Chapter 7.2
Vitamin d supplementation: a promising approach for the prevention and treatment of strokes*

portant goal to reduce the related burden of morbidity, mortality and health-care costs.

In this brief review we summarize the current knowledge on the relationship of vitamin D status and stroke starting with a brief summary on vitamin D metabolism. Then, we outline associations of vitamin D and risk factors for strokes. Furthermore, we present evidence from epidemiological studies on the association of a poor vitamin D status with the prevalence and incidence of strokes. Finally, we discuss possible health benefits of vitamin D for the treatment of stroke patients in order to reduce stroke related disabilities and co-morbidities.

**Literature search strategy**

For this review we performed a systematic literature search in Pubmed for relevant English language publications published until January 2010. We entered the following search terms: "vitamin D" and "stroke" as well as "vitamin D" and "cerebrovascular". We also used the search terms "25hydroxyvitamin D", "1,25-dihydroxyvitamin D" or "calcitriol" instead of vitamin D. Personal collections of articles on this topic as well as references from selected articles were also used to expand the search. Some articles were not cited due to space limitations.

**Vitamin D metabolism**

In general, sunlight (ultraviolet [UV]-B) induced vitamin D production in the skin is the main source for vitamin D whereas vitamin D intake by nutrition plays usually only a minor role [1]. Lifestyle and environmental factors which limit sunlight exposure of the skin are therefore mainly responsible for the current "pandemic" of vitamin D deficiency [1, 2]. It should also be mentioned that food fortification with vitamin D is performed in several countries but is often not effective in preventing vitamin D deficiency [24, 25]. On the other hand, vitamin D supplementation during the first 1 to 2 years of life is generally recommended and effective in preventing rickets [26]. Vitamin D itself is biologically not very active and has to be hydroxylated to exert its genomic and non-genomic effects as a steroid hormone. As a first step, vitamin D is hydroxylated to 25-hydroxyvitamin D (25[OH]D) in the liver. Then, 25(OH)D is further hydroxylated to 1,25(OH)2D which has the highest affinity for the vitamin D receptor (VDR) but circulates in much lower concentrations than 25(OH)D. The VDR is almost ubiquitously expressed and regulates approximately three percent of the human genome [27]. Circulating levels of 1,25(OH)2D are mainly determined by 1α-hydroxylation of 25(OH)D to 1,25(OH)2D in the kidney, which is stimulated by e.g. low calcium and high parathyroid hormone (PTH). Interestingly, it has been shown that 1α hydroxylation occurs on a local level in many different cells and organs [28]. Tissue levels of 1,25(OH)2D seem to be mainly a result of this local 1α-hydroxylation of 25(OH)D. Blood levels of kidney derived 1,25(OH)2D are, however, not a good estimate of locally produced 1,25(OH)2D in extra-renal tissues because of differentially regulated 1α-hydroxylase activities [28]. Considering that local extra-renal synthesis of 1,25(OH)2D is significantly determined by circulating 25(OH)D levels it is widely accepted that serum levels of 25(OH)D are the best estimate of
whole-body vitamin D status [1, 28]. 25(OH)D levels are therefore used to classify the vitamin D status into vitamin D deficiency (<20 ng/ml), vitamin D insufficiency (20 to 29 ng/ml) and vitamin D sufficiency (≥30 ng/ml) (multiply by 2.496 to convert ng/ml to nmol/l) [1]. Vitamin D intoxication occurs when 25(OH)D levels are higher than 150 ng/ml and adverse effects of vitamin D are almost exclusively driven by hypercalcemia [1,29]. 24-hydroxylation is a main step in the degradation of 25(OH)D and 1,25(OH)2D but the biological relevance of the resulting vitamin D metabolites is still largely unclear. Low 25(OH)D levels can be easily treated by vitamin D supplementation. It can be expected that supplementation of 1,000 IU vitamin D per day raises 25(OH)D levels by approximately 10 ng/ml [30]. Individual variations in the response to vitamin D supplementation should, however, be considered and therefore it appears reasonable to consider remeasurements of 25(OH)D after about 3 months of treatment. In particular obese individuals who are at increased stroke risk require much higher vitamin D doses compared to normal weight individuals to achieve a sufficient 25(OH)D status [31]. Of note, vitamin D can be supplemented in daily, weekly or monthly doses which result in similar increases in 25(OH)D levels [32]. Sun exposure can also increase vitamin D levels up to a maximum increase which is equivalent to daily vitamin D intakes of up to 20,000 IU, but possible side effects of increased sun exposure must be considered [33]. Active vitamin D treatment with 1,25(OH)2D is commonly performed in patients with endstage renal disease [34]. In contrast to natural vitamin D, supplementation of 1,25(OH)2D has a relatively narrow therapeutic window with the risk of hypercalcemia if 1,25(OH)2D is overdosed [34]. Hence, various analogues of vitamin D have been developed which exert less calcemic side effects and may offer some additional benefits compared to 1,25(OH)2D (e.g. enhanced antiproliferative or immunoregulative activity) [34, 35].

**Vitamin D deficiency and risk factors for strokes**

Previous studies have shown that low 25(OH)D levels are associated with an increased risk for cardiovascular events [5, 36-42]. This association seems to be at least in part mediated by associations of vitamin D deficiency with risk factors for ischemic and hemorrhagic strokes [20, 21]. In this chapter we will outline the possible pathways by which vitamin D deficiency might be related to increased stroke risk.

**Arterial Hypertension and Metabolic Syndrome**

Arterial hypertension, one of the most significant risk factors for strokes, has been associated with vitamin D deficiency [43]. Towards this, various clinical studies have largely but not consistently shown an association of vitamin D deficiency as well as low UV-B radiation with increased blood pressure [43]. Antihypertensive effects of vitamin D seem to be mainly mediated by suppression of the reninangiotensin-aldosterone system, prevention of hyperparathyroidism, renoprotective and anti-inflammatory effects as well as vasculoprotective properties [43]. Randomized controlled trials in this field are rare but a recent meta-analysis showed that natural vitamin D therapy reduces systolic blood pressure by -6.18 mm Hg (95% CI -12.32 to -0.04) and diastolic blood pressure by -2.56 mm Hg (95% CI -5.83 to 0.72) [44]. Beyond hyper-
tension, vitamin D deficiency has also been linked to all other components of the metabolic syndrome, which is a risk factor for strokes itself. In detail, it has been documented that vitamin D deficiency is associated with increased risk of type 2 diabetes mellitus [45]. Large interventional studies are still missing but results from small randomized controlled trials suggest that vitamin D supplementation improves insulin sensitivity and reduces insulin resistance [45-47]. Proposed anti-diabetic properties of vitamin D include stimulation of insulin secretion, upregulation of the insulin-receptor and anti-inflammatory effects [45]. Interestingly, type 1 diabetes may also be associated with vitamin D deficiency which is supported by an inverse association of both UV-B radiation and vitamin D intake during childhood with the incidence of type 1 diabetes [48, 49]. Pathophysiological mechanisms remain speculative but there is evidence that vitamin D increases regulatory T cells which protect against autoimmune diseases [50, 51]. Large epidemiological studies revealed an increased prevalence of dyslipidemia in patients with low 25(OH)D levels [5, 52, 53]. A recent randomized controlled trial has shown that vitamin D supplementation significantly increases HDL-cholesterol and lowers triglycerides but a slight increase in LDL-cholesterol levels was also observed [54]. Given that statin therapy is associated with reduced incidence of strokes it should be underlined that a recent study showed a better lipid response to atorvastatin in patients with high compared to low 25(OH)D levels [55]. In addition, previous study results suggest that statin treatment might increase 25(OH)D levels but data on this topic are inconsistent [55-57]. In observational studies vitamin D deficiency has also been linked to both increased body mass index as well as increased waist to hip ratio [5, 53]. Data from interventional trials are inconclusive but largely failed to show significant reductions in body weight or body fat after vitamin D supplementation [5, 54, 58]. Hence, it appears that low 25(OH)D levels in obese persons are rather the consequence of vitamin D storage in adipose tissue or reduced sunlight exposure than the cause of obesity.

Atherosclerosis

Atherosclerosis, in particular of the carotid arteries, contributes to cerebrovascular ischemia. Data on the association of carotid intima-media thickness and 25(OH)D levels are, however, inconsistent [59-62]. Some studies showed no association [59, 60] whereas others reported that low 25(OH)D levels are independently associated with carotid intima-media thickness [61, 62]. From a pathophysiological point of view, vitamin D deficiency may contribute to atherosclerosis by its proposed associations with classic cardiovascular risk factors but may additionally exert direct proatherosclerotic effects. In detail, vitamin D deficiency may contribute to endothelial dysfunction, pro-atherosclerotic changes of vascular smooth muscle cells (VSMC) and to increased macrophage to foam cell formation [63-66]. It should, however, be noted that supraphysiological doses of 1,25(OH)2D or its analogues can also be deleterious with promotion of vascular calcification [63].
Prothrombotic States

Thrombotic and thrombembolic events are the most common cause of ischemic strokes. Experimental animal studies suggest that vitamin D may prevent thrombosis by upregulation of thrombomodulin and by suppression of plasminogen activator inhibitor type-1 (PAI-1), thrombospondulin 1, and the procoagulant tissue factor [27]. Significant reductions of venous and arterial thrombosis in a placebo controlled trial with high doses of 1,25(OH)2D in prostate cancer patients are in favour of antithrombotic effects of the vitamin D endocrine system [67]. This is in line with a recent study on an inverse association of 25(OH)D levels with increased thrombotic activity [68]. In the same study, vitamin D supplementation, did, however, not affect parameters of the thrombogram [68]. Apart from this, it should be considered that myocardial diseases which predispose to cardio-embolic events and which are considered risk factors for strokes have also been associated with vitamin D deficiency [69-71].

Secondary Hyperparathyroidism

Vitamin D is a key regulator of calcium homeostasis. It is frequently observed that low calcium levels caused by vitamin D deficiency stimulate PTH secretion resulting in secondary hyperparathyroidism. Elevated PTH levels in secondary hyperparathyroidism maintain serum calcium levels within the normal range and stimulate renal conversion of 25(OH)D to 1,25(OH)2D but may also exert some deleterious effects. Of note, initial definitions of vitamin D deficiency were based on 25(OH)D cut-off levels at which PTH levels start to rise. Previous studies showed that elevated PTH was associated with a history of strokes and PTH was significantly higher in female stroke patients compared to age matched controls [72, 73]. PTH has also been shown to exert pro-atherosclerotic effects and is associated with arterial hypertension [74]. A recent community based study showed that PTH levels predicted overall cardiovascular mortality and similar results have been found in patients referred to coronary angiography [75, 76]. Hence, it can be hypothesized that PTH elevations in patients with vitamin D deficiency may also contribute to an increased risk of cerebrovascular events.

Inflammation

Inflammation is considered a risk factor for strokes [77]. Various studies suggest that vitamin D may exert anti-inflammatory effects [3, 27, 50, 54, 59]. Data on this topic are, however, not fully consistent but Zittermann and Schleithoff et al. demonstrated in randomized placebo controlled trials that vitamin D supplementation decreased the inflammatory parameter tumor necrosis factor-α (TNF-α) and increased the anti-inflammatory cytokine interleukin-10 [54, 78]. On the other hand it should also be stressed that vitamin D deficiency may increase the risk of infections which may trigger cerebrovascular events [13]. An overview of the associations of vitamin D deficiency with risk factors for stroke is shown in Fig. (1).
Epidemiology of vitamin D deficiency and stroke risk

A large body of evidence from epidemiological studies indicates that vitamin D deficiency is associated with increased risk of strokes. Interestingly, numbers of studies examined whether there are seasonal and regional differences in the incidence of strokes [79-91]. Results were inconsistent but the picture of many of these studies is that stroke incidence appears to increase in winter and at lower altitudes [79-91]. In general, winter season and lower altitude are associated with low UV-B radiation and subsequently lower \( 25(\text{OH})D \) levels. We are aware that there are many plausible explanations for these latter findings but in our opinion the seasonal and geographic differences in stroke incidences fit well to the hypothesis that low \( 25(\text{OH})D \) levels are a risk factor for cerebrovascular events [79-91]. In line with this, Poole et al. showed that patients within 30 days of a first-ever stroke presented with significantly lower \( 25(\text{OH})D \) levels when compared to healthy elderly subjects [15].

These data are supported by results from others, who observed reduced \( 25(\text{OH})D \) levels in patients with a history of strokes and in subjects with MRI indicators of cerebrovascular disease [16, 92-95]. A few prospective studies have already specifically addressed the question whether \( 25(\text{OH})D \) levels are predictive for future strokes [16, 41, 96-99]. Marniemi et al. examined 755 elderly subjects who were followed-up for up to 10 years [96]. Seventy strokes occurred during the observational period but there was no significant difference in \( 25(\text{OH})D \) levels between cases (11.9±7.2 ng/ml) and controls (12.5±7.8 ng/ml) [96]. However, compared to the lowest tertile in 1,25 (OH)2D levels, the risk of stroke was significantly reduced in the highest tertile with a relative risk of 0.41 (95% CI 0.22-0.77) [96]. Bolland et al. studied 1471 health com-

Fig. (1). Associations of vitamin D deficiency with risk factors for stroke.
munity-dwelling women (mean age 74 years) who participated in a 5-years randomized placebo controlled trial with calcium supplementation [97]. Hazard ratios (HR) (with 95% CI) for stroke in a crude model and a model adjusted for cardiovascular risk factors were 1.7 (1.0-3.0) and 1.4 (0.8-2.5), respectively, in women with seasonally adjusted 25(OH)D levels below 20 ng/ml compared to women with higher 25 (OH)D levels [97]. The increased stroke risk was particularly pronounced in women allocated to calcium, which showed a HR for stroke in the vitamin D deficient group of 2.5 (1.2-5.3) in unadjusted analyses [97]. After adjustments for possible confounders, however, all observed associations of low 25(OH)D levels and increased risk of stroke lost their significance [97]. We addressed this issue in the Ludwigshafen RIsk and Cardiovascular Health (LURIC) Study, a prospective follow-up study among 3299 patients referred for coronary angiography [16]. During a median follow-up time of 7.75 years, 42 patients died due to fatal strokes. Risk of fatal stroke was significantly reduced per increase in month of blood sampling adjusted z values of both 25(OH)D and 1,25(OH)2D. The HRs (with 95% CI) adjusted for cardiovascular risk factors were 0.67 (0.46-0.97) for 25(OH)D and 0.72 (0.52-0.99) for 1,25(OH)2D, respectively [16]. Kilikkinen et al. published data from the Mini-Finland Health Survey, a study among 6219 men and women aged ≥ 30 years who were free of cardiovascular disease at baseline [41]. During a median follow-up time of 27.1 years, 293 cerebrovascular disease deaths were recorded. After adjustment for cardiovascular risk factors, the HR for cerebrovascular death was 0.48 (0.31-0.75) in the highest versus the lowest 25(OH)D quintile. More in depth analyses revealed that the adjusted HRs for hemorrhagic stroke and ischemic stroke were 0.61 (0.26-1.46) and 0.60 (0.38-0.93), respectively, in the highest versus the lowest 25(OH)D tertile [41]. At the American Heart Association scientific sessions in 2009, Bair et al. presented yet unpublished data from a prospective follow-up analysis among 27,686 persons aged at least 50 years and with no history of cardiovascular disease [98]. After one year of follow-up persons with 25(OH)D levels below 15 ng/ml were at 78% higher risk to die due to stroke than individuals with 25(OH)D levels > 30 ng/ml [98]. Randomized controlled trials are rare and were not adequately powered to detect differences in the incidence of strokes [99-101]. In the Women’s Health Initiative (WHI), 36,282 postmenopausal women were randomly allocated to either 1000 mg calcium plus 400 IU vitamin D per day or placebo [99, 100]. During a follow-up of 7 years 739 strokes were recorded and the HR in the treatment versus the placebo group was 0.95 (0.82-1.10) [99]. In analyses of the WHI Study restricted to fatal cerebrovascular events (n=114), the HR was 0.89 (0.62-1.29) in the treatment versus the placebo group. Subgroup analyses revealed a respective HR of 0.62 (0.36-1.08) in patients younger than 70 years and a HR of 1.20 (0.72-2.01) in older study participants [100]. Interpretations of these above mentioned non-significant reductions in strokes in the calcium plus vitamin D group are difficult. Even the authors of the WHI Study acknowledged that main limitations such as the extremely low dose of 400 IU vitamin D daily and the poor adherence to study medication were significant drawbacks of their work which preclude any final conclusions on cardiovascular health benefits of vitamin D plus calcium supplementation [99, 100]. Another randomized controlled trial by Trivedi et al. among 2686 elderly persons was performed with a monthly supplementation of 100,000 IU vitamin D [101]. There were only 54 fatal strokes after a follow-up of five years with
no significant difference between the treatment and the placebo group (28 versus 26 fatal strokes) [101]. A limitation of most large vitamin D interventional trials is the lack of PTH measurements which are required to conclude whether the achieved 25 (OH)D levels were sufficient to treat or prevent potentially harmful PTH elevations. In general, randomized controlled trials did not consider individual variations in the response to vitamin D supplementation. This is an important point when considering that obese patients, which are at increased stroke risk, require doses up to 10,000 IU per day to replete their vitamin D status [31]. Taken together, observational studies are largely in favour of the hypothesis that vitamin D may protect against strokes but only few interventional studies are available until now, and these have some methodological limitations. Hence, whether vitamin D protects against stroke remains to be proven in randomized controlled trials.

Role of vitamin D for the treatment of stroke patients

Poststroke patients may benefit from a sufficient vitamin D status because apart from its proposed effects in the prevention of (recurrent) strokes, vitamin D is suggested to reduce neurological, psychological and musculoskeletal diseases in these patients.

Neuroprotective and Neuromuscular Effects of Vitamin D

Cerebral ischemia was shown to stimulate expression of VDR and 1α-hydroxylase along with increased VDR activation, indicating a role of the vitamin D endocrine system in stroke patients [102]. In a rat model of cerebral ischemia induced by ligation of the middle cerebral artery, pretreatment with 1,25(OH)2D for 8 days was associated with a significant reduction in infarct size of the ischemic brain [103]. In the same study Wang et al. found that 1,25(OH)2D treatment increased cerebral concentrations of glial cell linederived neurotrophic factor (GDNF), a member of the transforming growth factor (TGF)-β1 superfamily. GDNF and other vitamin D regulated neurotrophic factors have previously been shown to ameliorate ischemia induced brain damage [103-105]. Attenuated ischemic brain damage after 1,25(OH)2D supplementation was also confirmed in further experimental studies [106, 107]. Neuroprotective effects of vitamin D are partially mediated by antioxidative and immunomodulatory properties and by its trophic role in differentiation and maturation of neurons [107-111]. Experiments by Brewer et al. indicate that 1,25(OH)D may modulate neuronal calcium flux by regulating the expression of L-type voltage-sensitive Ca2+ channels (L-VSCCs) [112]. The authors concluded that their findings suggest an important role of vitamin D mediated regulation of calcium homoeostasis in the protection against neurodegenerative diseases. In addition, vitamin D was shown to potentiate axon regeneration in a rat model of peripheral nerve injury [113]. Hence, vitamin D metabolites, which can pass through the blood-brain barrier, exert various neuroprotective actions. From a clinical point of view, cognitive impairment is an important issue in stroke patients. Large epidemiological studies in older adults showed that low 25(OH)D levels are associated with impaired cognitive function [114-118]. It should, however, be noted that in a systematic review on this topic Annweiler et al. concluded that the association of 25(OH)D levels and cognitive function
is not yet clearly established [118]. Furthermore, most of the data on 25(OH)D and cognitive function were derived from crosssectional studies which precludes conclusions regarding the directionality of the observed associations. Apart from this, Jorde et al. reported about amelioration of depressive symptoms in a randomized placebo controlled trial among 441 overweight and obese subjects [119]. Further studies on vitamin D and depression are still needed but poststroke patients would significantly benefit from anti-depressive vitamin D effects [119, 120]. Finally, there is evidence that vitamin D exerts anticonvulsant effects which might be useful for prevention and treatment of poststroke epilepsy [121, 122]. One of the most important goals in the treatment of stroke patients is the functional recovery of paretic extremities and neuromuscular disorders [21]. In a 2 years randomized placebo controlled trial among 96 elderly women with poststroke hemiplegia Sato et al. found significantly improved muscle strength in the vitamin D group, which received 1,000 IU daily [17]. Furthermore, vitamin D intake was associated with a 59% (95% CI 28-81%) reduction in falls [17]. This is an important finding when considering the markedly increased risk of falls in poststroke patients with subsequently higher risk of (hip) fractures [17, 18]. Of note, Sato et al. recorded 4 hip fractures in the placebo group whereas there was no such event in the vitamin D group (p=0.049) [17]. These data are in line with a recent metaanalysis by Bischoff-Ferrari et al. who calculated that vitamin D intake of 700 to 1,000 IU per day reduces the risk of falling in older individuals by 19% [123]. Dhesi et al. studied the neuromuscular effects of an intramuscular injection of 600,000 IU vitamin D [124]. In this randomized placebo controlled trial among 139 ambulatory patients with history of falls and 25(OH)D levels ≤ 12 ng/ml there was a significant improvement in functional performance, reaction time and balance but no effect on muscle strength in the vitamin D group [124]. Hence, there is accumulating evidence that a sufficient vitamin D status may be beneficial for neuromuscular function in stroke patients.

### Osteoporosis and Fractures

Compared to a reference population, stroke patients are at a 2 to 4 times higher risk of fractures, in particular hip fractures which are associated with an increased mortality [125]. Sato et al. studied 236 stroke patients who were followed up for 2 years for occurrences of fractures. Patients with 25(OH)D levels below 10 ng/ml were at significantly increased risk of hip fractures [18]. Numerous further studies by the group of Sato et al. as well as of others have indicated that vitamin D deficiency is associated with accelerated bone resorption and reduced bone mineral density in stroke patients [126-136]. Importantly, a randomized trial with sunlight exposure among 258 stroke patients showed a significant increase in bone mineral density in the treatment group [137]. It should be considered that the adverse effects of vitamin D deficiency on bone metabolism seem to be aggravated by immobilisation of paretic extremities. Immobilisation associated hypercalcemia, which is mainly a result of increased bone resorption, is not uncommon in these patients and may lead to severe suppression of renal 1,25(OH)2D synthesis. Beyond low 25(OH)D levels, these suppressed 1,25(OH)2D concentrations may also be very deleterious when considering previous studies which showed increased all-cause and cardiovascular mortality in patients with low
The above mentioned evidence underlines that vitamin D therapy, which is routinely recommended for osteoporosis treatment, is a promising therapeutic approach to reduce the burden of osteoporosis in stroke patients. Vitamin D effects on neuromuscular function as well as on bone and mineral metabolism may act in concert to prevent poststroke fractures. Apart from this, various other suggested properties of vitamin D such as anti-infectious or anti-thrombotic properties might be beneficial for poststroke patients. An overview of the associations of vitamin D deficiency with stroke related comorbidities and complications is shown in Fig. (2).

![Diagram showing associations of vitamin D deficiency with stroke related comorbidities and complications.](image)

**Summary and discussion**

We have presented evidence that vitamin D deficiency is associated with an increased risk of strokes. This notion is supported by accumulating studies showing that several risk factors for cerebrovascular events are associated with low 25(OH)D levels. In addition, findings from cross-sectional and longitudinal studies underlined that vitamin D deficiency is common in patients presenting with acute stroke and indicates an increased risk for future strokes. Reverse causality may, however, also be present and we can therefore not exclude that depressed 25(OH)D levels are simply the consequence of strokes as well as other adverse health consequences related to vitamin D deficiency (see Fig. (1) and Fig. (2)). Hence, whether the association of vitamin D deficiency and strokes is of causal nature remains to be proven in further randomized controlled trials. Apart from this, it should be stressed that poststroke patients, who are usually less frequently exposed to sunlight, are at particularly increased risk of vitamin D deficiency. This is an important issue because vitamin D has been shown to exert neuroprotective, neuromuscular and osteoprotective effects which might...
minimize cognitive and functional impairments in poststroke patients. We also want to stress that vitamin D has been shown to exert multiple beneficial health effects (e.g. anti-carcinogenic effects) beyond its proposed role in the prevention and treatment of strokes. Hence, it could be hypothesized that a widely introduced vitamin D treatment might be beneficial for many diseases beyond strokes. This enthusiastic goal of public health strategies to fight against vitamin D deficiency is supported by a recent meta-analysis of randomized controlled trials, which showed a significant 7% reduction in total mortality in patients treated with vitamin D [141]. We have to acknowledge that we cannot uncritically raise a general recommendation to supplement vitamin D in the prevention and treatment of strokes unless we have supportive findings from adequately designed randomized controlled trials. We do, however, believe, that the possible health benefits outweigh the respective risks and costs of approaches to achieve a sufficient vitamin D status in the prevention and treatment of strokes. In this context we want to draw the attention towards the facts that (i) vitamin D insufficiency affects almost every second person worldwide as well as most stroke patients and (ii) that vitamin D supplementation is easy, safe and cheap. Nevertheless, further randomized controlled trials are urgently needed to prove whether vitamin D supplementation reduces the incidence of strokes and improves the outcome of poststroke patients.

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