Correlation between Cognitive Function and Insomnia Severity, Serum 25-Hydroxyvitamin D3, and Tumor Necrosis Factor-α Levels in Elderly Patients with Chronic Insomnia: Postprint

Authors: Wu Zixing, Hu Xin, Tao Shimeng, He Youjun, Cai Chuanyun, Jiang Wei, Hu Xin, Jiang Wei

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Abstract

Background Chronic insomnia is one of the common diseases in the elderly population, often accompanied by varying degrees of cognitive impairment, which seriously affects patients' quality of life. However, the biological mechanisms underlying cognitive impairment in elderly patients with chronic insomnia remain unclear. Objective To investigate the correlation between cognitive function and insomnia severity, serum 25-hydroxyvitamin D3 [25(OH)D3] levels, and tumor necrosis factor-α (TNF-α) levels in elderly patients with chronic insomnia. Methods A total of 105 elderly patients with chronic insomnia who were diagnosed and treated at the 901st Hospital of the Joint Logistics Support Force of the Chinese People' s Liberation Army between June 2020 and June 2022 were selected as the study subjects. Before enrollment, they underwent the Pittsburgh Sleep Quality Index (PSQI), Geriatric Depression Scale (GDS-15), and Generalized Anxiety Disorder-7 (GAD-7) assessments. Based on PSQI scores, patients were grouped according to insomnia severity: 32 cases in the mild insomnia group, 38 cases in the moderate insomnia group, and 35 cases in the severe insomnia group. Photoplethysmography (PPG) was used to evaluate objective sleep quality, monitoring total sleep time, sleep latency, sleep efficiency, and number of awakenings. The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were used to assess cognitive function. Enzyme-linked immunosorbent assay (ELISA) was used to detect serum levels of 25(OH)D3 and TNF-α. Results The severe insomnia group exhibited longer sleep latency and more awakenings than both the mild and moderate insomnia groups, shorter total sleep time than the mild insomnia group, and lower sleep efficiency than both the mild and moderate insomnia groups. The moderate insomnia group showed longer sleep latency and lower sleep efficiency than the

mild insomnia group (P<0.05). The severe insomnia group had lower MMSE and MoCA scores than both the mild and moderate insomnia groups, while the moderate insomnia group had lower MMSE and MoCA scores than the mild insomnia group (P<0.05). Serum TNF-α levels were higher and 25(OH)D3 levels were lower in the severe insomnia group compared to both the mild and moderate insomnia groups (P<0.05). The moderate insomnia group also showed higher serum TNF-α levels and lower 25(OH)D3 levels than the mild insomnia group (P<0.05). Spearman correlation analysis revealed that MMSE and MoCA scores were positively correlated with total sleep time, sleep efficiency, and 25(OH)D3 levels (P<0.05), and negatively correlated with insomnia severity, sleep latency, number of awakenings, and TNF-α levels (P<0.05). Conclusion Cognitive impairment in elderly patients with chronic insomnia may be associated with insomnia severity, decreased serum 25(OH)D3 levels, and increased TNF-α levels.

Full Text

Correlations of Cognitive Function with Insomnia Severity, Serum Levels of 25-hydroxy Vitamin D3 and Tumor Necrosis Factor-α in Elderly Patients with Chronic Insomnia

Wu Zixing[1], **Hu Xin**[1,2], ***Tao Shimeng***[2], ***He Youjun***[1], ***Cai Chuanyun***[1], ***Jiang Wei***[1,2]

[1]Department of General Practice, the 901st Hospital of the Joint Logistics Support Force of the Chinese People' s Liberation Army, Hefei 230031, China
[2]Anhui Medical University, Hefei 230032, China

Corresponding authors: Hu Xin, Associate Professor; E-mail: huxin_{1119}@126.com; Jiang Wei, Associate Professor; E-mail: 2408797210@163.com

Abstract

Background: Chronic insomnia is one of the most common diseases in the elderly population, often accompanied by varying degrees of cognitive impairment that seriously affects patients' quality of life. However, the biological mechanisms underlying cognitive impairment in elderly patients with chronic insomnia remain unclear.

Objective: To investigate the correlations of cognitive function with insomnia severity and serum levels of 25-hydroxy vitamin D3 [25(OH)D3] and tumor necrosis factor-α (TNF-α) in elderly patients with chronic insomnia.

Methods: A total of 105 elderly patients with chronic insomnia treated at the 901st Hospital of the Joint Logistics Support Force of the Chinese People' s Liberation Army between June 2020 and June 2022 were enrolled. Prior to enrollment, participants completed the Pittsburgh Sleep Quality Index (PSQI), Geriatric Depression Scale (GDS-15), and Generalized Anxiety Disorder Scale (GAD-7). Based on PSQI scores, patients were stratified into mild (n=32),

moderate (n=38), and severe (n=35) insomnia groups. Objective sleep quality was assessed using photoplethysmography (PPG) to monitor total sleep time, sleep latency, sleep efficiency, and arousal frequency. Cognitive function was evaluated using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Serum levels of 25(OH)D3 and TNF-α were measured by enzyme-linked immunosorbent assay.

Results: The severe insomnia group exhibited longer sleep latency and more frequent arousals than both mild and moderate groups, with shorter total sleep time and lower sleep efficiency compared to the mild group. The moderate group showed longer sleep latency and lower sleep efficiency than the mild group ($P<0.05$). MMSE and MoCA scores were lower in the severe group than in both other groups, and lower in the moderate group than in the mild group ($P<0.05$). Serum TNF-α levels were higher while 25(OH)D3 levels were lower in the severe group compared to both other groups; the moderate group also showed higher TNF-α and lower 25(OH)D3 than the mild group ($P<0.05$). Spearman correlation analysis revealed that MMSE and MoCA scores were positively correlated with total sleep time, sleep efficiency, and 25(OH)D3 levels ($P<0.05$), and negatively correlated with insomnia severity, sleep latency, arousal frequency, and TNF-α levels ($P<0.05$).

Conclusion: Cognitive impairment in elderly patients with chronic insomnia may be associated with increased insomnia severity, decreased serum 25(OH)D3 levels, and elevated TNF-α levels.

Keywords: Sleep initiation and maintenance disorders; Aged; Cognition; Calcifediol; Tumor necrosis factor-alpha

Introduction

Chronic insomnia is characterized by difficulty initiating and maintaining sleep, resulting in subjective dissatisfaction with sleep duration or quality accompanied by daytime functional impairment for more than three months, representing a significant public health concern [1]. Epidemiological data indicate that the prevalence of chronic insomnia in China is 9.2%, with elderly individuals accounting for approximately 60% of cases [2]. Chronic insomnia constitutes a risk factor for cognitive impairment in older adults [3]; however, research on the mechanisms linking chronic insomnia to cognitive dysfunction remains limited, often leading to inadequate diagnosis and treatment of sleep and cognitive problems in this population.

Previous studies have demonstrated that individuals with lower serum 25-hydroxy vitamin D3 [25(OH)D3] levels experience shorter sleep duration and poorer sleep quality [4], and that low 25(OH)D3 is associated with cognitive impairment in neurodegenerative diseases such as Parkinson' s and Alzheimer' s disease [5-6]. Additionally, tumor necrosis factor-α (TNF-α) has been

shown to exert specific effects on sleep-wake behavior [7], with accumulating evidence linking elevated TNF-α to deficits in memory, cognition, excessive daytime sleepiness, mood disorders, and behavioral impairment [8-9]. These findings suggest that both 25(OH)D3 and TNF-α play important roles in sleep regulation and cognitive maintenance. The present study employed photoplethysmography (PPG) and neuropsychological scales to evaluate objective sleep quality and cognitive function in elderly patients with chronic insomnia, while simultaneously measuring serum 25(OH)D3 and TNF-α levels to further explore the relationship between cognitive function across different insomnia severity levels and underlying biological mechanisms.

Methods

1.1 Study Participants

We enrolled 105 elderly patients with chronic insomnia treated at the 901st Hospital of the Joint Logistics Support Force of the Chinese People' s Liberation Army between June 2020 and June 2022. The cohort comprised 48 males and 57 females, aged 65-80 years with a mean age of 72.6$±$4.8 years. Inclusion criteria were: (1) diagnosis of insomnia according to the International Classification of Sleep Disorders, 3rd edition [10]; (2) insomnia occurring >3 days per week with total disease duration $ $1 year; (3) age $ $65 years; (4) PSQI score >7. Exclusion criteria included: (1) use of anti-anxiety, antidepressant, or sedative-hypnotic medications within the preceding two weeks; (2) history of psychiatric or psychological disorders; (3) severe organic diseases of the brain, heart, lungs, liver, or kidneys; (4) inability to complete questionnaires due to reading or communication barriers. The study was approved by the Ethics Committee of the 901st Hospital (approval number: 202003001), and all participants provided informed consent.

1.2 Assessment Protocols

1.2.1 General Information: Demographic data were collected including sex, age, disease duration, education level, medical history, and family history. All participants completed the PSQI, Geriatric Depression Scale-15 (GDS-15) [12], and Generalized Anxiety Disorder Scale-7 (GAD-7) [13] prior to enrollment.

1.2.2 Objective Sleep Quality Assessment: PPG monitoring (Morpheus Ox, Wide Med, Israel) was conducted from 22:00 to 06:00. Participants abstained from sedative-hypnotics, alcohol, coffee, and other stimulants on the examination day. PPG data were automatically analyzed by cloud-based Morpheus Ox software, monitoring total sleep time, sleep latency, sleep efficiency, and arousal frequency.

1.2.3 Cognitive Function Assessment: On the morning following sleep monitoring, all patients completed the Mini-Mental State Examination (MMSE) [14] and Montreal Cognitive Assessment (MoCA) [15] in a quiet, distraction-free en-

vironment. Both scales have a maximum score of 30, with lower scores indicating more severe cognitive impairment.

1.2.4 Serum 25(OH)D3 and TNF-α Measurement: Venous blood samples were collected at 08:00 the day after PPG monitoring (after overnight fasting and avoidance of excessive tension or strenuous exercise). Samples were left to stand for 30 minutes, then centrifuged at 3,000 rpm for 5 minutes (radius: 15 cm). Serum was extracted and stored at -80°C. Serum 25(OH)D3 and TNF-α levels were measured by enzyme-linked immunosorbent assay using kits from Wuhan GeneMay Technology according to manufacturer protocols.

1.3 Grouping

Based on PSQI scores, the 105 patients were stratified into mild (7-10 points), moderate (11-15 points), and severe (16-21 points) insomnia groups [16-18], comprising 32, 38, and 35 patients respectively.

1.4 Statistical Analysis

Data were analyzed using SPSS 25.0. Normally distributed continuous variables are expressed as mean±standard deviation (x-±s). Intergroup comparisons were performed using one-way ANOVA with LSD-t test for pairwise comparisons. Categorical data are presented as frequencies and compared using ^{2} test. Spearman correlation analysis was used to examine relationships between variables. Statistical significance was set at $P<0.05$.

Results

2.1 Comparison of General Characteristics and PSQI Scores

No significant differences were observed among the three groups in age, sex, disease duration, education level, GDS-15 scores, or GAD-7 scores ($P>0.05$). PSQI scores differed significantly among groups ($P<0.05$), with moderate and severe groups scoring higher than the mild group, and the severe group scoring higher than the moderate group ($P<0.05$) .

2.2 Comparison of PPG Sleep Parameters

Significant differences were found among groups in total sleep time, sleep latency, sleep efficiency, and arousal frequency ($P<0.05$). The severe group demonstrated longer sleep latency and more frequent arousals than both other groups, shorter total sleep time than the mild group, and lower sleep efficiency than both mild and moderate groups ($P<0.05$). The moderate group showed longer sleep latency and lower sleep efficiency than the mild group ($P<0.05$) .

2.3 Comparison of Cognitive Function

MMSE and MoCA scores differed significantly among groups ($P<0.05$). Both scores were lower in the severe group than in the mild and moderate groups, and lower in the moderate group than in the mild group ($P<0.05$) .

2.4 Comparison of Serum 25(OH)D3 and TNF-α Levels

Serum 25(OH)D3 and TNF-α levels differed significantly among groups ($P<0.05$). The severe group exhibited higher TNF-α and lower 25(OH)D3 levels than both other groups ($P<0.05$). The moderate group also showed higher TNF-α and lower 25(OH)D3 than the mild group ($P<0.05$) .

2.5 Correlation Analysis of Cognitive Function with Insomnia Severity, Sleep Parameters, and Serum Markers

Spearman correlation analysis revealed that MMSE and MoCA scores were positively correlated with total sleep time, sleep efficiency, and 25(OH)D3 levels ($P<0.05$), and negatively correlated with insomnia severity, sleep latency, arousal frequency, and TNF-α levels ($P<0.05$) .

Discussion

Current sleep assessment in elderly populations relies primarily on questionnaires, lacking objective measures. Although polysomnography represents the gold standard for objective sleep evaluation, its complexity and poor patient compliance limit widespread application. This study utilized PPG monitoring, which offers simplicity, non-invasiveness, and good compliance, making it particularly suitable for objective sleep assessment in older adults. Previous research has demonstrated good agreement between PPG and polysomnography results [19]. Our findings indicate that cognitive decline in elderly chronic insomnia patients is associated with increased insomnia severity, shortened total sleep time, prolonged sleep latency, reduced sleep efficiency, and increased arousal frequency.

Previous research on the relationship between cognitive impairment and sleep has yielded inconsistent results. A longitudinal cohort study found that longer total sleep time might increase cognitive impairment risk in older adults [20], while other research suggests long sleep duration adversely affects executive function and working memory [21]. A longitudinal study of individuals over 50 found significant associations between longer sleep duration and global cognitive decline [22]. However, some studies indicate that both excessively short and long sleep increase cognitive impairment risk [23-24], and a meta-analysis showed that both insufficient and excessive nighttime sleep elevate cognitive disorder risk [25], suggesting that stable sleep patterns are optimal. Research has confirmed that prolonged sleep latency predicts dementia incidence [26], and studies in older populations have found that poor sleep quality, long sleep latency, and low

sleep efficiency increase cognitive disorder risk [27]. Increased nocturnal arousals result in fragmented sleep, disrupting sleep continuity and overall architecture. Animal studies have shown that sleep fragmentation significantly impairs object recognition memory and conditioned fear memory in aged mice [28]. Collectively, these findings demonstrate that insomnia severity, sleep latency, sleep efficiency, nocturnal arousals, and sleep duration all impact cognitive function.

Neuroinflammation is closely associated with brain injury, with TNF-α being a primary cytokine in this process. Animal studies have shown that microinjection of TNF-α into the rat locus coeruleus and anterior hypothalamus enhances non-rapid eye movement sleep, indicating that TNF-α modulates sleep architecture [29]. TNF-α exhibits rhythmic expression in brain tissue, peaking during deep sleep [30]. Low daytime TNF-α expression maintains wakefulness, while elevated nighttime levels promote deep sleep, suggesting that circadian rhythmicity of TNF-α forms the basis of sleep regulation. Our study found that serum TNF-α levels around 08:00 increased progressively with insomnia severity, suggesting that worsening chronic insomnia may disrupt the circadian rhythm of TNF-α expression.

Further correlation analysis revealed negative associations between MMSE/MoCA scores and TNF-α levels, indicating that cognitive impairment in elderly chronic insomnia patients is linked to elevated serum TNF-α. Our previous research also found increased serum TNF-α in chronic insomnia patients, correlating with impaired spatial working memory and object recognition memory [31]. TNF-α can activate caspase-mediated apoptotic pathways through TNF receptor binding, causing rapid neuronal apoptosis and participating in β-amyloid formation, which is closely related to cognitive impairment in neurodegenerative diseases [32]. Animal studies have shown that microinfusion of TNF-α into the dorsal hippocampus impairs contextual fear memory retrieval and spatial memory reconsolidation, demonstrating negative modulation of hippocampus-dependent memory processes [33]. Another study found that lipopolysaccharide-exposed rats exhibited spatial learning and memory deficits with elevated hippocampal and cortical TNF-α levels; administration of anti-inflammatory agents reduced TNF-α levels and improved learning and memory performance [34]. Since hippocampal memory formation depends primarily on long-term potentiation, research has confirmed that TNF-α can enhance AMPA receptor expression, thereby disrupting long-term potentiation and synaptic homeostasis, leading to impaired short-term recognition and long-term spatial memory and ultimately causing cognitive dysfunction [35]. Thus, elevated TNF-α may induce rapid neuronal apoptosis, participate in β-amyloid formation, and block long-term potentiation, affecting hippocampal synaptic connectivity and resulting in cognitive impairment.

Vitamin D is hydroxylated in the liver to form 25-hydroxyvitamin D, with 25(OH)D3 being the primary metabolite. 25(OH)D3 exerts its physiological effects through binding to the vitamin D receptor (VDR), which is widely distributed in sleep-regulating brain regions including the hypothalamus, prefrontal

cortex, substantia nigra, pontine reticular nucleus, and periaqueductal gray matter [36]. Research shows that 25(OH)D3-VDR binding promotes synthesis of multiple neurotransmitters including dopamine, norepinephrine, glutamate, GABA, and serotonin, and upregulates glial cell line-derived neurotrophic factor expression, which is crucial for development and differentiation of midbrain dopaminergic neurons, thereby influencing cognitive function and sleep-wake cycles [37]. Our results demonstrate that serum 25(OH)D3 levels decrease progressively with increasing insomnia severity. A meta-analysis showed that vitamin D levels are inversely associated with sleep disorder risk, with significantly increased risk when vitamin D falls below 20 ng/mL [38]. Intervention studies in veterans found that vitamin D supplementation (50,000 IU/week) increased total sleep time [39], and another meta-analysis showed that vitamin D supplementation (50,000 IU every two weeks for eight weeks) improved sleep quality in patients with sleep disorders [40], collectively indicating vitamin D' s important role in sleep regulation.

Our correlation analysis further demonstrated positive associations between MMSE/MoCA scores and 25(OH)D3 levels, suggesting that cognitive impairment in elderly chronic insomnia patients is associated with reduced serum 25(OH)D3. The underlying mechanisms may involve effects on neurotrophic factor expression and neurotransmitter synthesis, as well as vitamin D' s influence on hippocampal neuronal development. Animal studies have shown that 25(OH)D3 enhances neural cadherin expression, promoting axonal growth in hippocampal neurons and facilitating memory formation [41]. Additionally, vitamin D supplementation can modulate inflammatory cytokine production during aging, particularly reducing TNF-α levels in the frontal lobe and hippocampus, thereby protecting against age-related spatial memory deficits [42]. Vitamin D also downregulates pro-inflammatory cytokine expression and reduces TNF-α synthesis, functioning as an immunomodulator [43].

In summary, cognitive impairment in elderly patients with chronic insomnia may be associated with insomnia severity, decreased serum 25(OH)D3 levels, and elevated TNF-α levels. Appropriate vitamin D supplementation may improve sleep quality and cognitive function through multiple pathways while modulating inflammatory responses and reducing TNF-α levels, offering potential clinical value for preventing and treating cognitive impairment in elderly chronic insomnia patients. However, this study had a relatively small sample size, and polysomnography was not performed due to the special characteristics of the elderly population. More direct evidence is needed regarding the relationship between 25(OH)D3 and TNF-α alterations and cognitive impairment in elderly chronic insomnia patients. Additionally, due to poor compliance in elderly populations and to simplify assessment procedures, the Insomnia Severity Index was not evaluated. Future research should expand sample sizes, optimize methodologies, and further explore the mechanisms of cognitive impairment in elderly chronic insomnia patients.

Author Contributions

Wu Zixing: conceptualization, manuscript writing, English revision; Tao Shimeng and He Youjun: data collection; Cai Chuanyun: statistical analysis; Jiang Wei and Hu Xin: research proposal, study design, final manuscript revision, overall responsibility.

Conflicts of Interest: None declared.

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Tables

Table 1 Comparison of General Characteristics and PSQI Scores Among Three Groups

Group	Age (years)	Sex (M/F)	Disease Duration (years)	Education (years)	GDS-15 Score	GAD-7 Score	PSQI Score
Mild Insomnia	72.4$±5.1|14/18|9.8±4.3|12.0±3.2|6.7±1.8|7.3±1.4|18.3±1.2||*ModerateInsomnia*|72.2±4.5|18/20|10.1±4						
value		0.092	0.023	0.721	0.098	0.027	0.002

Note: GDS-15=Geriatric Depression Scale-15, GAD-7=Generalized Anxiety Disorder Scale-7, PSQI=Pittsburgh Sleep Quality Index. P<0.05 vs. mild insomnia group; P<0.05 vs. moderate insomnia group; ^{2} value.

Table 2 Comparison of PPG Sleep Parameters Among Three Groups (mean ± SD)

Group	Total Sleep Time (min)	Sleep Latency (min)	Sleep Efficiency (%)	Arousal Frequency (times)
Mild Insomnia	375.16$±62.45\|28.44±10.18\|71.25±16.53\|9.34±3.31\|\|*ModerateInsomnia*\|354.27±78.33\|36.53±14.49^a|63			
P value	<0.001	<0.001	<0.001	<0.001

Note: P<0.05 vs. mild insomnia group; P<0.05 vs. moderate insomnia group; PPG=photoplethysmography.

Table 3 Comparison of Cognitive Function Among Three Groups (mean ± SD, points)

Group	MMSE Score	MoCA Score
Mild Insomnia	27.19$±1.87\|25.91±2.02\|\|*ModerateInsomnia*\|25.82±2.15^a\|24.47±2.01^a||*SevereInsomnia*|2	
P value	<0.001	<0.001

Note: P<0.05 vs. mild insomnia group; P<0.05 vs. moderate insomnia group; MMSE=Mini-Mental State Examination, MoCA=Montreal Cognitive Assessment.

Table 4 Comparison of Serum 25(OH)D3 and TNF-α Levels Among Three Groups (mean ± SD)

Group	n	25(OH)D3 (ng/mL)	TNF-α (pg/mL)
Mild Insomnia	32	53.29$±16.76|428.63±41.44||*ModerateInsomnia*|38|41.61±12.33[a]|494.38±50.37[a]||*Severe*	
P value	-	<0.001	<0.001

Note: P<0.05 vs. mild insomnia group; P<0.05 vs. moderate insomnia group; 25(OH)D3=25-hydroxy vitamin D3, TNF-α=tumor necrosis factor-α.

Table 5 Correlation Analysis of Cognitive Function with Insomnia Severity, Sleep Parameters, and Serum Markers in Elderly Chronic Insomnia Patients

Variable	MMSE Score	MoCA Score
Insomnia Severity	r=-0.512, P<0.001	r=-0.489, P<0.001
Total Sleep Time	r=0.421, P<0.001	r=0.398, P<0.001
Sleep Latency	r=-0.356, P<0.001	r=-0.341, P<0.001
Sleep Efficiency	r=0.445, P<0.001	r=0.412, P<0.001
25(OH)D3	r=0.378, P<0.001	r=0.365, P<0.001
TNF-α	r=-0.433, P<0.001	r=-0.421, P<0.001

Note: Figure translations are in progress. See original paper for figures.