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Clinical study

Correlation between serum 25(OH)D and cognitive impairment in Parkinson's disease

Han Wu, Hafiz Khuram Raza, Zhen Li, Zeheng Li, Jie Zu, Chuanying Xu, Di Yang, Guiyun Cui *

Department of Neurology, The Affiliated Hospital of Xuzhou Medical University, No. 99 Huaihai West Road, Xuzhou, Jiangsu 221000, People's Republic of China

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ABSTRACT

This study aimed to investigate the relationship between serum 25(OH)D and cognitive impairment in patients with Parkinson's disease (PD), hoping to provide possible ideas for the diagnosis and prevention of PD with cognitive impairment. Vitamin D is a neurosteroid with neurotrophic and neuroprotective functions, playing an important role in PD and its progression. In the present study, serum 25(OH)D levels were significantly decreased in PD patients (45.86 ± 14.81 nmol/L)compared to healthy controls(56.54 ± 14.00 nmol/L) ($P < 0.001$), and significant differences were also observed in PD patients with normal cognition (PD-NC), PD patients with mild cognitive impairment (PD-MCI)and PD patients with dementia (PDD)($P < 0.05$). Moreover, there was a positive correlation between serum 25(OH)D levels and Montreal cognitive assessment(MoCA) scores ($r = 0.489$,$P < 0.001$).The increased serum 25(OH)D was an independent protective factor of cognitive impairment in PD ($OR = 0.949$, $P = 0.005$), and the sensitivity, specificity, and AUC under the ROC curve area of serum 25(OH)D were 53.3%, 86.5%, and 0.713, respectively. These findings support the relationship between cognitive impairment and Vitamin D in PD patients. Serum 25(OH)D may be a useful biomarker for diagnosing cognitive impairment in patients with PD.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder [1]. Cognitive impairment is one of the most common and important non-motor symptoms and can occur at any stage of PD. Moreover, it is associated with poor quality of life, so its identification and intervention have significant clinical implications. Vitamin D is a neurosteroid whose receptor is ubiquitously expressed in the nervous system in addition to its traditional calcium-related effects. It can regulate not only nerve growth factors and neurotransmitters but also neurotoxic pathways and mitochondrial function, having neurotrophic and neuroprotective functions [2,3]. Inadequacy of vitamin D in the circulation may lead to nigral dysfunction and its apoptosis. This fact was confirmed in knockout mice, as well as in cell culture [4–7].

In recent years, numerous studies have shown that serum vitamin D plays a vital role in PD and its progression [8–11]. Low levels of vitamin D increased the risk of PD, and serum vitamin D levels were negatively correlated with the severity of PD, suggesting a predictive significance of serum vitamin D levels on the motor severity of the disease. In addition, several observational studies in multiple populations, including healthy people, MCI patients, and patients with neurodegenerative diseases, have shown an association between low vitamin D levels and cognitive impairment [12–15]. Therefore, it is reasonable to argue that vitamin D not only modifies the susceptibility to PD but also affects the cognitive impairment of PD patients.

However, the association between serum 25(OH)D and cognitive impairment in PD patients has been less studied, and the conclusions have been inconsistent [8,11,16]. It is well-known that serum 25(OH)D is susceptible to sunlight exposure, which previous studies have often overlooked. So, we designed a cross-sectional study in order to evaluate the relationship between serum 25(OH)D and cognitive impairment based on the inclusion of sunlight exposure, hoping to provide possible ideas for the diagnosis and prevention of PD with cognitive impairment.

2. Methods

2.1. Population

This prospective, observational, cross-sectional cohort study was conducted between December 2019 and May 2021. Patients suffering

* Corresponding author.
E-mail address: teachercuigy@126.com (G. Cui).

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from PD, who were admitted to the Parkinson's Center in the Affiliated Hospital of Xuzhou Medical University, diagnosed by the recommended criteria of the International Parkinson and Movement Disorder Society (MDS) in 2015, were all considered eligible for inclusion [17]. We excluded patients with the following features: history of familial PD; the use of dietary supplements containing vitamin D in the previous six months; disorders such as aphasia, deafness, delirium, major depression, mental disorders which may affect cognitive function and assessment. The PD patients were then further divided into PD-NC, PD-MCI, and PDD groups according to the diagnostic criteria for PD-MCI and PDD recommended by the MDS [18–19].In addition, 70 age- and sex-matched healthy individuals examined at our hospital's health examination center during the same period were selected as the healthy control group (HC). This study was reviewed and approved by the ethics committee of the affiliated hospital of Xuzhou Medical University, and all subjects voluntarily signed an informed consent form after knowing the contents of the study.

2.2. Data collection

Anthropometry and medical history – Anthropometry includes age, gender, alcohol consumption, smoking, and BMI. Medical history mainly includes whether there is a history of hypertension and diabetes.

Sunlight exposure – Patients or caregivers were asked, "Please recall the daily direct sunlight exposure time outdoors for recent seven days from yesterday, and write it down day by day." (Required to be accurate to 0.5 h). These numbers were summed and then divided by 7 to calculate the average daily sunlight exposure for nearly a week.

Evaluation of symptoms in PD patients – The following clinical parameters were collected: the rating of motor symptoms using the part-III scores of the Unified Parkinson Disease Rating Scale (UPDRS); disease severity by the Hoehn-Yahr (H-Y) staging system [20],global cognitive functions using the MoCA.

Measurement of serum 25(OH)D – 3 ml of fasting venous blood was collected from the hospitalized PD patients in the early morning of the following morning and the control group on the day of the health examination, followed by centrifugation at 3000 R/min for 5 min, and the serum was separated and stored in a − 80 °C freezer to be tested centrally. The 25(OH)D content of the serum was detected by ELISA. Human 25(OH)D kit was purchased from Guangzhou Phicon biotech Co., and the operation procedures were performed strictly according to the kit instructions.

Statistical analysis – Statistical analysis was performed using SPSS22.0. The measurement data that conformed to normal distribution were described by mean ± standard deviation (x ± s), and the independent samples *t*-test was used to compare data between two groups. The data of the three groups were compared by one-way ANOVA. Measurements that did not follow a normal distribution were expressed as a median and interquartile range, counts were statistically described using rate (%), and a chi-square test was used for the data comparison. Pearson correlation analysis was used to test the correlation between serum 25(OH)D and cognitive (MoCA scores) in the PD group. ROC curves were used to determine the diagnostic value of serum 25(OH)D in PD patients with cognitive impairment. $P < 0.05$ was considered statistically significant.

3. Results

3.1. General data and serum 25(OH)D in each group

The comparison of demographic, clinical, and laboratory data of study subjects in each group is shown in Table 1 and Table 2. There were no significant differences in age, gender, BMI, years of education, smoking, drinking, sunlight exposure, hypertension, and diabetes between the PD and control groups ($P > 0.05$). Serum 25(OH)D was significantly decreased in PD patients compared to controls ($P < 0.001$) (Table 1). When comparing PD-NC, PD-MCI, and PDD, there was no significant difference in age, BMI, smoking, drinking, sunlight exposure, hypertension, diabetes, or disease duration *($P > 0.05$)*. Years of education, MoCA score, and serum 25(OH)D were significantly lower in the PD-MCI and PDD groups compared with the PD-NC group ($P < 0.05$). Compared with the PD-MCI group, the serum 25(OH)D level in the PDD group was lower with significant differences ($P < 0.05$) (Table 2).

Table 1
Comparison of general data and serum 25(OH)D between patients and control groups

Characteristic	Healthy controls (n = 70)	PD patients (n = 112)	*P*
Age (years)	66.7 ± 8.7	65.0 ± 8.0	0.165
Gender, male/female	38/32	69/43	0.329
Years of education (year)	9.0(6.0,12.0)	9.0(6.0,12.0)	0.05
Body mass index (kg/m^2)	23.42 ± 3.10	24.03 ± 3.26	0.209
Smoking history [n (%)]	6(8.6)	13(11.6)	0.515
Drinking history [n (%)]	8(11.4)	13(11.6)	0.971
Hypertension [n(%)]	14(20.0)	26(23.2)	0.61
Diabetes mellitus [n (%)]	4(5.7)	5(4.5)	0.105
Sunlight exposure (h/d)	4.08 ± 1.25	3.98 ± 1.19	0.566
25(OH)D (nmol/L)	56.54 ± 14.00	45.86 ± 14.81	**< 0.001**

Table 2
Comparison of clinical characteristics and serum 25(OH)D between PD-NC, PD-MCI and PDD

Characteristic	PD-NC (n = 37)	PD-MCI (n = 51)	PDD (n = 24)	*P*
Age (years)	62.8 ± 8.9	65.3 ± 6.7	67.6 ± 8.3	0.058
Gender,male/female	28/9	31/20	10/14	**0.028**
Years of education (year)	9.0 (9.0,12.0)	9.0 (6.0,11.5)*	7.0 (0.0,9.0)*	**0.002**
Body mass index (kg/m^2)	23.68 ± 2.99	24.38 ± 3.77	23.83 ± 2.40	0.580
Smoking history [n (%)]	5 (13.5)	5 (9.8)	3 (12.5)	0.856
Drinking history [n (%)]	6 (16.2)	5 (9.8)	2 (8.3)	0.555
Hypertension [n (%)]	7 (18.9)	12 (23.5)	7 (29.2)	0.650
Diabetes mellitus [n(%)]	2 (5.4)	2 (3.9)	1 (4.2)	0.943
Disease duration (year)	7.1 ± 3.6	8.0 ± 4.4	7.8 ± 5.1	0.383
H-Y stage	2.5 (2.0,3.0)	3.0 (2.0,3.0)	3.0 (2.0,3.5)	0.500
UPDRS-III score	42 (33,57)	54 (35,63)	54 (40,67)	0.157
MoCA score	26 (26,28)	21 (18,23) ***	12 (9,15) ***△△△	**< 0.001**
Sunlight exposure (h/d)	4.13 ± 1.10	4.04 ± 1.29	3.60 ± 1.07	0.210
25(OH)D (nmol/L)	53.67 ± 15.19	44.57 ± 13.13*	36.53 ± 11.37***△	**< 0.001**

compared to the PD-NC,*$P < 0.05$,***$P < 0.001$.
compared to the PD-MCI,△$P < 0.05$,△△△$P < 0.001$.
PD-NC: Parkinson's disease patients with normal cognition.
PD-MCI: Parkinson's disease patients with mild cognitive impairment.
PDD: Parkinson's disease patients with dementia.

3.2. Correlation analysis between serum 25(OH)D and clinical features

The correlation analysis showed that serum 25(OH)D was negatively correlated with age and positively correlated with years of education

and MoCA scores ($P < 0.05$) in PD patients (Table 3). After adjusting for age, gender, BMI, years of education and sunlight exposure, partial correlation analysis was used to show that serum 25(OH)D was still positively associated with MoCA ($P < 0.001$).

3.3. Regression analysis between serum 25(OH)D and the occurrence of cognitive impairment in PD patients

Three regression models were constructed with the presence or absence of cognitive impairment as dependent variables (yes = 1, no = 0). The results of binary logistic regression analysis using these three model indicators as independent variables showed that higher serum 25 (OH)D was an independent protective factor for the cognitive impairment in PD(*OR* = 0.949, 95%*CI*=(0.915–0.984), $P = 0.005$). (Table 4).

3.4. ROC curve of serum 25(OH)D in diagnosing the occurrence of cognitive impairment in PD patients

The ROC curve for serum 25(OH)D in diagnosing the occurrence of cognitive impairment in PD patients is shown in Fig. 1. The area under the curve was 0.713 (95% *CI* 0.616–0.810), and the optimal cutoff value was 40.75 nmol/L with 53.3% sensitivity and 86.5% specificity. (Fig. 1).

4. Discussion

This is one of the few studies investigating the association between serum 25(OH)D and cognitive impairment in Chinese PD patients. This study showed decreased serum 25(OH)D in PD patients compared to healthy controls and no significant differences in light hours between the two groups, suggesting that there may be some endogenous alteration in serum 25(OH)D in PD patients. This is similar to the study by Wang L et al. [10]. However, compared with previous studies, both healthy controls and PD patients in this study had more prolonged sunlight exposure, which may be related to differences in local lifestyle habits and latitude of the area.

Furthermore, this study found no significant differences in disease duration and UPDRS-III score among the three groups, including PD-NC, PD-MCI, and PDD, but serum 25(OH)D decreased in turn, and partial correlation analysis showed that serum 25(OH)D was positively correlated with MoCA scores of the patients ($r = 0.489$, $P < 0.001$), which remained significant after adjusting for age, gender and BMI ($r = 0.383$, $P < 0.001$). Binary logistic regression analysis showed that increased serum 25(OH)D was an independent protective factor for cognitive impairment in PD. This further suggests that low serum 25(OH)D may be involved in the occurrence and development of cognitive impairment in PD patients. This is consistent with the findings of Barichella M et al. [21]. The underlying mechanisms of the association between 25(OH)D and cognitive impairment in PD may involve Amyloidβ (Aβ) deposition and inflammatory oxidative stress. The findings have shown that

Table 3
Correlation between serum 25(OH)D and each clinical indicator in the PD patients

variate	25(OH)D		25(OH)D (age, gender, BMI, years of education and sunlight exposure adjusted)	
	r	*P*-value	*r*	*P*-value
Age	−0.099	0.298	–	–
Gender	−0.190	**0.045**	–	–
BMI	−0.177	0.062	–	–
Years of education	0.232	**0.014**	–	–
Sunlight exposure	0.143	0.054	–	–
Disease duration	0.09	0.346	0.094	0.333
H-Y stage	−0.102	0.283	−0.084	0.389
UPDRS-III score	−0.082	0.392	−0.094	0.336
MoCA score	0.489	**<0.001**	0.358	**<0.001**

Table 4
Association between serum 25(OH)D and the risk of incident cognitive impairment in PD patients by binary logistic regression analysis

Model	*B*	*SE*	*Wald*χ^2	*OR(95% CI)*	*P*-value
Model 1	−0.059	0.016	13.33	0.943(0.914–0.973)	<0.001
Model 2	−0.056	0.017	10.67	0.946(0.915–0.978)	0.001
Model 3	−0.052	0.019	7.819	0.949(0.915–0.984)	0.005

Model 1:Unadjusted.
Model 2:After adjusting for age and sex.
Model 3:After adjustment for age, sex, BMI, years of education, disease duration and sunlight exposure.

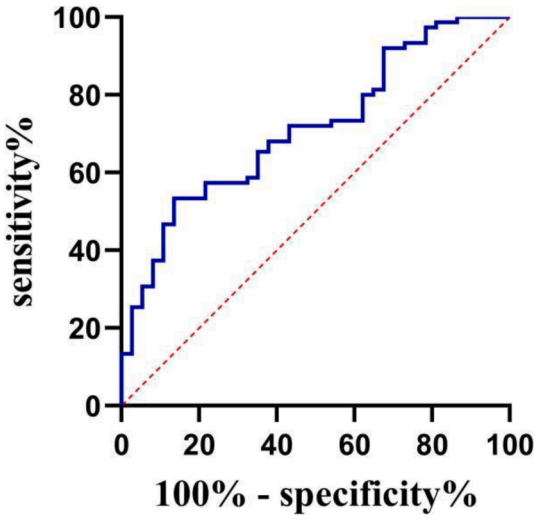

Fig. 1. ROC curve of serum 25 (OH)D in diagnosing the occurrence of cognitive impairment in PD patients

Vitamin D is beneficial for the alleviation of Aβ neurotoxicity, and it might elicit its neuroprotection against Aβ neurotoxicity through an interplay with GDNF-signaling [22]. In addition, vitamin D reduced the activity of the Aβ producing enzymes BACE1 and γ-secretase, increasing the activity of its degrading enzyme, neprilysin, to decreased Aβ-production and increased Aβ-degradation in neuroblastoma cells or vitamin D deficient mouse brains [23]. A prospective cohort study of patients with MCI found that vitamin D supplementation increased plasma levels of Aβ1-40 and improved cognitive function in patients, suggesting that Vitamin D may improve cognitive impairment by participating in the clearance of Aβ in the brain [24]. Moreover, vitamin D has anti-inflammatory effects, and studies have shown that vitamin D can inhibit the production of pro-inflammatory factors such as TNF-α and IL-6 from macrophages by targeting the MAPK pathway [25]. Vitamin D can also increase the expression of IL-10, creating a feedback loop via SOCS3 that downregulates the pro-inflammatory immune response by activated microglia, thus alleviating the nervous system inflammatory response [26]. In a model of systemic inflammatory response constructed by intraperitoneal injection of lipopolysaccharide (LPS), the passive avoidance and spatial learning ability of rats decreased. IL-6 and lipid peroxide expression, after pretreatment with oral vitamin D, were decreased, whereas the activity of catalase (CAT), superoxidase dismutase (SOD) and total thiol were significantly increased in hippocampal tissue, indicating that vitamin D had a protective effect against inflammation-induced impairment of memory function by inhibiting oxidative stress and inflammation in the hippocampus [27]. Moreover, low vitamin D status may be associated with the regulation of synaptic transmission and remodeling effects on the extracellular matrix and maybe with disruption of hippocampal structural connectivity, leading to synaptic abnormalities that contribute to cognitive impairment in

patients [3,28–29].

A *meta*-analysis showed that only 2% of the population with PD-NC developed dementia within three years, but 20% of the population with PD-MCI developed dementia [30]. Detection of mild cognitive decline in PD patients and possible interventions is of great clinical importance. In this study, we found that the area under the curve of serum 25(OH)D in diagnosing the occurrence of cognitive impairment in PD patients by ROC curve analysis was 0.713 (95% *CI* 0.616–0.810). Serum 25(OH)D may be helpful for us to diagnose PD patients with cognitive impairment. To date, there are fewer drugs worldwide for cognitive impairment in PD patients, and only the rivastigmine, a cholinesterase inhibitor, is approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of PDD [31]. It remains to be determined whether vitamin D supplementation is beneficial in delaying the development of cognitive impairment in patients with PD. However, long-term vitamin D supplementation carries a low risk and many possible benefits for patients [32]. Therefore, evaluating vitamin D for patients with PD and supplementing vitamin D for deficient patients are worth trying.

The main limitation of the study is its cross-sectional design, which did not allow us to identify causal relationships, so prospective studies are needed to clarify a causal relationship. Moreover, we used the level I criteria for PD-MCI of MDS to evaluate patients in our present study. However, the level II criteria can increase sensitivity and allow full subtyping of PD-MCI [19].

In conclusion, our study shows that serum 25(OH)D is decreased and associated with cognitive impairment in patients with PD compared with normal individuals, and it may be a useful biomarker for the diagnosis of cognitive impairment in PD patients. But the causal relationship between serum 25(OH)D and cognitive impairment in PD is unclear, which needs further demonstration with a larger sample and better-designed cohort study.

Author contributions

All authors have contributed substantially to the conception, design, drafting of the article, and approved the final version of the manuscript to be submitted. All authors have jointly decided to designate Prof Dr. Cui to be responsible for decision-making regarding the presence of authors and the order of their presence in the manuscript. Prof Dr. Cui has also been selected by all authors to be responsible for all future communication with the journal regarding this manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Balestrino R, Schapira AHV. Parkinson disease. Eur J Neurol 2020;27(1):27–42.
[2] Nagpal S, Na S, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. Endocr Rev 2005;26:662–87.
[3] Mayne PE, Burne THJ. Vitamin D in Synaptic Plasticity, Cognitive Function, and Neuropsychiatric Illness. Trends Neurosci 2019;42(4):293–306.
[4] Wang J-Y, Wu J-N, Cherng T-L, Hoffer BJ, Chen H-H, Borlongan CV, et al. Vitamin D(3) attenuates 6-hydroxydopamine-induced neurotoxicity in rats. Brain Res 2001;904(1):67–75.
[5] Burne T, Mcgrath J, Eyles D, Mackaysim A. Behavioural characterization of vitamin D receptor knockout mice. Behav Brain Res 2005;157(2):299–308.
[6] Smith MP, Fletcher-Turner A, Yurek DM, Cass WA. Calcitriol Protection against Dopamine Loss Induced by Intracerebroventricular Administration of 6-Hydroxydopamine. Neurochem Res 2006;31(4):533–9.
[7] Mizwicki MT, Liu G, Fiala M, Magpantay L, Sayre J, Siani A, et al. 1α,25-Dihydroxyvitamin D3 and Resolvin D1 Retune the Balance between Amyloid-β Phagocytosis and Inflammation in Alzheimer's Disease Patients. JAD 2013;34(1):155–70.
[8] Zhang H-J, Zhang J-R, Mao C-J, Li K, Wang F, Chen J, et al. Relationship between 25-Hydroxyvitamin D, bone density, and Parkinson's disease symptoms. Acta Neurol Scand 2019;140(4):274–80.
[9] Wang J, Yang D, Yu Y, Shao G, Wang Q. Vitamin D and Sunlight Exposure in Newly-Diagnosed Parkinson's Disease. Nutrients 2016;8:142.
[10] Wang L, Evatt ML, Maldonado LG, Perry WR, Ritchie JC, Beecham GW, et al. Vitamin D from different sources is inversely associated with Parkinson disease: VITAMIN D2, D3, AND PARKINSON'S DISEASE. Mov Disord 2015;30(4):560–6.
[11] Sleeman I, Aspray T, Lawson R, Coleman S, Duncan G, Khoo TK, et al. The Role of Vitamin D in Disease Progression in Early Parkinson's Disease. J Parkinsons Dis 2017;7(4):669–75.
[12] Miller JW, Harvey DJ, Beckett LA, Green R, Farias ST, Reed BR, et al. Vitamin D Status and Rates of Cognitive Decline in a Multiethnic Cohort of Older Adults. JAMANeurol 2015;72(11):1295.
[13] Shih E-J, Lee W-J, Hsu J-L, Wang S-J, Fuh J-L. Effect of vitamin D on cognitive function and white matter hyperintensity in patients with mild Alzheimer's disease. Geriatr Gerontol Int 2020;20(1):52–8.
[14] Pavlovic A, Abel K, Barlow CE, Farrell SW, Weiner M, DeFina LF. The association between serum vitamin d level and cognitive function in older adults: Cooper Center Longitudinal Study. Prev Med 2018;113:57–61.
[15] Lee EY, Lee SJ, Kim KM, Yun YM, Song BM, Kim JE, et al. Association of metabolic syndrome and 25-hydroxyvitamin D with cognitive impairment among elderly Koreans. Geriatr Gerontol Int 2017;17(7):1069–75.
[16] Santangelo G, Raimo S, Erro R, Picillo M, Amboni M, Pellecchia MT, et al. Vitamin D as a possible biomarker of mild cognitive impairment in parkinsonians. Aging Ment Health 2021;25(11):1998–2002.
[17] Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease: MDS-PD Clinical Diagnostic Criteria. Mov Disord 2015;30(12):1591–601.
[18] Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007;22(12):1689–707.
[19] Litvan I, Goldman JG, Tröster AI, Schmand BA, Weintraub D, Petersen RC, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines : PD-MCI Diagnostic Criteria. Mov Disord 2012;27(3):349–56.
[20] Opara J, Małecki A, Małecka E, Socha T. Motor assessment in Parkinson's disease. Ann Agric Environ Med 2017;24(3):411–5.
[21] Barichella M, Cereda E, Iorio L, et al. Clinical correlates of serum 25-hydroxyvitamin D in Parkinson's disease. Nutr Neurosci 2020:1–9.
[22] Lin CI, Chang YC, Kao NJ, Lee WJ, Cross TW, Lin SH. 1,25(OH)(2)D(3) Alleviates Aβ(25-35)-Induced Tau Hyperphosphorylation, Excessive Reactive Oxygen Species, and Apoptosis Through Interplay with Glial Cell Line-Derived Neurotrophic Factor Signaling in SH-SY5Y Cells. Int J Mol Sci 2020;21.
[23] Grimm M, Thiel A, Lauer A, Winkler J, Lehmann J, Regner L, et al. Vitamin D and Its Analogues Decrease Amyloid-β (Aβ) Formation and Increase Aβ-Degradation. Int J Mol Sci 2017;18(12):2764.
[24] SanMartín CD, Henriquez M, Chacon C, Ponce DP, Salech F, Rogers NK, et al. Vitamin D Increases Aβ140 Plasma Levels and Protects Lymphocytes from Oxidative Death in Mild Cognitive Impairment Patients. CAR 2018;15(6):561–9.
[25] Li W, Liu Z, Tang R, Ouyang S, Li S, Wu J. Vitamin D inhibits palmitate-induced macrophage pro-inflammatory cytokine production by targeting the MAPK pathway. Immunol Lett 2018;202:23–30.
[26] Boontanrart M, Hall SD, Spanier JA, Hayes CE, Olson JK. Vitamin D3 alters microglia immune activation by an IL-10 dependent SOCS3 mechanism. J Neuroimmunol 2016;292:126–36.
[27] Mokhtari-Zaer A, Hosseini M, Salmani H, Arab Z, Zareian P. Vitamin D3 attenuates lipopolysaccharide-induced cognitive impairment in rats by inhibiting inflammation and oxidative stress. Life Sci 2020;253:117703.
[28] Al-Amin M, Bradford DanaKai, Sullivan RKP, Kurniawan ND, Moon Y, Han S-H, et al. Vitamin D deficiency is associated with reduced hippocampal volume and disrupted structural connectivity in patients with mild cognitive impairment. Hum Brain Mapp 2019;40(2):394–406.
[29] Taghizadeh M, Talaei SA, Djazayeri A, Salami M. Vitamin D supplementation restores suppressed synaptic plasticity in Alzheimer's disease. Nutr Neurosci 2014;17(4):172–7.
[30] Saredakis D, Collins-Praino LE, Gutteridge DS, Stephan BCM, Keage HAD. Conversion to MCI and dementia in Parkinson's disease: a systematic review and meta-analysis. Parkinsonism Related Disord 2019;65:20–31.
[31] Sun C, Armstrong MJ. Treatment of Parkinson's Disease with Cognitive Impairment: Current Approaches and Future Directions. Behav Sci (Basel) 2021;11.
[32] Fullard ME, Duda JE. A Review of the Relationship Between Vitamin D and Parkinson Disease Symptoms. Front Neurol 2020;11:454.