



Research Progress on the Correlation Between Vitamin D and Neurological Disorders

Mengjie WANG^{1,2}, Changmeng CUI², Feng JIN^{2,3}

¹Jining Medical University, Clinical Medical College, Jining, Shandong, China

²Affiliated Hospital of Jining Medical University & Shandong Provincial Key Laboratory of Stem Cells and Neuro-oncology, Department of Neurosurgery, Jining, Shandong, P.R. China

³University of Virginia, Department of Radiology and Medical Imaging, Charlottesville, VA, USA

Corresponding author: Feng JIN ✉ jinfeng1223@mail.jnmc.edu.cn

ABSTRACT

AIM: To review the correlation between vitamin D (VD) and several common neurological disorders with the aim of providing directions and ideas for using VD to treat neurological disorders.

MATERIAL and METHODS: VD, 1,25-dihydroxyvitamin D₃, stroke, epilepsy, and cognitive dysfunction were used as keywords. The PubMed and Embase databases were searched for articles published from 2010 to 2021. The inclusion criteria were as follows: clear introduction of the research sample, detailed explanation of the sample selection in the research, intervention, and control measures, and available odds ratio and 95% confidence interval. The exclusion criteria were as follows: duplicate reports, defects in research design and poor quality, incomplete data and unclear results, and unmodifiable errors in the statistical method.

RESULTS: Initially, 1,360 articles were retrieved from the PubMed and Embase databases. Finally, 81 articles were included, 76 of which were published within the last 5 years.

CONCLUSION: VD deficiency is very common in the population and is associated with a variety of neurological diseases. VD, a neuroactive steroid, plays an important role in the protection of the central nervous system. In contrast, stroke can cause epilepsy and varying degrees of changes in cognitive function. Furthermore, seizure and epilepsy can cause changes in cognitive function. The degree of alteration in cognitive function affects the occurrence and progression of stroke and epilepsy. Therefore, VD can be used for the comprehensive treatment of neurological diseases.

KEYWORDS: Vitamin D, Stroke, Cerebral apoplexy, Epilepsy, Cognitive impairment

INTRODUCTION

Vitamin D (VD) is a group of fat-soluble steroid derivatives; in the human body, it is mainly present in the form of vitamins D₂ and D₃. Vitamin D₂ is mainly obtained from plant foods. Meanwhile, vitamin D₃ is mainly produced through the ultraviolet radiation-induced conversion of 7-deoxycholesterol in the skin; a small amount is also obtained from food. Both forms of VD require 25-hydroxyvitamin D [25 (OH) 2D], which is produced by 25-hydroxylase in the liver (37). VD then plays an important role in metabolism.

Stroke, also known as cerebral vascular accident, is an acute cerebrovascular disorder. It causes brain tissue

damage due to the sudden rupture of blood vessels in the brain or the inability of blood to flow into the brain because of vascular blockage. Stroke is mainly divided into ischemic and hemorrhagic types. The incidence of ischemic stroke is higher than that of hemorrhagic stroke, accounting for 69.8%–70.8% of all strokes. Cerebral ischemic stroke, also known as cerebral infarction, is associated with blood circulation disorders, ischemia, and hypoxia in the brain caused by localized avascular necrosis or brain tissue softening. Epilepsy is a chronic brain disease characterized by repeated seizures. Seizures are mainly caused by the abnormal discharge of brain neurons. Epilepsy can occur at any age, and its incidence in Taiwan is 5%–7%. This disorder

is repetitive and transient. Cognitive dysfunction refers to one or more impairments related to memory, language, visual space, execution, calculation, and comprehension judgment that affect an individual's daily or social abilities.

In recent years, many studies have confirmed that VD plays a crucial role in neurological disorders. Stroke, epilepsy, and cognitive dysfunction are common neurological disorders that are closely related. This article reviews the correlation between VD and several common neurological disorders with the aim of providing directions and ideas for using VD to treat neurological disorders.

■ VD and STROKE

Participation Mechanism

VD plays a crucial role in stroke. It mainly functions through the VD receptor, which exists in vascular smooth muscle cells, platelets, and many other immune cells. These cells play a critical role in stroke and are the link between VD and stroke. In addition, Eyles et al. (15) observed that a gene encodes a catalytic enzyme in 1.25 (OH) 2D metabolism in neurons and glial cells. Researchers have also conducted experiments at the animal level. Zhou et al. (81) stated that a low VD status is related to renin-angiotensin system (RAS) upregulation in experimental mice and healthy individuals; thus, RAS regulation is another possible mechanism for the effect of VD on stroke.

Relationship Between the VD Level and Stroke

Numerous experiments have supported the effect of VD on stroke. In a cross-sectional study, Talebi et al. (71) showed that a decreased serum vitamin D3 level is related to ischemic stroke occurrence. They demonstrated that patients in the stroke group had lower VD levels than those in the control group (15.1 [8.2–27.9] vs. 22.7 [10.4–39.2], $p=0.004$). Other studies have shown that insufficient VD can increase the stroke risk, and a low plasma 25 (OH) D level is the main risk factor for ischemic stroke. In this study, the odds ratio (OR) for ischemic stroke was 0.98 (95% confidence interval [CI]: 0.86–1.13) (1). In these studies, the type of stroke that was more closely related to VD was ischemic stroke. Gu's (24) analysis of 402 patients with acute stroke revealed that these patients had a high incidence of VD deficiency. Schneider (66) reached a similar conclusion in a study of 382 patients with stroke. Among patients with acute stroke, the incidence of VD deficiency was high, and low VD intake was found as an independent risk factor for stroke. In recent years, supplementary research has been conducted on the form of VD affecting patients with stroke. Feng et al. (17) found that VD deficiency can increase the risk of cerebral small vessel disease in patients with stroke. In their study, they included 234 patients based on MRI load values to evaluate the severity of cerebral small blood vessel lesions. The study results indicated that patients with low 25 (OH) D levels were more likely to have severe white matter lesions (OR: 3.31; 95% CI: 1.74–9.67; $p=0.004$), enlarged perivascular spaces (OR: 2.35; 95% CI: 1.11–6.02, $p=0.046$), and a high total MRI cSVD burden (OR: 3.00; 95% CI: 1.36–6.53, $p=0.006$). Conversely, some studies have suggested that low VD levels

do not increase the stroke risk but affect stroke outcomes and that only severe VD deficiency leads to stroke (8).

VD Level and Stroke Prognosis

As research progressed, VD was also found to be related to stroke prognosis. Nie et al. (56) proposed that the 25 (OH) D level is a prognostic indicator of ischemic stroke after the diagnosis of cardio-cerebrovascular disease. Wajda et al. (74) conducted a retrospective study and reached similar conclusions: The VD level is an important prognostic indicator of ischemic stroke, and the lower the VD level, the worse the prognosis. Wu and He (76) showed that in patients with stroke and severe VD deficiency and those without severe VD deficiency, the mortality rates were 4.81 and 1.89, respectively, with an incidence rate of 2.52, and the probability rates were 4.34 and 1.77, respectively, with an incidence rate of 2.42. Thus, he suggested that low VD levels are related to a poor stroke prognosis. VD has direct and indirect effects on the prognosis of patients. Sayeed et al. (65) observed that VD deficiency can lead to increased blood-brain barrier damage after stroke, stroke severity, and disease complexity. The indirect effects are mainly associated with related stroke complications. In a controlled study of 180 patients with stroke, Wu and He (76) found an independent correlation between VD deficiency and deep vein thrombosis (OR: 4.683, 95% CI: 1.396–15.703, $p=0.012$). In addition, the VD level plays a crucial role in the association between seasons and post-stroke depression (24).

VD as An Adjuvant Treatment for Stroke

Many researchers have studied the effects of VD on adjuvant stroke. In this study of the effect of VD as an adjuvant treatment for cerebral infarction, 105 patients with cerebral infarction were included, and VD was administered continually for 6 months after adjuvant therapy. The analysis showed that the NIHSS score of the intervention group was lower than that of the control group, and the modified Fugl-Meyer motor function score and Barthel index were significantly higher in the former than in the latter. In terms of cerebral hemodynamics, the maximum flow rate, end-diastolic flow rate, and blood flow resistance index of the intervention group were higher than those of the control group. Moreover, the recurrence rates in the intervention group at 1 and 2 years after infarction were significantly lower than those in the control group. The survival rate in the intervention group was also higher than that in the control group. However, another study reached an opposite conclusion (48). VD inhibits proinflammatory factor production through MKP-1 upregulation (79). VD supplementation can suppress proinflammatory cytokine expression and reduce inflammatory responses in patients (22). As a steroid, VD is closely related to nerve function (60) and can effectively promote nerve function recovery after supplementation (78). In addition, a correlation exists between VD and intima-media thickness (IMT) (63). Studies have shown that VD supplementation can also reduce the IMT and plaque area (53). Sultan et al. (70) observed that VD supplementation can improve the hypercoagulable state of platelets and prevent thrombosis. Sufficient VD supplementation after stroke can improve neuromuscular function, increase muscle strength, reduce

fall incidence during recovery, change bone density, and reduce the fracture risk. Views on how VD is supplemented vary. Narasimhan and Balasubramanian (55) found that patients receiving intramuscular VD injection showed a significant improvement in stroke prognosis after 3 months. The SSS score of the intervention group was significantly higher than that of the control group. In contrast, Momosaki et al. (51) found that oral VD supplementation did not improve the rehabilitation of patients after acute stroke. In summary, the use of VD as an adjuvant treatment for cerebral infarction is clinically important (Figure 1).

VD and EPILEPSY

VD Level and Epilepsy

In recent years, the role of VD in epilepsy treatment has received increasing attention. Studies have revealed that during the acute phase of epilepsy and when the condition worsens, vitamin D3 metabolism in the body is dysregulated, and the plasma 25 (OH) D3 level declines rapidly; thus, the VD level can be used as a marker of seizures (27). J  sus et al. (33) conducted a 46-patient study on the VD status of patients with epilepsy and showed that their average VD level was 15.3 ± 99.9% and that 87.0% and 40.0% of the patients had VD deficiency and severe VD deficiency (< 10 ng/mL), respectively. The VD levels in children with epilepsy have been studied. Kija et al. (36) selected 75 children with epilepsy and 75 healthy children for a controlled trial. The analysis showed that the proportion of patients with VD deficiency in the experimental group was 60.3%, whereas that in the control group was 48.5%. The average VD level [24, 25 (OH) 2D3 level] in the experimental group was significantly lower than that in the

control group. These data show that the level of VD affects the occurrence of epilepsy, and this influence is thought to be related to hormones and genes. VD can regulate the expression of dopamine, norepinephrine, serotonin, and other neurotransmitters. These neurotransmitters are susceptible to inducing epilepsy; thus, they can reduce seizure frequency (47,67). In addition, Wang et al. (75) studied the genetic link between VD and epilepsy. This controlled study included 220 patients with epilepsy and 210 healthy individuals. Polymorphisms of different VDBP genotypes were detected by PCR testing, including rs4588, rs7041, rs2298849, and rs2282679. The results indicated that VDBPrs4588 and rs2282679 polymorphisms may play an essential role in the susceptibility to epilepsy in the Chinese Han population.

VD Supplementation and Epilepsy

The medical community has diverse opinions regarding the effect of VD supplementation on epilepsy. In a case-control study, the serum levels of inflammatory factors, such as IL-1  , IL-2, IL-6, IL-8, and TNF-  , in patients with epilepsy were significantly higher than those in the controls. Furthermore, these factors may have synergistic effects on the process of epilepsy. Li (43) found that after vitamins B12 and D were administered to patients with epilepsy, the serum levels of these inflammatory factors were significantly reduced. A controlled study of VD treatment in patients with epilepsy showed that the seizure frequency in the treatment group was reduced by 40% compared with that in the controls (29). In contrast, Tombini et al. (72) pointed out that although studies have indicated that patients with epilepsy have a higher likelihood of VD deficiency than healthy individuals, oral supplementary VD preparations did not reduce the seizure

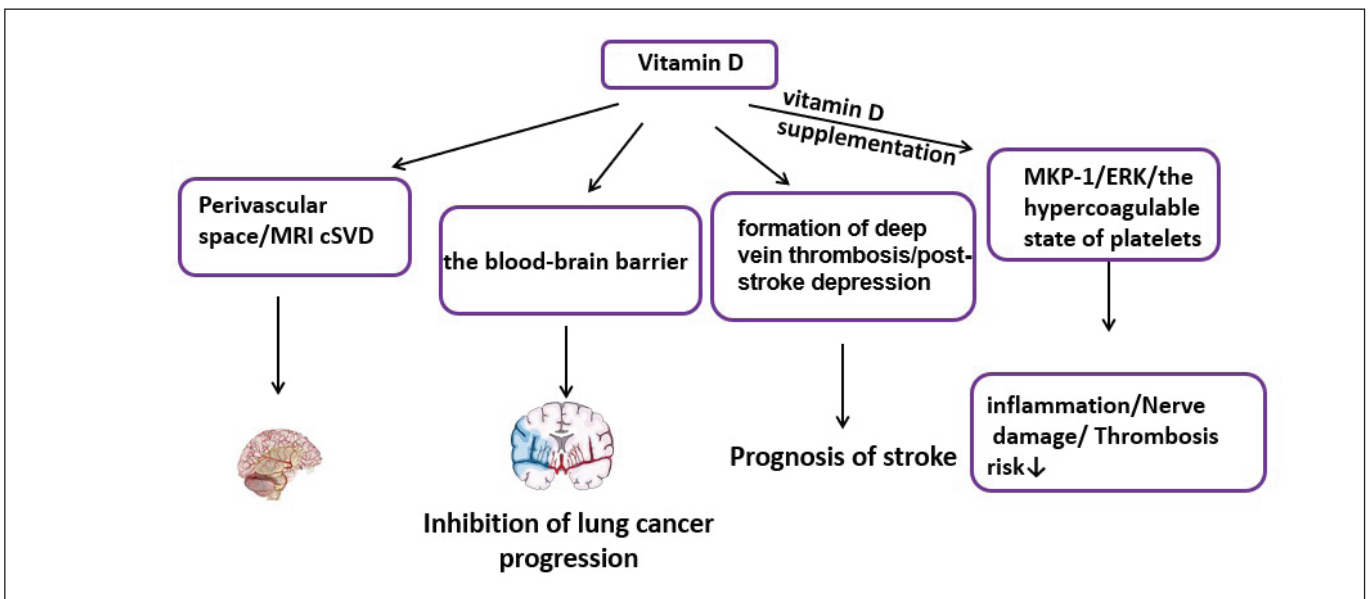


Figure 1: Vitamin D deficiency increases the risk of cerebral small blood vessels. Vitamin D deficiency can lead to increased damage to the blood-brain barrier and increase the severity and complexity of stroke. Vitamin D deficiency is associated with deep vein thrombosis and post-stroke depression. Vitamin D protects nerve insufficiency and neurons by activating ERK. Vitamin D inhibits the production of pro-inflammatory factors by up-regulating MKP-1 and reduces inflammation. Improve the platelet hypercoagulability in the body and prevent thrombosis.

frequency after 3 months. Therefore, more evidence is required to determine whether a direct correlation exists between VD supplementation and seizure frequency.

VD Level and Antiepileptic Drugs

The VD levels are also closely related to the treatment with antiepileptic drugs. Most recent studies have suggested that antiepileptic drugs reduce the VD levels in patients with epilepsy. Lee et al. (42) conducted a study to assess the VD levels in patients taking antiepileptic drugs. Their analysis showed that the VD level decreased significantly compared to that at the start of the study. The average level at the start of the study was 31.1 ± 14.7 ng/mL and dropped to 20.2 ± 14.9 ng/mL during the last test ($p < 0.01$). The detection rate of VD deficiency increased significantly from 56.6% (81/143) at the beginning of the study to 79.0% (113/143) ($p < 0.01$). Other researchers have studied several antiepileptic drugs and arrived at the same conclusion (20). There are many studies on the commonly used antiepileptic drug, sodium valproate. Xu et al. (77) noted that patients with epilepsy treated with sodium valproate had significantly lower average VD levels than healthy individuals, with a standard mean difference of $-0.313 [-0.457, -0.169]$, and their symptoms worsened over time. Durá-Travé and Gallinas-Victoriano (13) conducted a similar experiment to study the association of sodium valproate and levetiracetam with VD deficiency in children with epilepsy. Their cross-sectional clinical study included 90 patients with epilepsy and 244 healthy children. The analysis showed that the VD deficiency rates of the sodium valproate and levetiracetam groups were significantly higher than those of the control group (24.1%, 35.5%:14%; $p < 0.05$). With a decrease in the VD levels, corresponding disorders occur; for example, low VD levels increase the likelihood of sudden epilepsy (71). In addition, studies have shown that antiepileptic drugs can affect bone health by reducing the serum VD level and that VD has certain benefits for the bone health of adult patients with epilepsy (18) (Figure 2).

VD and Cognitive Dysfunction

Participation Mechanism

Cognitive dysfunction refers to the impairment of one or more cognitive functions, such as memory, language, and execution, and affects the daily or social abilities of individuals. Many studies have shown that VD plays a crucial role in cognitive function. The literature shows that VD exerts various effects on the brain through the VD receptor and VD-activating enzyme 1 α -hydroxylase, and these effects are widely present in neurons and glial cells in many cognitive fields of the human brain (9). Moreover, studies have found that VD plays an important role in maintaining brain homeostasis and nerve development (23). Studies have demonstrated that arterial hypertension, endothelial dysfunction, and atherosclerosis are risk factors for cognitive impairment and dementia, among which atherosclerosis plays a key role in cognitive impairment. Reduction in the VD levels affects the activity of macrophages and lymphocytes in atherosclerotic plaques and promotes chronic inflammation of the arterial wall. Therefore, the VD levels are important for protecting against cognitive impairment and dementia. VD activates tryptophan hydroxylase 2 in the brain and inhibits tryptophan hydroxylase 1 transcription in tissues outside the blood-brain barrier. Excessive tryptophan hydroxylase 1 affects digestive system functions, resulting in immune system weaknesses that lead to low serotonin transmission and abnormal social behavior (52).

In recent years, a new hypothesis that VD interacts with the aggregation of the extracellular matrix-peri nerve cell network (PNNS) to regulate brain plasticity has emerged. Hence, VD level imbalance causes a PNNS regulation imbalance to trigger cognition obstacles (49). VD deficiency plays a role in neurodegenerative processes involved in Alzheimer's disease (AD). In the case of severe VD deficiency, a decrease in nerve conduction velocity has been observed (4,9). In addition, VD supplementation was found to reduce the content of

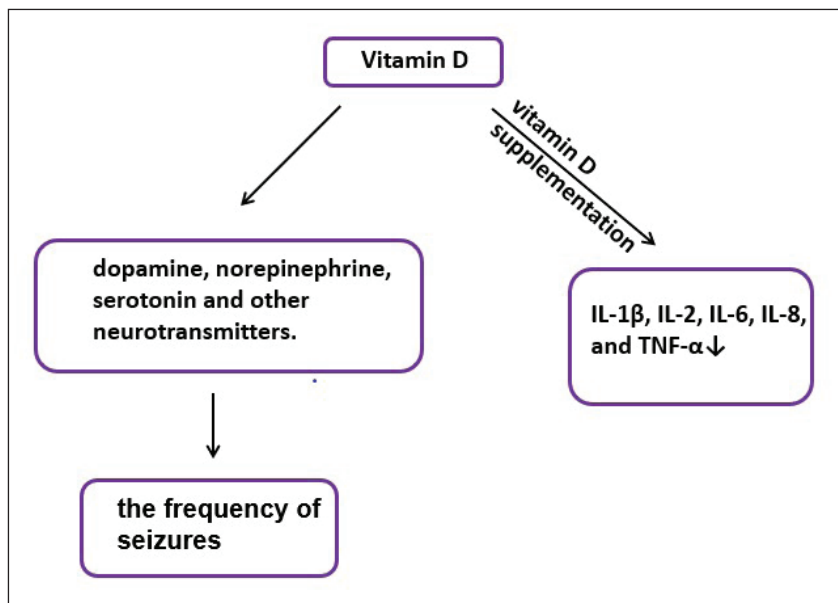


Figure 2: Vitamin D can regulate the expression of dopamine, norepinephrine, serotonin and other neurotransmitters to reduce the frequency of seizures. Serum inflammatory factors such as IL-1 β , IL-2, IL-6, IL-8 and TNF- α , which may have a synergistic effect during epileptic seizures, are significantly reduced after vitamin D supplementation.

hippocampal nuclear factor-B, increase the level of brain-derived neurotrophic factor, regulate blood-brain barrier permeability, and reverse high fat-related cognitive impairment due to blood sugar spikes in an animal experiment (25).

Link Between the VD Level and Cognitive Function

Many studies have examined the relationship between the VD levels and cognitive function, and the perspectives vary considerably. Song and colleagues observed significant differences between an adequate VD group and a VD deficiency group in terms of daytime dysfunction. Sleep is an important factor in this association (69). In addition, relevant studies have demonstrated that the VD levels are significantly and negatively correlated with executive function and that low VD levels can lead to an increased likelihood of cognitive dysfunction in elderly adults and those with dementia (9,31). Shih et al. (68) included 146 patients in a related study and found that the 25 (OH) D level was an independent predictor of the Concise Psychiatric Scale score ($\beta=0.322$, $p<0.001$). A decrease in the (OH) D level reduced the Concise Psychiatric Scale score. In addition, Aspell et al. (6) stated that serum 25 (OH) D may affect brain health. Nagel et al. (54) found that VD deficiency affects cognitive functions in specific areas, such as executive function, vocabulary coding, and visual memory (coding and recall). However, some scholars believe that the VD levels are not associated with cognitive dysfunction. Lee et al. (40) conducted a multiple regression analysis on subject data and found that the association between 25 (OH) D and

cognitive function was not significant. In addition, Gepner (39) stated that low VD levels cannot predict the trajectory of cognitive function.

VD Supplementation and Cognitive Function

Relatively few studies have investigated whether VD supplementation improves cognitive function. After 18 weeks of supplementation with high-dose VD (4000 U/day) in the study by Pettersen, the Beck Depression Scale 2 and a standardized cognitive test package (including a digital modal test and digital span forward and backward tests) were used for the assessment. After learning of the function, spatial visual memory was found to have improved; however, no effect was found on other cognitive fields (58). Jia et al. (34) found that elderly patients with AD taking oral VD (800 IU/day) for 12 months showed improved cognitive function. Regarding supplement dosage, the researchers stated that compared with low-dose VD supplements, high-dose calcium plus VD supplements may have better cognitive effects, and the concise mental state score increased from 0.11 ± 0.72 to 0.14 ± 0.69 (64). Furthermore, animal experiments have shown the potential effect of vitamin D3 supplementation on the cognitive function of diabetic animals (2) (Figure 3).

■ VD and OTHER VASCULAR DISEASES

VD is closely associated with vascular diseases, and its connection with atherosclerosis is particularly important.

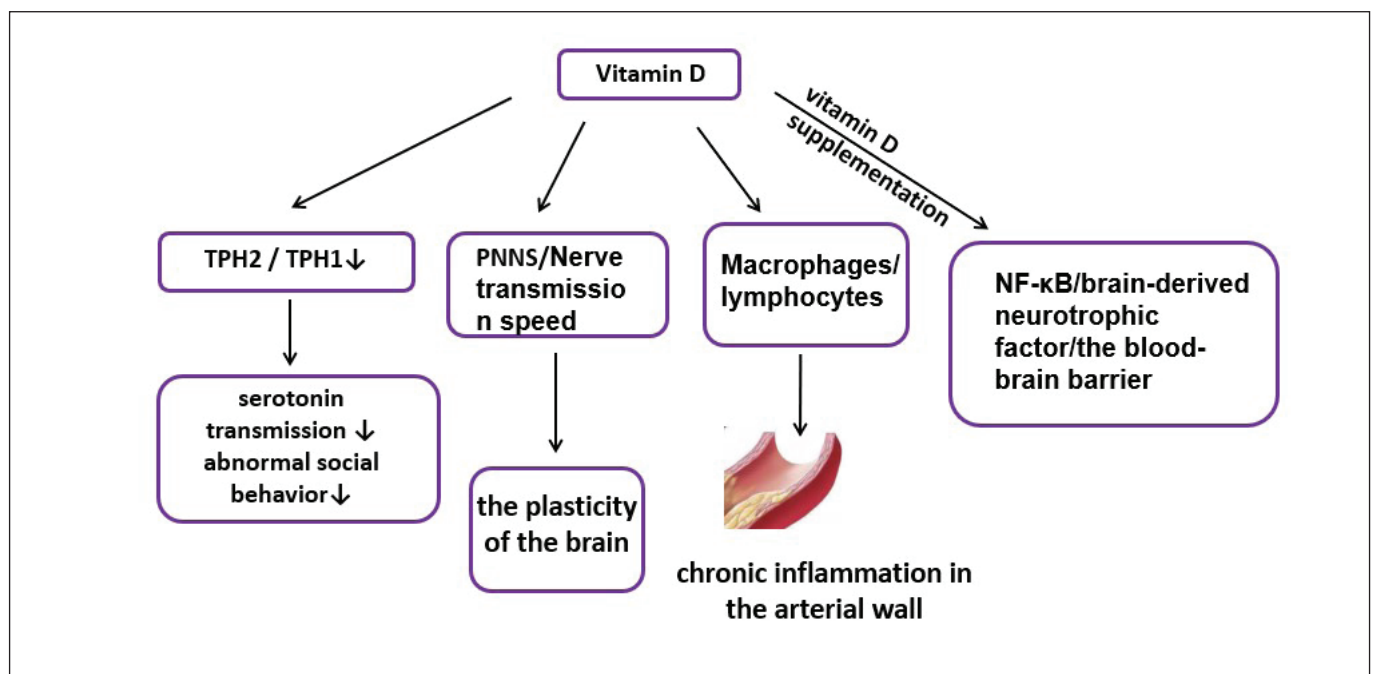


Figure 3: Decline in vitamin D levels will reduce the inhibition of tryptophan hydroxylase 1 (TPH1) transcription, leads to low serotonin transmission and abnormal social behavior. The imbalance of vitamin D levels will cause the imbalance of PNNS regulation to trigger cognition obstacle. The reduction of vitamin D level will affect the activity of macrophages and lymphocytes in atherosclerotic plaques, and promote the occurrence of chronic inflammation in the arterial wall. vitamin D supplementation can reduce the content of NF-κB (hippocampal nuclear factor-B) in the hippocampus, increase the concentration of brain-derived neurotrophic factor, regulate the permeability of the blood-brain barrier, and improve cognitive dysfunction.

Studies have shown that decreased serum 25 (OH) D levels can cause perivascular endothelial dysfunction, leading to accelerated conversion of macrophages to foam cells, which consequently accelerates atherosclerosis (7). Furthermore, studies have found that the 25 (OH) D levels in patients with cardiovascular and cerebrovascular diseases are negatively correlated with the levels of inflammatory markers IL-6 and hypersensitive C-reactive protein (hsCRP), whereas the hsCRP levels are stable with plaque. Further, sex had a negative correlation (11). In addition, Ameri et al. (3) conducted a study on the relationship between VD regulation of circulating insulin-like growth factor (IGF)-1 and carotid IMT. Their analysis showed that circulating IGF-1 in the low VD group was negatively correlated with the carotid IMT (ITM is a sign of vascular aging). In vitro experiments revealed that IGF-1 can promote the inhibitory effect of low-dose VD on H₂O₂-induced oxidative stress and apoptosis in endothelial cells.

VD can weaken cerebral artery remodeling and vasospasm by upregulating osteopontin phosphorylation, activated protein kinase, and eNOS at the Ser1177-dimer in the cerebral arteries (14). Qian et al. (59) conducted a study on the relationship between VD and myocardial ischemia. They found that VD had a protective effect on the heart (the infarct area in the I/R group was 39.31% ± 3.71%, while that in the VD group was 15.33% ± 3.05%); VD can improve myocardial damage (myocardial fiber atrophy, interstitial enlargement, and vasodilation with hyperemia in the I/R group and non-inflammatory cell infiltration in the VD group) and can be reduced. Myocardial marker enzyme activity improves coronary blood flow and increases cardiac output. Furthermore, VD can reduce blood pressure by slowing hypoparathyroidism. VD deficiency can then increase blood pressure (57).

■ STROKE and EPILEPSY

Stroke and epilepsy are common neurological disorders that are closely related. Stroke is an important cause of epilepsy in adults, especially in older adults, and accounts for approximately 10% of all seizures in adults. Studies have revealed that the number of post-stroke seizures and patients with epilepsy has increased with an increase in the number of patients with stroke in recent years. Nearly 50% of patients with newly diagnosed epilepsy > 60 years of age have post-stroke epilepsy (PSE) (78). After a stroke, 3%–30% of patients may develop PSE, which negatively affects patients' prognosis and quality of life (80). The incidence of PSE was 23/1000 person-years. A total of 240 patients who met the inclusion criteria were included, and the median follow-up time was 1062 days. According to the research criteria, 13 patients were diagnosed with PSE. The median time from stroke onset to PSE diagnosis was 237 days (26). A cohort analysis conducted by Hsu et al. revealed that patients with epilepsy of different ages and sexes have a higher stroke risk after admission than healthy populations (30).

Most seizures after stroke are focal; however, secondary generalized seizures are common, especially in patients with late-onset seizures. Status epilepticus is a relatively rare condition. Stroke-associated epilepsy is divided into

early (≤ 7 days) and late (> 7 days) types according to pathophysiological differences. Furthermore, it can be divided into early-onset and late-onset types, which may be related to local ion transfer. Ion transfer is related to the release of high levels of excitotoxic neurotransmitters in the area of ischemic injury. The risk of late-onset seizures may increase over time, leading to potentially permanent damage as a result of continuous changes in neuronal excitability. Ion transfer seems to be the cause of late-onset epilepsy after stroke. Meanwhile, early-onset epilepsy has a poor prognosis and high in-hospital mortality rates. It is common in patients with hemorrhagic stroke. Late-onset epilepsy refers to an epileptic seizure that occurs between 6 months and 2 years after a stroke, with a high recurrence rate. As 20% of seizures that occur in patients with previous cerebral infarction are new, the clinical manifestations of early- and late-onset seizures are arbitrary. However, the differences between these seizures are uncertain. Moreover, post-stroke epileptic seizures are closely related to stroke severity and cortical location (19,62).

■ STROKE and COGNITIVE FUNCTION

A mutual relationship exists between stroke and cognitive function. In recent years, stroke has gradually been recognized as an important cause of cognitive problems and has a strong correlation with AD and vascular dementia, both of which affect cognitive function (45).

Using a rat model to study cognitive function after a stroke, Livingston-Thomas et al. found that damage to the prefrontal cortex of rats led to cognitive deficits similar to those in humans after a stroke, such as impaired recognition function and behavioral flexibility as well as increased anxiety. Such behaviors change significantly, whereas spontaneous alternation and motor function remain unchanged (44). Delavaran et al. applied the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) to survey 145 stroke survivors 10 years after they had a stroke; they found that the post-stroke cognitive impairment (PSCI) rate was 46% based on the MMSE findings and 61% based on the MoCA findings. Among 25 patients with stroke, 35% had an MMSE score of ≥ 27 (p<0.001). The probability of severe cognitive impairment in the stroke survivors was indicated by an MMSE score of < 23, which was higher than that of the 354-member control group. Therefore, PSCI is considered to be common among stroke survivors. Compared with patients without stroke, stroke survivors have severe cognitive impairment (12). Some scholars believe that the cognitive function of patients with stroke is impaired, and the mechanism of which is related to decreased cAMP and p-CREB levels and increased p-Tau levels (10). Moreover, exercise ability recovery and sleep quality after stroke are factors that influence cognitive function after a stroke (16,38).

Research suggests that low cognitive function increases the stroke risk (61). In the acute stroke stage, the number of years of education can predict alertness, working memory, executive function, overall cognition, cognitive deficits, and disability (modified Rankine scale) (73).

■ EPILEPSY and COGNITIVE FUNCTION

Cognitive problems are common in patients with epilepsy. They are considered secondary to or caused by epilepsy and often occur during seizures. Epilepsy and seizures are hypothesized to cause brain damage, leading to changes in cognitive function and social behavior. Wang et al. (75) used the Webster's Adult Intelligence Scale (Chinese version) and Eysenck Personality Questionnaire to assess the cognitive function and personality traits of patients with epilepsy and found that these patients had obvious cognitive impairment and specific personality traits. Furthermore, age at onset, epilepsy duration, and seizure frequency were related to the observed cognitive and personality trait defects. Moreover, Helmstaedter and Witt (28) posited that a bidirectional relationship exists between epilepsy and cognition and that a functional relationship exists between epilepsy and behavior because epileptic activity can affect behavior, and behavior can change epileptic activity. Cognitive deficits are related to the epilepsy type. Lee et al. observed that patients with idiopathic generalized epilepsy (IGE) had significantly lower total IQ and performance IQ scores than patients with idiopathic local-related epilepsy (ILRE) (89.0 ± 17.6 vs. 96.3 ± 14.8 , $p=0.030$ and 88.9 ± 16.3 vs. 97.0 ± 16.4 , $p=0.016$). Patients with ILRE having unilateral IEDs had significantly higher full-scale intelligence quotient scores than patients with ILRE having bilateral IEDs and patients with IGE (99.9 ± 12.2 vs. 93.7 ± 16.1 vs. 89.0 ± 17.6 ; $p=0.039$) (41).

■ CLINICAL APPLICATION and PROSPECT of VD

VD has a wide range of applications in current clinical practice: it can be used to treat multiple sclerosis (50). Geier found that VD can significantly reduce the serum ALT levels in patients with non-alcoholic fatty liver disease. Histology also showed that VD treatment can reduce liver steatosis. Animal experiments have also found that VD can be used to treat obese mice. It has beneficial effects in the non-alcoholic steatohepatitis model (21,32). Relevant experiments conducted by Jolliffe et al. (35) and other researchers have shown that VD supplementation can promote the negative conversion of sputum culture in patients with drug-resistant tuberculosis. Related personnel are also exploring the application of VD in the treatment of newly treated AIDS (5). The active metabolism of VD drugs has also been applied to the treatment of psoriasis (46).

In recent years, animal experiments and clinical trials have shown that VD not only participates in the regulation of calcium and phosphorus homeostasis but is also a new type of neuroactive steroid that can play an important role in central nervous system protection. VD deficiency is very common in the population and is associated with a variety of neurological diseases. Therefore, it is necessary to design reasonable observational studies, case-control experiments, and prospective cohort studies to explore the relationship between the VD levels and various neurological diseases. As a neurosteroid, VD is likely to be a promising therapeutic drug for neurological diseases. It has the advantages of economic benefits, convenient access, few side effects, and long-term

application. The treatment of patients with systemic diseases opens up new ideas that have certain clinical prospects and significance.

■ CONCLUSION

VD can be used for the comprehensive treatment of neurological diseases, which advantages of economic benefits, convenient access, few side effects, and long-term application.

■ ACKNOWLEDGEMENTS

This study was supported by grants from the Key Research and Development Program of Jining Science and Technology (2018SMNS005), A Project of Shandong Province Medical Health and Technology Development Program (2014WS0518) and Research Support Fund for Teachers of Jining Medical University (JYFC2018FKJ100).

■ AUTHORSHIP CONTRIBUTION

Study conception and design: MW

Data collection: MW

Analysis and interpretation of results: MW

Draft manuscript preparation: MW

Critical revision of the article: JF, CC

Other (study supervision, fundings, materials, etc.): MW

All authors (MW, CC, FJ) reviewed the results and approved the final version of the manuscript.

■ REFERENCES

1. Afzal S, Nordestgaard BG: Vitamin D, hypertension, and ischemic stroke in 116 655 individuals from the general population: A genetic study. *Hypertension*, 2017 (Online ahead of print)
2. Alrefaie Z, Alhayani A: Vitamin D(3) improves decline in cognitive function and cholinergic transmission in prefrontal cortex of streptozotocin-induced diabetic rats. *Behav Brain Res* 287:156-162, 2015
3. Ameri P, Canepa M, Fabbi P, Leoncini G, Milaneschi Y, Mussap M, AlGhatrif M, Balbi M, Viazzi F, Murialdo G, Pontremoli R, Brunelli C, Ferrucci L: Vitamin D modulates the association of circulating insulin-like growth factor-1 with carotid artery intima-media thickness. *Atherosclerosis* 236(2):418-425, 2014
4. Annweiler C, Bartha R, Goncalves S, Karras SN, Millet P, Feron F, Beauchet O: Vitamin D-related changes in intracranial volume in older adults: A quantitative neuroimaging study. *Maturitas* 80 (3):312-317, 2015
5. Ashenafi S, Amogne W, Kassa E, Gebreselassie N, Bekele A, Aseffa G, Getachew M, Aseffa A, Worku A, Hammar U, Bergman P, Aderaye G, Andersson J, Brighenti S: Daily nutritional supplementation with Vitamin D(3) and phenylbutyrate to treatment-naive HIV Patients tested in a randomized placebo-controlled trial. *Nutrients* 11(1):133, 2019

6. Aspell N, Lawlor B, O'Sullivan M: Is there a role for vitamin D in supporting cognitive function as we age? *Proc Nutr Soc* 77:124-134, 2018
7. Barthelmes J, Nagele MP, Ludovici V, Ruschitzka F, Sudano I, Flammer AJ: Endothelial dysfunction in cardiovascular disease and Flammer syndrome-similarities and differences. *EPMA J* 8(2):99-109, 2017
8. Berghout BP, Fani L, Heshmatollah A, Koudstaal PJ, Ikram MA, Zillikens MC, Ikram MK: Vitamin D status and risk of stroke: The rotterdam study. *Stroke* 50(9):2293-2298, 2019
9. Chen H, Liu Y, Huang G, Zhu J, Feng W, He J: Association between vitamin D status and cognitive impairment in acute ischemic stroke patients: A prospective cohort study. *Clin Interv Aging* 13:2503-2509, 2018
10. Chen HG, Wang M, Jiao AH, Tang GT, Zhu W, Zou P, Li T, Cui GQ, Gong PY: Research on changes in cognitive function, beta-amyloid peptide and neurotrophic factor in stroke patients. *Eur Rev Med Pharmacol Sci* 22(19):6448-6455, 2019
11. Chen RH, Jiang XZ, Jiang Q, Gu Z, Gu PL, Zhou B, Zhu ZH, Xu LY, Zou YF: Correlations between serum levels of 25-hydroxyvitamin D and carotid atherosclerosis in patients with type 2 diabetes in Shanghai. *Ann Endocrinol (Paris)* 75(4):206-212, 2014
12. Delavaran H, Jonsson AC, Lovkvist H, Iwarsson S, Elmstahl S, Norrving B, Lindgren A: Cognitive function in stroke survivors: A 10-year follow-up study. *Acta Neurol Scand* 136(3):187-194, 2017
13. Dura-Trave T, Gallinas-Victoriano F: Dietary pattern among schoolchildren with normal nutritional status in Navarre, Spain. *Nutrients* 6(4):1475-1487, 2014
14. Enkhjargal B, Malaguit J, Ho WM, Jiang W, Wan W, Wang G, Tang J, Zhang JH: Vitamin D attenuates cerebral artery remodeling through VDR/AMPK/eNOS dimer phosphorylation pathway after subarachnoid hemorrhage in rats. *J Cereb Blood Flow Metab* 39(2):272-284, 2019
15. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ: Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. *J Chem Neuroanat* 29:21-30, 2005
16. Falck RS, Best JR, Davis JC, Eng JJ, Middleton LE, Hall PA, Liu-Ambrose T: Sleep and cognitive function in chronic stroke: A comparative cross-sectional study. *Sleep* 42(5):zs040, 2019
17. Feng C, Tang N, Huang H, Zhang G, Qi X, Shi F: 25-Hydroxy vitamin D level is associated with total MRI burden of cerebral small vessel disease in ischemic stroke patients. *Int J Neurosci* 129(1):49-54, 2019
18. Fernandez H, Mohammed HT, Patel T: Vitamin D supplementation for bone health in adults with epilepsy: A systematic review. *Epilepsia* 59(4):885-896, 2018
19. Feyissa AM, Hasan TF, Meschia JF: Stroke-related epilepsy. *Eur J Neurol* 26:13-18, 2019
20. Fong CY, Kong AN, Poh BK, Mohamed AR, Khoo TB, Ng RL, Noordin M, Nadarajaw T, Ong LC: Vitamin D deficiency and its risk factors in Malaysian children with epilepsy. *Epilepsia* 57:1271-1279, 2016
21. Geier A, Eichinger M, Stirnimann G, Semela D, Tay F, Seifert B, Tschopp O, Bantel H, Jahn D, Marques ME, Saleh L, Bischoff-Ferrari HA, Mullhaupt B, Dufour JF: Treatment of non-alcoholic steatohepatitis patients with vitamin D: A double-blinded, randomized, placebo-controlled pilot study. *Scand J Gastroenterol* 53(9):1114-1120, 2018
22. Gepner AD, Ramamurthy R, Krueger DC, Korcarz CE, Binkley N, Stein JH: A prospective randomized controlled trial of the effects of vitamin D supplementation on cardiovascular disease risk. *PLoS One* 7(5):e36617, 2012
23. Grubler MR, Marz W, Pilz S, Grammer TB, Trummer C, Mullner C, Schwetz V, Pandis M, Verheyen N, Tomaschitz A, Fiordelisi A, Laudisio D, Cipolletta E, Iaccarino G: Vitamin-D concentrations, cardiovascular risk and events - a review of epidemiological evidence. *Rev Endocr Metab Disord* 18(2):259-272, 2017
24. Gu Y, Luan X, Ren W, Zhu L, He J: Impact of seasons on stroke-related depression, mediated by vitamin D status. *BMC Psychiatry* 18(1):359, 2018
25. Hajiluijan G, Nameni G, Shahabi P, Mesgari-Abbasi M, Sadigh-Eteghad S, Farhangi MA: Vitamin D administration, cognitive function, BBB permeability and neuroinflammatory factors in high-fat diet-induced obese rats. *Int J Obes (Lond)* 41(4): 639-644, 2017
26. Hassani M, Cooray G, Sveinsson O, Cooray C: Post-stroke epilepsy in an ischemic stroke cohort-Incidence and diagnosis. *Acta Neurol Scand* 141:141-147, 2020
27. Heischmann S, Quinn K, Cruickshank-Quinn C, Liang LP, Reisdorph R, Reisdorph N, Patel M: Exploratory metabolomics profiling in the kainic acid rat model reveals depletion of 25-Hydroxyvitamin D3 during epileptogenesis. *Sci Rep* 6:31424, 2016
28. Helmstaedter C, Witt JA: Epilepsy and cognition - A bidirectional relationship? *Seizure* 49:83-89, 2017
29. Holló A, Clemens Z, Kamondi A, Lakatos P, Szűcs A: Correction of vitamin D deficiency improves seizure control in epilepsy: A pilot study. *Epilepsy Behav* 24:131-133, 2012
30. Hsu SPC, Yeh CC, Chou YC, Shih CC, Hu CJ, Cherng YG, Chen TL, Liao CC: Stroke risk and outcomes in epilepsy patients: Two retrospective cohort studies based on National Health Insurance in Taiwan. *Atherosclerosis* 280:147-154, 2019
31. Hussein HA, Daker LI, Fouad NA, Elamir A, Mohamed SR: Does Vitamin D deficiency contribute to cognitive dysfunction in patients with systemic lupus erythematosus? *Innov Clin Neurosci* 15(9-10):25-29, 2018
32. Jahn D, Dorbath D, Kircher S, Nier A, Bergheim I, Lenaerts K, Hermanns HM, Geier A: Beneficial effects of vitamin D treatment in an obese mouse model of non-alcoholic steatohepatitis. *Nutrients* 11(1): 77, 2019
33. Jesus P, Godet B, Darthou-Pouchard L, Fayemendy P, Abdallah-Lebeau F, Villeneuve O, Marcon C, Gimenez L, Preux PM, Couratier P, Desport JC: Vitamin D status among patients with drug-resistant and non-drug-resistant epilepsy. *Int J Vitam Nutr Res* 90(3-4):205-209, 2020

34. Jia J, Hu J, Huo X, Miao R, Zhang Y, Ma F: Effects of vitamin D supplementation on cognitive function and blood Abeta-related biomarkers in older adults with Alzheimer's disease: A randomised, double-blind, placebo-controlled trial. *J Neurol Neurosurg Psychiatry* 90:1347-1352, 2019
35. Jolliffe DA, Ganmaa D, Wejse C, Raqib R, Haq MA, Salahuddin N, Daley PK, Ralph AP, Ziegler TR, Martineau AR: Adjunctive vitamin D in tuberculosis treatment: Meta-analysis of individual participant data. *Eur Respir J* 53(3):1802003, 2019
36. Kija E, Gidal BE, Shapson-Coe A, Cader S, van der Watt G, Delport S, Wilmshurst JM: Vitamin D abnormalities and bone turn over analysis in children with epilepsy in the Western Cape of South Africa. *Seizure* 69:186-192, 2019
37. Kim DH, Meza CA, Clarke H, Kim JS, Hickner RC: Vitamin D and endothelial function. *Nutrients* 12(2):575, 2020
38. Kim J, Yim J: Effects of an exercise protocol for improving handgrip strength and walking speed on cognitive function in patients with chronic stroke. *Med Sci Monit* 23:5402-5409, 2017
39. Laughlin GA, Kritz-Silverstein D, Bergstrom J, Reas ET, Jassal SK, Barrett-Connor E, McEvoy LK: Vitamin D insufficiency and cognitive function trajectories in older adults: The rancho bernardo study. *J Alzheimers Dis* 58(3):871-883, 2017
40. Lee DH, Chon J, Kim Y, Seo YK, Park EJ, Won CW, Soh Y: Association between vitamin D deficiency and cognitive function in the elderly Korean population: A Korean frailty and aging cohort study. *Medicine (Baltimore)* 99:e19293, 2020
41. Lee SY, Park JH, Park SJ, Kim Y, Lee KY: Cognitive function and neuropsychological comorbidities in children with newly diagnosed idiopathic epilepsy. *J Korean Med Sci* 33(3):e17, 2018
42. Lee YJ, Park KM, Kim YM, Yeon GM, Nam SO: Longitudinal change of vitamin D status in children with epilepsy on antiepileptic drugs: Prevalence and risk factors. *Pediatr Neurol* 52(2):153-159, 2015
43. Li XH, Hou XY, Chen R: The roles of vitamin B12 and vitamin D in children with intractable epilepsy. *Int J Clin Exp Med* 8(1): 764-769, 2015
44. Livingston-Thomas JM, Jeffers MS, Nguemeni C, Shoichet MS, Morshead CM, Corbett D: Assessing cognitive function following medial prefrontal stroke in the rat. *Behav Brain Res* 294:102-110, 2015
45. Lo CD, Lopez G, Corrao S: Cognitive impairment and stroke in elderly patients. *Vasc Health Risk Manag* 12:105-116, 2016
46. Lourencetti M, Abreu MM: Use of active metabolites of vitamin D orally for the treatment of psoriasis. *Rev Assoc Med Bras* 64(7):643-648, 2018
47. Mahfoz AM, Abdel-Wahab AF, Afify MA, Shahzad N, Ibrahim I, ElSawy NA, Bamagous GA, Al GS: Neuroprotective effects of vitamin D alone or in combination with lamotrigine against lithium-pilocarpine model of status epilepticus in rats. *Naunyn Schmiedebergs Arch Pharmacol* 390:977-985, 2017
48. Markisic M, Pavlovic AM, Pavlovic DM: The impact of homocysteine, Vitamin B12, and Vitamin D levels on functional outcome after first-ever ischaemic stroke. *Biomed Res Int* 2017:5489057, 2017
49. Mayne PE, Burne T: Vitamin D in synaptic plasticity, cognitive function, and neuropsychiatric illness. *Trends Neurosci* 42(4):293-306, 2019
50. McLaughlin L, Clarke L, Khalilidehkordi E, Butzkueven H, Taylor B, Broadley SA: Vitamin D for the treatment of multiple sclerosis: A meta-analysis. *J Neurol* 265(12): 2893-2905, 2018
51. Momosaki R, Abo M, Urashima M: Vitamin D supplementation and post-stroke rehabilitation: A randomized, double-blind, placebo-controlled trial. *Nutrients* 11(6):1295, 2019
52. Moradi H, Sohrabi M, Taheri H, Khodashenas E, Movahedi A: The effects of different combinations of perceptual-motor exercises, music, and vitamin D supplementation on the nerve growth factor in children with high-functioning autism. *Complement Ther Clin Pract* 31:139-145, 2018
53. Muggeo P, Muggeo V, Giordano P, Delvecchio M, Altomare M, Novielli C, Ciccone MM, D'Amato G, Faienza MF, Santoro N: Cardiovascular dysfunction and vitamin D status in childhood acute lymphoblastic leukemia survivors. *World J Pediatr* 15(5):465-470, 2019
54. Nagel G, Herbolzheimer F, Riepe M, Nikolaus T, Denking MD, Peter R, Weinmayr G, Rothenbacher D, Koenig W, Ludolph AC, von Arnim CA: Serum Vitamin D concentrations and cognitive function in a population-based study among older adults in South Germany. *J Alzheimers Dis* 45(4):1119-1126, 2015
55. Narasimhan S, Balasubramanian P: Role of Vitamin D in the outcome of ischemic stroke- a randomized controlled trial. *J Clin Diagn Res* 11(2):CC06-CC10, 2017
56. Nie Z, Ji XC, Wang J, Zhang HX: Serum levels of 25-hydroxyvitamin D predicts infarct volume and mortality in ischemic stroke patients. *J Neuroimmunol* 313:41-45, 2017
57. Pamuk N, Akkan T, Dagdeviren M, Koca AO, Beyan E, Ertugrul DT, Altay M: Central and peripheral blood pressures and arterial stiffness increase in hypoparathyroidism. *Arch Endocrinol Metab* 64(4):374-382, 2020
58. Pettersen JA: Does high dose vitamin D supplementation enhance cognition?: A randomized trial in healthy adults. *Exp Gerontol* 90:90-97, 2017
59. Qian X, Zhu M, Qian W, Song J: Vitamin D attenuates myocardial ischemia-reperfusion injury by inhibiting inflammation via suppressing the RhoA/ROCK/NF-kB pathway. *Biotechnol Appl Biochem* 66(2):850-857, 2019
60. Qiu M, Wen HX, Huang XL, Yi LF, Cao XX, Wang WJ: Effect of vitamin D deficiency on cardiac autonomic nerve function in obese pre-school children. *Zhongguo Dang Dai Er Ke Za Zhi* 20(9):753-757, 2018
61. Rajan KB, Schneider JA, Aggarwal NT, Wilson RS, Everson-Rose SA, Evans DA: Racial differences in cognitive function and risk of incident stroke. *J Stroke Cerebrovasc Dis* 24(12): 2854-2859, 2015
62. Rodriguez LF, Alet M, Ameriso SF: Post-stroke epilepsy. *Medicina (B Aires)* 78:86-90, 2018
63. Sacmaci H, Tanik N, Balbaloglu O, Akturk T, Inan LE: Electrophysiological evaluation of carpal tunnel syndrome female patients after vitamin D replacement. *Arq Neuropsiquiatr* 78(4):224-229, 2020

64. Safer U, Safer VB, Demir SO, Yanikoglu I: Effects of bisphosphonates and calcium plus Vitamin-D supplements on cognitive function in postmenopausal osteoporosis section sign. *Endocr Metab Immune Disord Drug Targets* 16(1):56-60, 2016
65. Sayeed I, Turan N, Stein DG, Wali B: Vitamin D deficiency increases blood-brain barrier dysfunction after ischemic stroke in male rats. *Exp Neurol* 312:63-71, 2019
66. Schneider MA: The importance of educating patients with stroke about Vitamin D. *J Neurosci Nurs* 49(6):387-389, 2017
67. Seyedi M, Gholami F, Samadi M, Djalali M, Effatpanah M, Yekaninejad MS, Hashemi R, Abdolahi M, Chamari M, Honarvar NM: The effect of Vitamin D3 supplementation on serum BDNF, dopamine, and serotonin in children with attention-deficit/hyperactivity disorder. *CNS Neurol Disord Drug Targets* 18(6):496-501, 2019
68. Shih EJ, Lee WJ, Hsu JL, Wang SJ, Fuh JL: Effect of vitamin D on cognitive function and white matter hyperintensity in patients with mild Alzheimer's disease. *Geriatr Gerontol Int* 20(1):52-58, 2020
69. Song EK, Wu JR: Associations of Vitamin D intake and sleep quality with cognitive dysfunction in older adults with heart failure. *J Cardiovasc Nurs* 33(4):392-399, 2018
70. Sultan M, Twito O, Tohami T, Ramati E, Neumark E, Rashid G: Vitamin D diminishes the high platelet aggregation of type 2 diabetes mellitus patients. *Platelets* 30(1):120-125, 2019
71. Talebi A, Amirabadizadeh A, Nakhaee S, Ahmadi Z, Mousavi-Mirzaei SM: Cerebrovascular disease: Hypertension, and ischemic stroke in 116 655 individuals from the general population. *BMC Neurol* 20:116, 2020
72. Tombini M, Palermo A, Assenza G, Pellegrino G, Benvenga A, Campana C, Naciu AM, Assenza F, Lazzaro VD: Calcium metabolism serum markers in adult patients with epilepsy and the effect of vitamin D supplementation on seizure control. *Seizure* 58:75-81, 2018
73. Umarova RM, Sperber C, Kaller CP, Schmidt C, Urbach H, Kloppel S, Weiller C, Karnath HO: Cognitive reserve impacts on disability and cognitive deficits in acute stroke. *J Neurol* 266(10):2495-2504, 2019
74. Wajda J, Swiat M, Owczarek AJ, Brzozowska A, Olszanecka-Glinianowicz M, Chudek J: Severity of Vitamin D deficiency predicts mortality in ischemic stroke patients. *Dis Markers* 2019:3652894, 2019
75. Wang H, Guo Y, Li G, Xie R, Zhang Z, Han W, Yang M, Chen D, Jiang P: The association between Vitamin D binding protein polymorphisms and Vitamin D level on epilepsy in China. *DNA Cell Biol* 37(9):786-790, 2018
76. Wu WX, He DR: Low Vitamin D levels are associated with the development of deep venous thromboembolic events in patients with ischemic stroke. *Clin Appl Thromb Hemost Suppl* 9:69S-75S, 2018
77. Xu Z, Jing X, Li G, Sun J, Guo H, Hu Y, Sun F, Wen X, Chen F, Wang T, Lu XP: Valproate decreases vitamin D levels in pediatric patients with epilepsy. *Seizure* 71:60-65, 2019
78. Yang H, Rajah G, Guo A, Wang Y, Wang Q: Pathogenesis of epileptic seizures and epilepsy after stroke. *Neurol Res* 40(6):426-432, 2018
79. Zhang Y, Leung DY, Richers BN, Liu Y, Remigio LK, Riches DW, Goleva E: Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. *J Immunol* 188(5):2127-2135, 2012
80. Zhao Y, Li X, Zhang K, Tong T, Cui R: The progress of epilepsy after stroke. *Curr Neuropharmacol* 16(1):71-78, 2018
81. Zhou R, Wang M, Huang H, Li W, Hu Y, Wu T: Lower vitamin d status is associated with an increased risk of ischemic stroke: A systematic review and meta-analysis. *Nutrients* 10(3):277, 2018