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Study on the relationship between 25-hydroxyvitamin D level and rehabilitation of stroke patients

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Abstract

Aim of the study: *To analyse the relationship between 25-hydroxyvitamin D (25(OH)D) level and rehabilitation in stroke patients.*

Material and methods: *100 stroke patients hospitalized in the Neurorehabilitation Department of China Rehabilitation Research Center from November 2019 to April 2020 were selected as the research subjects. And set up a case group. 50 subjects who underwent outpatient physical examination in China Rehabilitation Research Center in the same period were selected as the control group. The differences of biochemical and bone metabolism indexes such as serum 25(OH)D, blood lipid, liver and kidney function between the two groups were analysed. We took rehabilitation efficacy as the dependent variable, Pearson correlation analysis and multivariate logistic regression analysis were performed to analyse the indicators affecting rehabilitation efficacy.*

Results: *The average level of 25(OH)D in the case group was significantly lower than that in the control group ($p < 0.05$). The rehabilitation efficacy was significantly positively correlated with 25(OH)D level ($p < 0.003$) and significantly negatively correlated with duration of disease ($p < 0.01$) and NIHSS score ($p < 0.05$).*

Conclusions: *The increase in 25(OH)D is a protective factor for non-occurrence of cerebral infarction, and the increase in the 25(OH)D level is conducive to the prognosis of cerebral infarction.*

Key words: *stroke, 25-hydroxyvitamin D, rehabilitation efficacy, vitamin D deficiency.*

Introduction

Stroke is a common cerebrovascular disease in the emergency department. It has the characteristics of high incidence rate, high disability rate and high mortality rate. It is the second leading cause of death and disability worldwide [3]. Relevant data show that in 2020, there were 17.8 million stroke patients among people over 40 years old in China, 3.4 million new stroke patients and 2.3 million deaths due to stroke [2]. The survey in 2019 showed that within one year after discharge, the mortality of stroke patients was 8.64%. Among the surviving patients, 58.4% were patients with residual neurological dysfunction and 31.69% were disabled, including 14.8% with mild disability and 16.89% with moderate and severe disability [33].

In recent years, vitamin D has become a hot topic in domestic and foreign academic research. In addition to classic regulation of calcium and phosphorus

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metabolism and maintenance of bone health, vitamin D has gradually been recognized for its role in cardiovascular disease, diabetes, and autoimmune diseases and has become the focus of research [10,24]. Studies have shown that vitamin D deficiency is independently related to the occurrence of major chronic diseases related to oxidative stress, inflammation and aging, stroke, myocardial infarction, hypertension, neurodegenerative diseases, diabetes and cancer [6,28]. In particular, the cardiovascular and cerebrovascular systems appear to be highly sensitive to vitamin D deficiency, which may be caused by endothelial dysfunction and vascular defects through a variety of mechanisms. The active form of vitamin D, 25-hydroxyvitamin D (25(OH)D), can exert various potential cardiovascular and cerebrovascular benefits after combining with vitamin D receptor (VDR), including reducing the production of renin, causing the vasodilation of smooth muscle cells and reducing the production of foam cells formed by atherosclerosis [13,25]. There are few studies on vitamin D levels and stroke rehabilitation efficacy. This study analyses the level of 25(OH)D in hospitalized stroke patients and its relationship with the disease, reveals the effect of vitamin D deficiency on the movement disorders of stroke patients during the recovery period, and provides some help for the rehabilitation of patients.

Material and methods

General information

100 stroke patients hospitalized in the Neurorehabilitation Department of China Rehabilitation Research Center from November 2019 to April 2020 were selected as the research objects. The diagnosis was established in line with the "Chinese guidelines for the diagnosis and treatment of acute ischemic stroke 2018" of the neurology branch of the Chinese Medical Association [3]. And set up a case group. Fifty subjects who underwent physical examination in the outpatient department of China Rehabilitation Research Center in the same period were selected as the control group. There was no significant difference in age and sex between the two groups ($p > 0.05$); serum 25(OH)D in the case group was significantly lower than that in the control group ($p < 0.005$). This study was reviewed and approved by the medical ethics committee of China Rehabilitation Research Center. All subjects participated voluntarily and signed informed consent.

Inclusion and exclusion criteria

Inclusion criteria for the case group: 1) Onset time ≥ 2 weeks, < 6 months (i.e., 2 weeks – 6 months); 2) age ≥ 18 years; and 3) patients who have signed informed consent.

Exclusion criteria for the case group: 1) those who used antibiotics for fever and cold within the last two weeks; 2) those who had taken vitamin D and its derivatives or calcium for the last three consecutive months; 3) those who had severe heart, lung, liver, and kidney dysfunction; 4) those who were pregnant or breastfeeding; 5) those with abnormal thyroid function; 6) those with tracheotomy; and those with impaired consciousness; and 7) patients whose data were incomplete or non-cooperative patients [24,33]. Inclusion criteria for the control group: patients who underwent outpatient medical examination with age and gender matching those in the case group. Exclusion criteria for the control group: patients with (1) limb dyskinesia, (2) various bone diseases, and one of (3) malignant tumours.

Methods

Scale evaluation

After admission, neurologists used Fugl-Meyer motor function score, Fugl-Meyer balance function score, modified Barthel Index (MBI) and National Institutes of Health Stroke Scale (NIHSS) to score a series of scales for patients in the case group, and evaluated and grouped patients according to the efficacy of different types of functional rehabilitation.

Blood biochemical determination

Serum 25-OH D level, biochemical indexes of bone metabolism (using Roche Cobas e411 electrochemiluminescence immunoassay analyser), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), total cholesterol (TC), liver and kidney function, blood calcium (CA), blood phosphorus (P) and other biochemical indexes were collected. The glomerular filtration rate (EGFR) was calculated (by using Beijing Mindray automatic biochemical analyser bc2000m and supporting kit to apply the improved simplified MDRD formula).

MRI

The case group underwent head MRI with Philips lngenia 3.0T superconducting magnetic resonance scanner, including conventional axial T1 weighted imaging, T2 weighted imaging and diffusion weighted imaging. The new infarct focus was determined according to diffusion weighted imaging, and the infarct volume was calculated.

Vitamin D nutritional status evaluation criteria

Currently, serum 25(OH)D levels are used to evaluate vitamin D nutritional status. Judging criteria: sufficiency (> 30 ng/ml), insufficiency (20 ~ 30 ng/ml) and deficiency (< 20 ng/ml) [30].

Efficacy assessments

The basic assessment was made within 24 hours after admission, and the intermediate assessment was made within 4 weeks of hospitalized rehabilitation training. PT teacher, OT teacher and language trainer participated in the evaluation. Finally, the clinical physician in charge of the ward combined various scale scores, duration of disease, size, location, age of the lesion, complications and other conditions to make the overall evaluation of the rehabilitation effect.

The rehabilitation efficacy was assessed based on the improvement score of MBI, (expressed by Δ), which was divided into ineffective ($\Delta = 0$), effective ($\Delta = 5$) and markedly effective ($\Delta \geq 10$). In the logistic regression analysis, the ineffective group and the effective combination were co-located in the general efficacy group. After adjusting for hypertension, diabetes and other factors, 25(OH)D, duration of disease, and NIHSS brought into the regression equation analysis by binomial multivariate logistic regression analysis.

Statistical analysis

We used the software program SPSS 22.0 (IBM, Chicago, USA) to conduct the statistical analysis. Normality test was performed on the measurement data. The continuous variables of normal distribution were expressed as mean ± standard deviation and each value was compared by *t*-test. The continuous variables of non-normal distribution were expressed as median (interquartile range [IQR]), the categorical variables were expressed as frequency (percentage [%]), and the non-normally distributed continuous data were compared using non-parametric tests. The count data were tested by χ^2 test. Taking the results of rehabilitation evaluation (effective and markedly effective) as the dependent variable, Pearson correlation and multivariate logistic regression were used to analyse the influencing factors of the rehabilitation efficacy; the significance level was $\alpha = 0.05$. A value of $p < 0.05$ was considered statistically significant.

Results

Baseline data analysis

In this study, there were 69 males and 31 females in the case group, aged 33-82 years, with an average age of 54.75 ±10.61 years; 58 cases were diagnosed as cerebral infarction and 42 cases as intracerebral haemorrhage. The duration of disease ranged from 14 days to 6 months. In the control group, there were 36 males and 14 females, aged 30-78 years, with an average age of 56.28 ±9.46 years. There was no significant difference in age, sex, EGFR, CA, P, TG and LDL-C between the two groups ($p > 0.05$). The level of serum 25(OH)D in the case group was lower than that in the control group, and there was a significant difference between the two groups ($p < 0.05$). The details were listed in Table I.

The age and gender distribution characteristics of patients' serum 25(OH)D levels

According to the definition of the elderly by the World Health Organization (WHO), patients were divided into two groups based on the age of 65 years. The 25(OH)D level of the elderly group was 12.97 ±5.28 ng/ml, and the 25(OH)D level of the young and middle-aged group was 13.86 ±7.85 ng/ml; there was no significant difference in the level of 25(OH)D between the two groups. In addition, there was no statistical difference in the 25(OH)D level by grouping according to disease duration and aetiology.

Comparison of rehabilitation outcomes in stroke patients with different serum 25(OH)D levels

In the case group, the level of 25(OH)D was deficient and the number of sufficient cases was small. Therefore, 25(OH)D of 20 ng/ml was divided into the insufficient group (29 cases) and the relatively sufficient group (25 cases). Firstly, the baseline indicators, such as age and duration of disease of patients,

Table I. General information of subjects

Baseline indicators	Control group (*n* = 50)	Case group (*n* = 100)	*t* value/χ^2	*P*-value
Age (years)	56.28 ±9.46	54.75 ±10.6	1.49	0.57
Sex (M/F)	68/32	69/31	1.12	0.37
BMI (kg/m^2)	23.75 ±3.58	26.08 ±3.63	4.11	0.01*
CHOL-C (mmol/l)	4.53 ±1.35	4.71 ±1.12	1.18	0.43
LDL-C (mmol/l)	2.69 ±0.48	2.87 ±0.76	0.65	0.57
HDL-C (mmol/l)	1.13 ±0.42	1.02 ±0.23	0.01	0.81
TG (mmol/l)	1.56 ±1.92	1.78 ±1.62	1.39	0.17
eGFR	102.53 ±12.28	101.35 ±30.12	1.40	0.26
Ca	2.32 ±0.08	2.30 ±0.06	0.05	0.93
P	1.08 ±0.12	1.19 ±0.16	3.01	0.08
25(OH)D (ng/l)	17.67 ±3.89	13.54 ±5.28	3.15	0.03*
PTH	24.64 ±6.78	34.90 ±36.51	1.38	0.17
PINP	81.02 ±44.12	61.52 ±39.68	1.41	0.16
β-CTX	0.98 ±0.33	0.67 ±0.38	–1.20	0.23
Hypertension, *n* (%)	22 (44)	76 (76)	5.16	0.02*
Hyperlipidaemia, *n* (%)	33 (66)	81 (81)	6.39	0.01*
Diabetes, *n* (%)	12 (24)	29 (29)	6.95	0.01*

*M – male, F – female, BMI – body mass index, CHOL-C – total cholesterol, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, TG – triglycerides, eGFR – glomerular filtration rate, Ca – blood calcium, P – blood phosphorus, PTH – parathyroid hormone, PINP – procollagen type I N-terminal propeptide, β-CTX – β-collagen type I C-terminal telopeptide, *p < 0.05*

Table II. General information comparison between the relatively sufficient 25(OH)D group and the insufficient 25(OH)D group before treatment

Baseline indicators	Insufficient 25(OH)D group (*n* = 29)	Relatively sufficient 25(OH)D group (*n* = 25)	*P*-value
Age (years)	56.9 ±12.7	56.1 ±11.8	0.800
Duration of a disease (day)	62.3 ±64.4	63.3 ±60.8	0.616
Rehabilitation training time (h/day)	3.3 ±1.0	3.5 ±1.3	0.100
Stroke type, *n* (%)			
Brain infarction	19 (65.5)	17 (68.0)	0.847
Encephalorrhagia	10 (34.5)	8 (32.0)	0.847
Degree of nerve damage (NIHSS score)	8.05 ±4.74	8.03 ±4.18	0.989
Focal site, *n* (%)			
Basal ganglia	16 (55.2)	13 (52.0)	0.816
Brain lobe	11 (37.9)	9 (36.0)	0.885
Other	2 (6.9)	3 (12.0)	0.519
Complications, *n* (%)			
Lower extremity venous thrombosis	1 (3.4)	0 (0.0)	0.349
Shoulder-hand syndrome	8 (27.6)	7 (28.0)	0.975
Fracture	2 (6.9)	1 (4.0)	0.467
Anxiety/depression	12 (41.4)	10 (40.0)	0.916

NIHSS – the National Institute of Health Stroke Scale

between the two groups before rehabilitation treatment were compared. There was no statistical difference between the two groups ($p > 0.05$) as shown in Table II. After 30 days of rehabilitation treatment, all indicators of the high-level group were better than those of the low-level group, and the difference was statistically significant ($p < 0.05$) as shown in Table III.

Table III. Changes of evaluation indexes between the relatively sufficient 25(OH)D group and the insufficient 25(OH)D group after rehabilitation treatment

Evaluation indexes	Insufficient 25(OH)D group (*n* = 29)	Relatively sufficient 25(OH)D group (*n* = 25)	*P*-value
The Fugl-Meyer motor function score			
Pre-treatment	32.69 ±27.57	37.11 ±29.15	0.505
After treatment	38.58 ±24.36	47.78 ±28.23	0.050*
The Fugl-Meyer balance function score			
Pre-treatment	4.36 ±3.47	5.23 ±3.65	0.230
After treatment	5.86 ±4.36	8.09 ±4.85	0.030*
MBI			
Pre-treatment	33.9 ±24.40	33.4 ±27.90	0.445
After treatment	47.70 ±23.9	50.0 ±21.8	0.040*

*Insufficient 25(OH)D group, 25(OH)D < 20 ng/ml, relatively sufficient 25(OH)D group, 25(OH)D ≥ 20 ng/ml, MBI – Modified Barthel Index, *p < 0.05*

Table IV. Multiple factors related to rehabilitation effect logistic regression analysis

Variable	B	SE	Wald	*P*-value	Exp(B)
25(OH)D	0.534	0.267	3.991	0.04*	1.706
Duration of disease	–1.805	0.85	4.511	0.03*	0.281
NIHSS	–0.916	0.125	6.37	< 0.001*	1.32

*NIHSS – the National Institute of Health Stroke Scale, *p < 0.05*

The correlation between serum 25(OH)D level and rehabilitation efficacy

Pearson correlation analysis showed that rehabilitation efficacy was significantly positively correlated with the 25(OH)D level ($r = 0.562$, $p < 0.003$) and significantly negatively correlated with BMI ($r = –0.347$, $p < 0.05$), duration of disease ($r = –0.480$, $p < 0.01$), and NIHSS score ($r = –0.533$, $p < 0.05$).

Taking rehabilitation efficacy as the outcome, a multivariate logistic regression analysis was performed. After adjusting for factors such as hypertension and diabetes, 25(OH)D level, duration of disease, and NIHSS score were entered into the regression equation. The results showed that the duration of the disease and NIHSS score were independent risk factors affecting rehabilitation efficacy ($p < 0.05$), and the 25(OH)D level was a protective factor ($p < 0.05$) as shown in Table IV.

Discussion

Vitamin D is stored in adipose tissue in the form of 25-OH D in the body, with a half-life of 2 to 3 weeks, and its chemical properties are very stable. There are targets for its action in multiple organs, such as vascular smooth muscle cells, vascular endothelial cells, breast epithelial cells, colonic epithelial cells, lymphocytes, and pancreatic islet cells, and it plays various roles in improving insulin resistance, anti-arteriosclerosis, and immune regulation, etc. [13]. Studies have shown that vitamin D deficiency is closely related to the occurrence and development of cerebrovascular diseases [31]. Therefore, accurate assessment of the vitamin D nutritional status of stroke patients is of great importance to the rehabilitation efficacy of stroke patients.

The level of 25-OH D represents the nutritional status of vitamin D in the human body. Vitamin D deficiency and insufficiency is a common health problem. Serum 25(OH)D ≥ 30 ng/ml (75 nmol/l), 20~30 ng/ml (50~75 nmol/l) and < 20 ng/ml (50 nmol/l) were defined as vitamin D adequacy, insufficiency and deficiency, respectively [30]. Vitamin D deficiency is a global problem. 61% of whites and 91% of African Americans in the United States have vitamin D deficiency [14]. Relevant flow survey data show that the proportion of 25(OH)D deficiency and deficiency in elderly men in Beijing is 84.53% [32]. In this study, the vitamin D deficiency or insufficiency rate of stroke patients was 94%. Excluding the differences in the population (the population in this study was hospitalized patients with stroke, not the normal population) and regions, the rate of vitamin D deficiency or insufficiency has shown a clear upward trend year by year, especially in the patient population, where it is more serious.

The decrease of the 25(OH)D level is very common in patients with cardiovascular and cerebrovascular diseases [10]. Manson *et al*. reported that 75% of hospitalized patients with acute stroke had the blood level of clear 25(OH)D lower than 20 ng/ml [22]. Tu *et al*. showed that the serum 25(OH)D level in AIS group was lower than that in the normal control group [29]. In this study, the conclusion was the same. 25(OH)D can inhibit renin angiotensin aldosterone system activity, improve insulin resistance, reduce hypertension and hyperglycaemia risk of arteriosclerosis [5,10]; 25(OH)D can also inhibit thrombosis and inflammatory response to protect vascular endothelial function. Endothelial dysfunction is a common way to mediate atherosclerotic vascular disease and is cardiovascular disease independent predictors of events [36].

Generally, vitamin D levels may vary slightly in different populations, regions, and seasons. It is higher in the southern region than in the north, and it is higher in summer than in winter. With the increase in age, the level of vitamin D gradually decreases, which is related to the decline in the ability of skin synthesis of vitamin D in elderly patients. Gender is also an important factor affecting vitamin D levels. There is no significant difference in vitamin D deficiency between men and women in infants and young children [9]. With age, women's vitamin D levels are lower than those of men in most areas. Therefore, the incidence of vitamin D deficiency is closely related to age and gender. In this study, the average level of 25(OH)D in men was 14.11 ng/ml, which was slightly higher than that of women, but there was no statistical difference. When the participants in this study were divided into two groups based on the age of 65 years and the differences in vitamin D levels between different ages were compared, the results showed that there was no statistical difference in vitamin D levels between the two groups. In short, not only was the prevalence of vitamin D deficiency or insufficiency in stroke patients high, but also, there was no age difference and no gender difference.

Fugl-Meyer assessment (FMA), NIHSS, and MBI are recognized scales for evaluating patients' functional impairment at home and abroad. The neurological rehabilitation team of our hospital has very rich experience in evaluating rehabilitation efficacy. This study shows that the nutritional status of vitamin D is related to the rehabilitation efficacy of stroke patients. It has been reported in the literature that vitamin D participates in the regulation of the body's muscle movement and balance and maintains the body's effective vitamin D level, which can improve the patient's exercise ability and balance ability [1,11]. This is confirmed by animal experiments and follow-up studies in the population. Animal experiments have shown that in the absence of vitamin D, rat skeletal muscle fibre atrophy and muscle strength decreases [2,7,18,26]; after appropriate vitamin D supplementation, the diameter and ratio of skeletal muscle fibres will increase significantly [18]. In clinical practice, people with vitamin D deficiency often have reduced muscle strength and reduced balance function. After appropriate vitamin D supplementation, the subjects' lower limb muscle strength (hip adductor strength) and upper limb muscle strength (grip strength) will be significantly improved, while the patient's risk of falls is reduced, and the balance function is improved [12,15,35,37,38].

This study suggests that low 25(OH)D levels are associated with advanced age, diabetes, hypertension and hyperlipidaemia. With the increase in age, the outdoor activity time decreased, the sunshine was insufficient, and the loss of 25(OH)D increased. Wang *et al*. [34] included 326 patients with acute ischemic stroke in the study on the predictive value of serum 25(OH)D in patients with ischemic stroke. The results suggest that vitamin D may be a predictor of the prognosis of ischemic stroke, which is consistent with the conclusion of this study. In addition, this study suggests that the admission NIHSS score is an independent risk factor for poor short-term prognosis in patients with ischemic stroke, which is basically consistent with the research conclusions of Daubail *et al*. [4]. This study found that the 25(OH)D level is a protective factor for the prognosis of ischemic stroke suggesting that vitamin D-related intervention research can be carried out in the future. The protective mechanism of serum 25(OH)D on the short-term prognosis of acute ischemic stroke is mainly because 25(OH)D inhibits the activity of human RASS system to reduce blood pressure and protect blood vessels [19]. In addition, studies have shown that 25(OH)D may reduce insulin resistance, reduce the risk of diabetes and reduce the level of blood lipids, thereby indirectly or directly plays a protective role [16,21]. When Enkhjargal *et al*. [8] gave 103 rats with cerebral haemorrhage enough vitamin D, the volume of cerebral haemorrhage was significantly reduced. Moreover, the severity and risk of death in patients with ischemic stroke were negatively correlated with vitamin D levels [17,20,23,27].

In conclusion, this study preliminarily discussed the effect of the 25(OH)D level on the rehabilitation efficacy of stroke patients, and found that the serum 25(OH)D level is a protective factor and has a positive impact on the prognosis of stroke patients. Further large sample studies are needed to confirm this result in the future.

Limitations: There were several limitations in this study. Firstly, this trial was not a randomized controlled trial. Secondly, this study was only a single-centre trial, another multiple-centre trial is still needed in the future. Thirdly, the sample size of this study was really limited, another larger trial with more participants is necessary.

Disclosure

The authors report no conflict of interest.

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