
Statistic (Z)		-3.876	-0.815	-1.396	-2.304	-4.927	-3.770
P values		< 0.001	0.856	0.163	0.021	< 0.001	< 0.001

Table 2: Cognitive function between the two groups.

Abbreviations: MoCA-C: Chinese-Beijing Version of Montreal Cognitive Assessment Scale; ORcM: Object Recognition Memory; ORM: Object Reference Memory; OWM: Object Working Memory; SRM: Spatial Reference Memory; SWM: Spatial Working Memory.

*Compared to the controls, $P < 0.05$.

Serum 25(OH)D3 concentration

The CID group had significantly lower serum concentration of 25(OH)D3 (38.0 ± 9.8 ng/mL) than the controls (61.5 ± 13.9 ng/mL), with $t = -9.367, P < 0.001$ (See table 1 and figure 1).

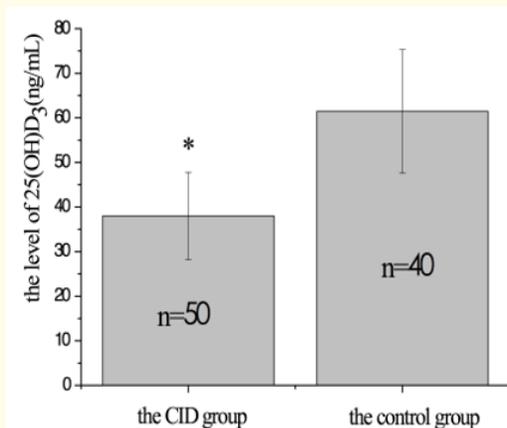


Figure 1: Serum 25(OH)D3 levels.

Note: Compared with the control group, $*P < 0.001$

The patients with chronic insomnia disorder had significantly lower serum concentration of 25(OH)D3 than the good sleepers.

Correlations between serum 25(OH)D3 level and clinical parameters

In the CID group, the partial correlation analysis (with age, gender, education, and HAMD-17 under control) indicated that the serum 25(OH)D3 level correlated negatively with the PSQI score ($r = -0.320, P = 0.030$), the number of errors in SWM ($r = -0.497, P = 0.001$) and

illness duration ($r = -0.360, P = 0.014$), and positively with MoCA score ($r = 0.422, P = 0.003$) and only total sleep time in the PSG sleep parameters (See table 3).

Illness duration (month)	PSQI (score)	MoCA (score)	ORM (error)	SRM (error)	OWM (error)	SWM (error)
-0.360* (0.014)	-0.320* (0.030)	0.422* (0.003)	-0.105 (0.486)	-0.251 (0.093)	-0.050 (0.743)	-0.300* (0.043)
ORcM (error)	TST (min)	SOL (min)	SE (%)	NA	WASO (min)	N1 (min)
0.191 (0.204)	0.515 ^a (0.014)	0.340 (0.122)	-0.236 (0.289)	0.000 (0.998)	0.109 (0.628)	-0.301 (0.173)
N1%	N2 (min)	N2%	N3 (min)	N3%	REM (min)	REM%
-0.193 (0.390)	-0.120 (0.594)	0.205 (0.360)	-0.140 (0.534)	-0.146 (0.518)	-0.036 (0.873)	0.116 (0.607)

Table 3: Results of partial correlation analysis for serum 25(OH)D3 concentration with illness duration, sleep quality, cognitive performance in 26 CID patients [r(P)].

Abbreviations: NA: Numbers of Awakening; MoCA-C: Chinese-Beijing Version of Montreal Cognitive Assessment Scale; ORcM: Object Recognition Memory; ORM: Object Reference Memory; OWM: Object Working Memory; PSQI: Pittsburgh Sleep Quality Index; SRM: Spatial Reference Memory; SWM: Spatial Working Memory; WASO time of awakenings after sleep onset. The other abbreviations of PSG-parameters see Methods.

^aP < 0.05.

Discussion

Insomnia is the most prevalent sleep disorder, affecting approximately 10 - 30% of the population worldwide [30], with about 6% - 10% of adults struggling with CID [31]. CID-stricken people often proactively complain about cognitive impairment, which results in severe impact on their study performance, work efficiency and quality of life [2]. There is still, however, no effective intervention for CID itself and the related problems on cognition. The reasons resulting in this condition can at least partially be attributable to unclear causes or/and mechanisms under this disorder.

Vitamin D, a fat-soluble pro-hormone, is mainly (90%) synthesized *in vivo* when solar ultra-violet B radiation interacts with 7-dehydrocholesterol in the skin [32]. Therefore, under modern lifestyle characterized by low sunlight exposure due to convenient transportation, using sunscreen, busy schedule, etc., with aging, skin color, season, altitude, and latitude, vitamin D deficiency is prevalent worldwide [33]. Vitamin D firstly is hydroxylated to 25-(OH)D in the liver, and then converted to the metabolically active form, 1,25-(OH) D, primarily in the kidneys [33]. Due to notably ease of analysis, stability and long half-life in blood circulation, 25-(OH)D3 is the major circulating form of vitamin D to determine vitamin D status [33,34]. Vitamin D insufficiency has been linked many diseases, and the neurologic and psychiatric diseases are included among them [35,36]. Past decade, several epidemiological studies have shown that low levels of vitamin D are associated with short sleep duration or poor sleep quality in different population [22,35]. Therefore, theory that vitamin D play a role in sleep regulation has been hypothesized [18,22]. However, the clinic studies on vitamin D still is rare.

The current study found that serum 25(OH)D3 level significantly ($P < 0.001$) reduced in patients with CID (38.0 ± 9.8 ng/mL) compared to the good sleepers (61.5 ± 13.9 ng/mL). The finding generally is consistent with the results from epidemiological studies [21,37,38] and only clinic study from China [23]. However, the mean concentration of serum 25(OH)D3 in our good sleepers was 61.5 ng/mL that met the normal criteria (54 - 90 ng/mL) in sunny countries [39], but appeared higher relative to the epidemiological continuity populations (where

the clear information don't be reported in good sleepers) [3,21,37,38]. For instance, the mean volume of serum 25(OH)D concentrations is 21.2 ± 9.3 ng/mL shown in a continuity population consisted of 6139 participants aged 16 and above regardless of the sleep status [21]. To date, the optimal level of vitamin D for human health is still unclear. In western countries, the recommended serum levels of 25(OH)D3 is more than 20 - 30 ng/mL [33] and the most widely recognized and commonly cited clinical threshold for serum sufficiency 25(OH)D3 in the general population is 30 ng/mL over [40]. In our CID patients (come from the hospital in the middle-sunny district between 30 - 33° in north latitude), the average serum level of 25(OH)D3 was 38.0 ng/mL, which only was about 60% concentration in our good sleepers, and trended to the clinical cut-off value [40].

Our results also indicated that the serum level of 25(OH)D3 in the CID patients was linked positively to the total sleep time, and negatively to the sleep efficiency, the times in REM sleep and all stages (N1, N2 and N3) of NREM sleep measured with PSG and PSQI score (See table 2), suggesting low 25(OH)D3 concentration was associated with the insomnia characterized by objective short sleep time. These findings were consistent with the results from epidemiological studies in continuity-dwelling populations using cross-sectional or prospective methods in men or women, old or all adults or children [3,21,23,37,38,41]. In addition, this study also showed that serum 25(OH)D3 level negatively correlated with the illness duration ($r = -0.360$, $P = 0.014$), suggesting that the longer the illness duration was, the lower the serum 25(OH)D3 levels was. The cause may be partial attributable to that patients with longer illness duration have greater severity of insomnia relative to the ones with shorter illness duration.

In the insomniacs, the cognitive dysfunction is a group of common damages of daytime functions, including memory, attention, executive function [42], or in detail including subjective cognitive performance, and objective measures of perceptual function, manipulation and retention/capacity in working memory, complex attention, alertness, episodic memory, and problem solving in executive functions [43]. In the current study, the results showed that the patients with CID had lower MoCA-C score and more numbers of errors in the SWM, OWM and ORcM tasks. These results were in accordance with findings in above review [43], i.e. impairment of working memory (SWM, OWM) and episodic memory (ORcM) in the insomniacs, and duplicated our previous findings [28,29]. However, the cause or/and mechanism underlying the damage of memory in the subjects suffering from CID remains to be explored. In the Health Survey for England 2000, the result suggests low serum 25(OH)D3 is associated with increased odds of cognitive impairment in adults aged 65 years and older [44]. Though conflicting results, most of existed meta-analyses or systematic reviews show a positive association between low serum concentration of 25(OH)D and memory function tests [45]. On the basis of the results of the study, for patients with CID, the higher serum 25(OH)D3 level, the stronger their overall cognitive function (MoCA-C score) and stronger spatial working memory ability as well. This may be the first exploration for relationship between serum vitamin D level and cognitive function in the CID sufferers.

In addition to the impact on the neurotransmitter synthesis, the mechanisms involved in this relationship between low serum vitamin D concentration and insomnia and cognitive impairment in the CID sufferers may also be to weaken the protection action to nerves (with the increase of the neurocadherin expression by promoting the growth of axons in hippocampal neurons) due to the influence of the deficiency of vitamin D on the expression of neurotrophic factors [46-48]. In addition, deficiency of vitamin D can also lead to up-regulation of the expression of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)- α [49]. Conversely, increased synthesis and secretion of TNF- α will increase in the absence of vitamin D. In is well-known that elevated level of TNF- α is involved in the pathogenesis of neurological and mental diseases, such as insomnia, cognitive impairment. Our previous studies of CID-stricken patients showed elevated serum concentration of TNF- α was linked to the impairment in multidimensional memories [50].

Conclusion

In summary, the study explored the effects of changes in serum 25(OH)D3 levels on sleep quality and cognitive function in the patients with CID. With the guidance of the results obtained, supplementation with an appropriate amount of vitamin D may improve the sleep quality of the patients, reduce the degree of cognitive impairment, and have potential clinical value for the prevention and treatment of

CID. However, there were some limitations in the study, that is, the small sample size and fewer cases of PSG monitoring at night, more direct basis for the relationship between vitamin D deficiency and CID could not be provided. From this point, it is necessary to further increase the sample size in the future to implement in-depth exploration of the specific mechanism of vitamin D acting on sleep and cognition.

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Conflicts of Interest

None declared.

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