VITAMIN D
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The role of vitamin D in post-stroke rehabilitation: between light and shadow

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Despite medical advances in the 20th century, vitamin D deficiency is still a pandemic 1: approximately 1 billion people worldwide suffer from vitamin D deficiency. Classically, vitamin D deficiency is associated with rickets in children while, in adults, vitamin D deficiency manifests itself as osteomalacia, a painful condition of defective skeletal mineralisation, or as osteoporosis causing skeletal fragility and fractures [1,2]. Vitamin D also plays an important role in regulating proliferation and differentiation in a variety of cells and tissues not associated with calcium metabolism [1-4]. Vitamin D receptors (VDRs) have been found in a variety of tissues and body cells, including brain, heart, breast, prostate, gonads, colon, pancreas, monocytes and activated T- and B lymphocytes [3-6]. Vitamin D is important for maintaining muscle strength through its action on VDRs in muscle tissue [7].
Inpatients and outpatients undergoing rehabilitation are a high-risk population prone to develop vitamin D deficiency and to manifest the consequences of this condition [8,9]. The functional results of these patients will depend on the correct diagnosis and appropriate treatment of the vitamin Deficiency.
In order to evaluate the effectiveness of vitamin D supplementation in patients undergoing rehabilitation programmes, we took into account studies concerning rehabilitation after cerebral strokes. The efficacy of rehabilitation after vitamin D supplementation in stroke patients was investigated, the efficacy of supplementation, and the type, form and amount of vitamin D administered. The inclusion criteria, the duration of the study and the scales used were discussed (Fig. 1).

THE EFFECT OF VITAMIN D SUPPLEMENTATION ON POST-STROKE REHABILITATION

Vitamin D deficiency may be associated with an increased risk of stroke onset, severity and future prognosis. It also affects cognitive decline and physical performance, which is observed in stroke patients who have worse outcomes in neurological rehabilitation [10].
Due to the numerous limitations of serum vitamin D testing and the method and quantity of its administration, there is little certainty as to whether rehabilitation outcomes in stroke survivors can be improved [11]. Many studies presented optimistic results and showed that vitamin D supplementation after stroke improved quality of life and facilitated patients' return to normal life.
Small sample studies showed better results for patients who supplemented with vitamin D after stroke [12,13].
Two small open trials conducted by Gupta et al. in India showed that intramuscular injection of high-dose cholecalciferol (600,000 IU) improved scores on various stroke scales and increased survival of post-stroke patients. A randomised, controlled, open trial included 73 patients with acute ischaemic stroke. Each patient was tested for serum 25(OH)D levels before entering the trial. A total of 53 patients with baseline 25(OH) D < 75 nmol/L were randomly assigned to the two trials. The first group received an intra-muscular injection of 600,000 IU of cholecalciferol once and oral cholecalciferol at a dose of 60,000 IU once a month with one gram of elemental calcium per day along with the usual post-stroke care. The second control group only received normal hospital care. Serum levels of vitamin D and iPTH were tested at 3 and 6 months after the study, and the follow-up itself lasted 6 months. The modified Rankin scale (mRS) was used in the study and high scores were obtained after 6 months. This result confirms the beneficial effect of vitamin D supplementation in post-stroke patients [10].
A randomised, controlled and unblinded study by Narasimhan and Balasubramani-

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Conflict of interest
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Benefits of adequate vitamin D levels

More and more studies suggest that maintaining a normal level of vitamin D improves cardio- and cerebrovascular function. In addition, vitamin D influences the progression, development and prognosis of stroke.

HAEMORRHAGIC STROKE

- There is no scientific evidence that low vitamin D levels influence the risk of haemorrhagic stroke.
- Patients with haemorrhagic stroke often suffer from vitamin D deficiency and vitamin D supplementation reduces the damaging effects of the disease.

ISCHAEMIC STROKE

- Scientific studies suggest that low vitamin D levels may be associated with an increased risk of ischaemic stroke. $1,25(OH)_2D_3$ may induce the expression of IGF-, which contributes to the control and protection of nerve cells.
- IGF-1 has been shown to have anticoagulant properties via plasminogen activation.

FIGURE 1.
Role of vitamin D in ischaemic and haemorrhagic stroke.

an compared the results in patients with ischaemic stroke taking vitamin D supplementation with those without supplementation. The study used the Scandinavian Stroke Scale (SSS), a reliable and widely used scale in patients with ischaemic cerebrovascular disease. The first group of patients received a 60,000 IU dose of cholecalciferol administered by intramuscular injection; the second group did not receive vitamin D. Patients in both groups were examined at the beginning of the study and after three months. The results indicate a significant improvement in outcome among post-stroke patients taking vitamin D supplements [13]. Vitamin D supplementation in post-stroke patients had a positive effect on rehabilitation outcomes.

A small Japanese study by Momosaki et al. on 100 patients showed no improvement in stroke patients treated with vitamin D. After randomisation, each of the 100 subjects took an oral form of vitamin D_3 at a dose of 2000 IU/day or a placebo. Each patient received 450 capsules, each containing 400 IU of vitamin D_3, which means that the patients took the capsules five times a day. Vitamin D_3 was always taken at the same time, after lunch. The study with rehabilitation and vitamin D supplementation lasted eight weeks. During the patient's recovery and 8 weeks after discharge, the rehabilitation staff assessed each patient's Barthel index, Brunnstrom stage (arm, hand and leg on the affected side), hand grip strength (bilaterally) and calf circumference (bilaterally). A total of 97 patients completed the Japanese study. There was an improvement in Barthel index scores at week eight of rehabilitation as the primary endpoint; secondary outcomes were observed in Barthel index performance, hand compression strength and circumference of the calf. No differences were found in the other secondary endpoints between the groups.

None of these differences were statistically significant, indicating that daily supplementation with 2000 IU vitamin D_3 in patients after an acute stroke was ineffective and did not provide the expected benefits. A potential error was due to the fact that serum 25-hydroxyvitamin D levels were not considered as a patient inclusion criterion for the study; the researchers justified the choice with the assumption that almost all elderly patients undergoing rehabilitation have a vitamin D deficiency and, therefore, the deficiency study itself was not included in the patients participating in the study [14,15]. Other limitations highlighted by the authors include the small size of the study group, the short duration of supplementation and of the entire study, making it impossible to accurately determine the long-term and sporadic role of vitamin D supplementation in stroke patients. Another extremely important limitation was the comparison of a single vitamin D sample with a placebo sample [11].

The 2021 study by Torrisi et al. showed improvements in stroke patients undergoing deliberate neurorehabilitation and vitamin D supplementation, as well as in stroke patients undergoing vitamin D supplementation, after neurorehabilitation itself. A randomised, double-blind, parallel, single-centre, 12-week trial of 40 patients after ischaemic and haemorrhagic stroke was conducted. The participants were randomly allocated in a 1:1 ratio between two parallel groups: the experimental group in which 2000 IU/day of cholecalciferol was administered hourly and the control group in which the patients received no vitamin D supplementation. All patients enrolled in the study underwent intensive neurorehabilitation consisting of cognitive and motor training. All patients completed the rehabilitation cycle. All study participants were screened in two phases, at the beginning and at the end of the rehabilitation. The patients were assessed using the GSE scale, the Montgomery Aasberg Depression Rating Scale (MADRS) and the Functional Independence Measure (FIM). Serum levels of vitamin D and calcium were monitored. Significant improvements were observed in patients in the experimental

and control group in both psychological and functional performance. Patients taking vitamin D supplements showed greater variability than patients not taking them. The results indicated that intensive neurorehabilitation had a beneficial effect on functional recovery after a stroke; furthermore, a clear improvement was demonstrated in the experimental group, suggesting that vitamin D supplementation may also play a positive role [16]. However, vitamin D supplementation in stroke patients did not improve outcomes in a statistically significant manner.

According to Utkan Karasu and Kaymak Karataş, vitamin D supplementation can increase the effectiveness of rehabilitation in post-stroke patients. This is particularly important in patients who are in the first three months after a stroke and will undergo neurological rehabilitation for the first time. The retrospective study included 76 stroke patients. The patients in the study had a stroke (ischaemic/hemorrhagic) for the first time in their lives. The Brunnstrom Recovery Stage (BRS) for the lower limb and the Functional Assessment of Movement (FAC) scale were used to measure results in terms of motor function. Serum levels of 25(OH)D measured in ng/mg were examined during the first week of the study. The patients were divided into two groups: those undergoing vitamin D supplementation during rehabilitation and those who did not receive such supplementation. For 4-12 weeks, patients took oral vitamin D (50,000 IU) during rehabilitation and the total vitamin D dose ranged from 200,000 to 600,000 IU. Levels of vitamin D before rehabilitation and BRS and FAC scores, as well as changes in scores before and after the rehabilitation process, in stroke patients were recorded and compared in both the control and the study group. After the rehabilitation period, a positive and statistically significant change in FAC and BRS scores was found in the group receiving vitamin D. In addition, the effect of vitamin D supplementation on FAC and BRS scores in patients who started the rehabilitation treatment within the first three months after the stroke was compared. It was found that the change in FAC and BRS scores was statistically significant in patients treated with vitamin D. These results demonstrated the beneficial effect of taking vitamin D in patients during the rehabilitation after stroke. Vitamin D supplementation during post-stroke rehabilitation can have a positive effect on lower limb mobility and motor function according to Utkan Karasu and Kaymak Karataş [17]. In this study, vitamin D supplementation in stroke patients had a positive effect and patients had better rehabilitation results.

Sari et al. [12] investigated the effects of vitamin D supplementation on rehabilitation results and balance in patients with hemiplegia due to ischemic stroke. Seventy-two ischaemic stroke patients with low blood levels of vitamin D recovered in hospital for rehabilitation of hemiplegia were included in the study. A division into two groups was made: group A received vitamin D by intra-muscular injection (300,000 IU of vitamin D); group B received saline solution by intramuscular injection. Patients were examined at the beginning of the study and in the third month. To examine the effects, the Brunnstrom scale, the modified Barthel index, the Berg balance scale and the functional ambulation scale (FAS). By the end of the third month, a significant difference was found between the two groups in the modified Barthel index and Berg's balance scale. No statistically significant change was observed in the scores of the Brunnstrom scale or the Functional Ambulation Scale (FAS). In patients after ischaemic stroke, vitamin D supplementation (300,000 IU) did not significantly affect motor recovery and mobility. The study showed that vitamin D supplementation accelerated recovery and increased activity levels in patients. The result confirms the validity of the hypothesis that it would be appropriate to extend follow-up studies with more patients after stroke [12]. Vitamin D supplementation in post-stroke patients clearly did not improve outcomes.

A recent study was conducted in Poland on 94 patients undergoing rehabilitation treatment after an ischaemic stroke. The subjects included in the study (no. = 80) underwent a six-week rehabilitation therapy using proprioceptive neuromuscular facilitation (PNF, 60 minutes per day), mirror therapy (MT, 30 minutes per day) and occupational therapy (OT, 45 minutes per day). The Barthel index (BI) and the modified Rankin scale (mRS) were used for functional assessments. Laboratory tests were conducted for serum levels of vitamin D and Insulin-like Growth Factor-1 (IGF-1). There was a significant increase in BI scores (median difference = 2.0 points [pc]; $P < 0.001$) and IGF levels (median difference = 124.6 ng/ml; $P < 0.001$) after rehabilitation. There was a significant decrease in mRS scores (median difference = 7.0 pc; $P < 0.001$), but no significant difference in vitamin D levels ($P = 0.40$). The effect of age ($B = -0.01$, $P = 0.04$) and serum vitamin D level ($B = -0.02$, $P = 0.01$) on the BI score was demonstrated. The effect of body mass index (BMI) results ($B = -0.07$, $P = 0.02$) on the mRS score was observed. Lower serum vitamin D levels and older age may be associated with worse functional outcomes in patients with first ischemic stroke [18].

CONCLUSIONS

There is a lack of consistency in the results obtained among the studies investigating the correlation between supplementation with vitamin D in stroke patients and improved rehabilitation outcomes. Research has many limitations. Sometimes, serum 25-hydroxyvitamin D levels were not measured in the patients included in the study, which means that the authors selected patients with high or normal vitamin D levels rather than with deficiency. Another major limitation is the sample size, which is often too small. A larger number of participants might have led to different results, moreover, the authors considered different models, different administration regimens, quantities of vitamin D or even longer treatment times for patients. Often the short study period did not allow the long-term effects of supplementation to be examined. Since stroke is the leading cause of disability and the elderly often have severe vitamin D deficiencies, studies evaluating the effectiveness of vitamin D supplementation should be expanded. The results presented above include much information relevant to the planning of rehabilitation in ischaemic stroke patients in the recovery and compensation period, but further research is needed for the implementation of this knowledge in clinical practice.

There is increasing evidence that vitamin D has a positive impact on the prevention of cardiovascular diseases and contributes to better rehabilitation outcomes in stroke patients. Numerous studies testing the efficacy of vitamin D supplementation in post-stroke patients come up against the many limitations in methodology that invalidate the results. Due to the low number of studies and other limitations, it is not un-

equivocal that vitamin D supplementation in stroke patients always has a positive effect on improving rehabilitation. Considering that stroke is the leading cause of disability and that the elderly have high vitamin D deficiencies, it is necessary to expand studies testing the effectiveness of vitamin D supplementation. It is desirable that future studies on vitamin D supplementation in subjects undergoing rehabilitation treatment are controlled and randomised, conducted with a large sample of more than 1000 patients and with at least 5 years of follow-up.

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