Ageing Research Reviews 96 (2024) 102244

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review Article

Vitamin D and ischemic stroke - Association, mechanisms, and therapeutics

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ARTICLE INFO

Keywords:
Vitamin D deficiency
Cardiovascular disease
Ischemic stroke
Vitamin D receptor
Non-linear association

ABSTRACT

Confronting the rising tide of ischemic stroke and its associated mortality and morbidity with ageing, prevention and acute management of ischemic stroke is of paramount importance. Mounting observational studies have established a non-linear association of vitamin D status with cardiovascular diseases, including ischemic stroke. Paradoxically, current clinical trials fail to demonstrate the cardiovascular benefits of vitamin D supplementation. We aim to update recent clinical and experimental findings on the role of vitamin D in the disease course of ischemic stroke, from its onset, progression, recovery, to recurrence, and the established and alternative possible pathophysiological mechanisms. This review justifies the necessities to address stroke etiological subtypes and focus on vitamin D-deficient subjects for investigating the potential of vitamin D supplementation as a preventive and therapeutic approach for ischemic stroke. Well-powered clinical trials are warranted to determine the efficacy, safety, timing, target individuals, optimal dosages, and target 25OHD concentrations of vitamin D supplementation in the prevention and treatment of ischemic stroke.

1. Introduction

Stroke is a major cause of disability in people aged more than 50 years and the leading cause of mortality worldwide (Diseases GBD, 2020). Ischemic stroke, accounting for 84 % of all strokes, represents a serious public health problem due to its high prevalence, disability, and mortality (Johnson et al., 2019; Li et al., 2022). Prevention and acute management of ischemic stroke is thus of paramount importance. Apart from ageing, a crucial nonmodifiable risk factor, a series of modifiable risk factors, including but not limited to hypertension, diabetes mellitus, atrial fibrillation, and smoking, predispose to the occurrence of ischemic stroke (Cui et al., 2021). Considering that ischemic stroke is highly preventable, it is imperative to resolve these unequivocal risk factors to reduce the burden of ischemic stroke. Furthermore, there is a pressing need to raise awareness and knowledge of novel potential risk factors that may suggest potential druggable targets for the management of ischemic stroke.

Vitamin D deficiency affects nearly 50 % of the population worldwide (Cui et al., 2023a). In addition to calcium and phosphorus homeostasis of musculoskeletal health, vitamin D is a pleiotropic steroid hormone with extensive extra-skeletal actions. The potential roles of vitamin D in cardiovascular diseases (CVD) have been rigorously debated in recent years without consensus being reached. For clarification, stroke is included within the concept of CVD in this review.

The non-linear association of vitamin D status with CVD and all-cause mortality has been emergingly revealed in large observational studies (Crowe et al., 2019; Dai et al., 2021; Sha et al., 2022; Sofianopoulou et al., 2024; Sutherland et al., 2022; Wan et al., 2022; Xiao et al., 2022; Zhou et al., 2021). Conflictingly, current clinical trials fail to demonstrate the efficacy of vitamin D supplementation on reducing the risk of CVD and more specifically, stroke (Manson et al., 2019; Pittas et al., 2019; Scragg et al., 2017). Here, we will outline the shortcomings in the trial design that hinder the reliability of any interpretation, lessons that should be learned, and implications for future clinical trials to investigate any of these CVD endpoints.

In this review, we specifically aim to highlight the importance of vitamin D in ischemic stroke and its etiological subtypes. Literature mining supported the potential roles of vitamin D in the disease course of ischemic stroke, from its onset, progression, outcomes, and recurrence. Mounting observational evidence has indicated that hypovitaminosis D is associated with an increased risk of ischemic stroke (Afzal and Nordestgaard, 2017; Navale et al., 2022). However, no

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https://doi.org/10.1016/j.arr.2024.102244
Received 17 August 2023; Received in revised form 7 February 2024; Accepted 19 February 2024
Available online 21 February 2024

clinical trials have shown the benefits of vitamin D supplementation in stroke prevention among the general population. Administration of bioactive vitamin D and high-dose vitamin D precursor was reported to mitigate ischemic brain injury in experimental stroke models and disease severity among patients with acute ischemic stroke (AIS), respectively. Collectively, we will update recent clinical and experimental findings on the impact of vitamin D on the incidence, severity, and prognosis of ischemic stroke, as well as the established and alternative possible pathophysiological mechanisms. On the basis of these findings, we further address the translational significance of vitamin D as a potential intervention option for the prevention and treatment of ischemic stroke.

2. Vitamin D metabolic process

Vitamin D mainly derives from local synthesized vitamin D3 in the skin on ultraviolet B (UVB) irradiation during sun exposure (Fig. 1). Approximately 20 % of vitamin D comes from exogenous intake from diet and vitamin D supplements, including vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Vitamin D metabolites are translocated in the bloodstream by vitamin D binding protein (DBP). Vitamin D3 reaches the liver and is hydroxylated by 25-hydroxylase into 25OHD (calcidiol), a reliable indicator of vitamin D status. After reaching the proximal renal tubule, 25OHD is then converted by 1α-hydroxylase (CYP27B1) into bioactive $1,25(OH)_2D_3$ (calcitriol). Notably, owing to genetic variations in the crucial enzymes for 25OHD synthesis and metabolism, changes in circulating 25OHD levels show different responsiveness to dietary vitamin D intake and solar UVB exposure (Gospodarska et al., 2023).

In addition to its predominant distribution in the kidney, 1α-hydroxylase is expressed throughout the cardiovascular system, immune system, and central nervous system (CNS) at low levels, contributing to the extrarenal local production of $1,25(OH)_2D_3$ (Christakos et al., 2016; Galoppin et al., 2022; Pilz et al., 2016). Locally produced $1,25(OH)_2D_3$ functions in an autocrine or paracrine manner and its availability critically depends on the levels of circulating 25OHD. $1,25(OH)_2D_3$ functions via activating the vitamin D receptor (VDR), which is widely expressed in a variety of tissue cells, for instance, musculoskeletal cells, immune cells, endothelial cells, vascular smooth muscle cells, cardiomyocytes, islet β cells, and neural cells (Galoppin et al., 2022). Once liganded, VDR heterodimerizes with the retinoid X receptor, which binds to vitamin D response elements in the promoter region of target genes and regulates gene expression of approximately 3 % of the genome. Apart from mineral homeostasis, vitamin D engages in modulating immune function, endothelial function, the activity of the renin-angiotensin-aldosterone system, insulin sensitivity, oxidative stress, and cell proliferation and apoptosis, thereby involved in musculoskeletal conditions, autoimmune diseases, infectious diseases, CVD, and cancer (Bouillon et al., 2022).

There is no consensus regarding the cutoff defining vitamin D deficiency. The most widely acknowledged criterion defines vitamin D deficiency as a 25OHD level of below 50 nmol/L (Holick et al., 2011), whereas several guidelines advocate using a cutoff of 25 or 30 nmol/L (Roth et al., 2018). The prevalence of vitamin D deficiency is largely affected by race/ethnicity and sun exposure that depends on latitude, seasonal variation, and sociocultural factors, which is higher in Asia, the Middle East, and Northern Europe, during winter, and among populations with obesity and limited sun exposure (Cui et al., 2023a). It bears mentioning that the term "vitamin D" is generally used to refer to its precursors, but not $1,25(OH)_2D_3$, the two of which have different pharmacological effects. Many studies refer to "$1,25(OH)_2D_3$" as vitamin D/vitamin D3 (Vieth, 2022). This inaccurate use of terminology easily causes confusion and even leads to false interpretation on the health effects of vitamin D supplementation. For clarification, this

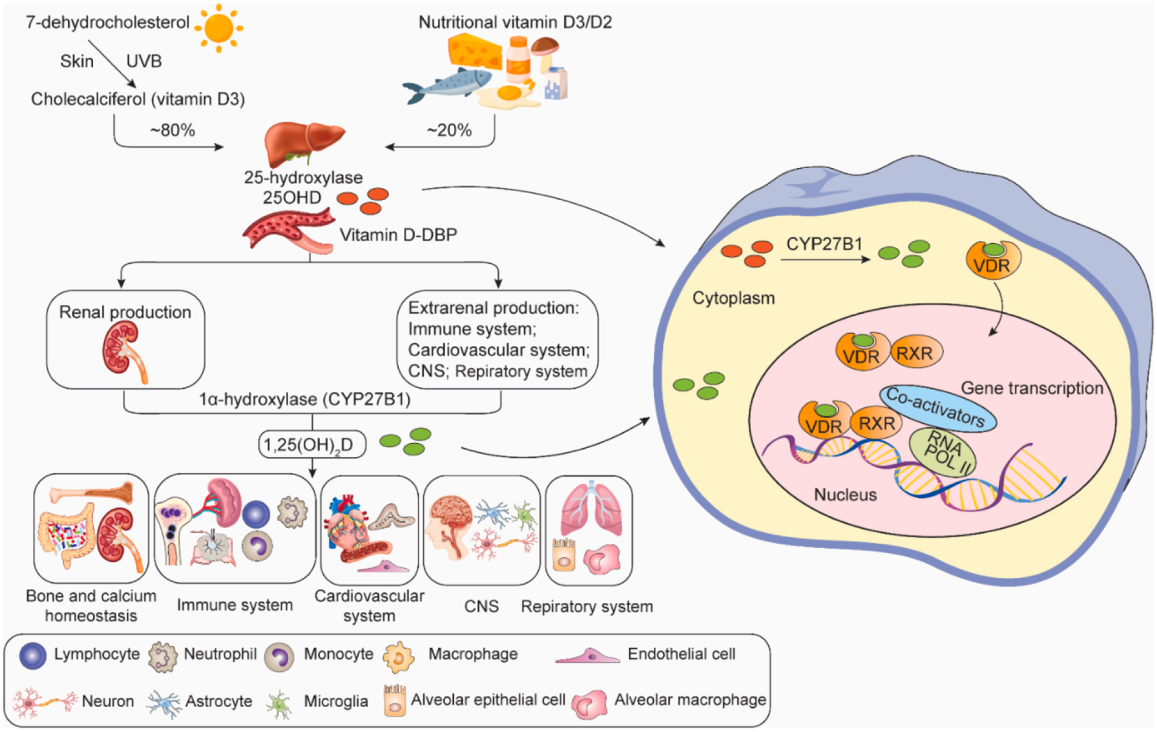

Fig. 1. Vitamin D metabolic processes and pleiotropic impacts on the organism. Vitamin D mainly derives from local synthesized vitamin D3 in the skin on ultraviolet B (UVB) irradiation during sun exposure. The renal source contributes to the majority of circulating $1,25(OH)_2D_3$ that functions in an endocrine manner, while extrarenally synthesized $1,25(OH)_2D_3$ by *in situ* 1α-hydroxylase permits its local functions. $1,25(OH)_2D_3$ functions by binding to vitamin D receptor (VDR), which then heterodimerizes with the retinoid X receptor (RXR). The ligand-bound VDR-RXR complex binds to vitamin D response elements (VDRE) in the promoter region of target genes and regulates gene expression involving the musculoskeletal system, cardiovascular system, immune system, central nervous system (CNS), and respiratory system. DBP, vitamin D binding protein. RNA POL II, RNA polymerase II.

review refers to "vitamin D" as its precursors unless otherwise specified.

3. Vitamin D and ischemic stroke risk

3.1. Observational studies

Overwhelming observational evidence has suggested a non-linear inverse association between serum 25OHD levels and stroke risk (Table 1), with the lowest risk mostly observed at a 25OHD level of 50 nmol/L (Afzal and Nordestgaard, 2017; Navale et al., 2022; Sofianopoulou et al., 2024). A prospective cohort study in Hong Kong also elucidated this non-linear association, with the lowest risk observed at a 25OHD level of 70–80 nmol/L (Leung et al., 2017). Several large prospective studies and meta-analyses revealed that the association between 25OHD and stroke risk held true only for ischemic stroke, but not for hemorrhagic stroke (Brondum-Jacobsen et al., 2013; Judd et al., 2016; Leung et al., 2017; Shi et al., 2020; Zhou et al., 2018). Additionally, vitamin D intake was suggested to be associated with reduced incident stroke, particularly for ischemic stroke (Kojima et al., 2012; Shi et al., 2020). Furthermore, lower serum 25OHD was associated with an increased risk of recurrent stroke in ischemic stroke patients (Liu et al., 2020; Qiu et al., 2017).

Among participants with established coronary heart disease or stroke, the non-linear association also holds true for the recurrence of CVD or specifically stroke, as indicated by two large prospective analyses of 8–11-year follow-up (Li et al., 2022; Lin et al., 2023). The lowest risk of recurrent stroke was reported to lay at a 25(OH)D level of about 60–70 nmol/L. Specifically for recurrent ischemic and hemorrhagic stroke, the minimal risk was observed at 40 nmol/L and 60 nmol/L, respectively (Li et al., 2022; Vergatti et al., 2023).

The association between vitamin D status and ischemic stroke appears to differ with ethnicity, for which vitamin D metabolism, as well as the susceptibility to distinct stroke subtypes, varies substantially (Hsu et al., 2020; Ornello et al., 2018). Compared with African Americans, hypovitaminosis D was a stronger risk factor for CVD in whites and Chinese populations (Robinson-Cohen et al., 2013; Wang et al., 2021). However, another study suggested that the strength of association did not differ by community-living blacks and whites in the United States (Judd et al., 2016).

Ischemic stroke is a heterogeneous disease with distinct etiologies and pathogenesis, including large-artery atherosclerosis (LAA), cardioembolism (CE), small-artery occlusion (SAO), other determined causes, and undetermined causes (Adams et al., 1993). So far, the association between 25OHD levels and the risk of ischemic stroke subtypes has remained a subject of debate. Two cohort studies suggested that the association appeared most robust for SAO subtypes (Judd et al., 2016; Sun et al., 2012). An association between 25OHD and pathologies of chronic small vessel disease on brain magnetic resonance imaging was also reported among patients with AIS or transient ischemic attack (Chung et al., 2015), which instead was found to be null among the general population without prior stroke (Michos et al., 2014). By contrast, several cross-sectional studies suggested serum 25OHD levels were only associated with or showed stronger association with LAA subtypes (Buell et al., 2010; Chaudhuri et al., 2014; Daubail et al., 2013; De Silva et al., 2013; Manouchehri et al., 2017).

Approximately a quarter of ischemic stroke was attributed to LAA subtypes worldwide, and this proportion was further increased to 33 % in Asians (Ornello et al., 2018). The major direct pathological causes of LAA lie in the atherosclerotic stenosis of major intracranial or extracranial cerebral arteries. In regard to extracranial lesions, inconsistent conclusions were drawn on the correlation of vitamin D with carotid intima media thickness and carotid plaque burden. Several studies revealed a correlation between vitamin D deficiency and subclinical carotid atherosclerosis (Carrelli et al., 2011; Chen et al., 2018a; Lupoli

Table 1
Observational evidence indicating the association between vitamin D levels and ischemic stroke risk.

Outcomes involving stroke	Design	Duration of follow-up (years)	Sample	Country	25OHD levels (nmol/L)	Finding	Study
Stroke	Prospective	10.9	500,962[a]	Europe	<50 (55 %)	Non-linear association, with a 25OHD threshold of 50 nmol/L	(Sofianopoulou et al., 2024)
Stroke and dementia	Prospective	10.9	427,690	Europe	46.8[b]	Non-linear association, with a 25OHD threshold of 50 nmol/L	(Navale et al., 2022)
Ischemic stroke	Prospective	9.3	114,398	Europe	<25 (13.8 %), 25–49 (36.6 %)	Non-linear association, with a 25OHD threshold of 50 nmol/L	(Afzal and Nordestgaard, 2017)
Stroke; ischemic and hemorrhagic stroke	Prospective	15	3458	Hong Kong	<50.96 (40 %)	Non-linear association with stroke and ischemic stroke, with a 25OHD threshold of 70–80 nmol/L	(Leung et al., 2017)
Recurrent stroke; ischemic and hemorrhagic subtypes	Prospective	7.6	6824	Europe	<50 (60.7 %)	Non-linear association, with different 25OHD thresholds for ischemic and hemorrhagic stroke (60 and 40 nmol/L, respectively)	(Li et al., 2022)
Recurrent CVD (MI, CHF, and stroke)	Prospective	11.2	22,571	Europe	<50 (58.6 %)	Non-linear association with recurrent CVD, MI, CHF, and stroke, with a 25OHD threshold of 50 nmol/L	(Lin et al., 2023)
Stroke; ischemic and hemorrhagic stroke	Prospective	21	10,170	Europe	44[b]	Stepwise association with ischemic stroke, but not hemorrhagic stroke	(Brondum-Jacobsen et al., 2013)
Stroke; ischemic (LAA, CE, SAO, and unclassified) and hemorrhagic subtypes	Prospective	3.1	1547	USA	NA	Association with stroke and ischemic stroke (specifically SAO and unclassified subtypes), but not hemorrhagic stroke	(Judd et al., 2016)
Stroke; ischemic and hemorrhagic stroke	Meta-analysis	NA	217,235	Europe, USA, Asia, and New Zealand	NA	Non-linear association with stroke and ischemic stroke, with a 25OHD threshold of 50 nmol/L	(Shi et al., 2020)
Ischemic stroke subtypes (LAA, SAO, and other)	Prospective	16	464 case-control pairs	USA	Cases: 45.3 %< 50, controls: 41.6 %<50	Non-linear association with ischemic, stroke, particularly for SAO, with a 25OHD threshold of 40 nmol/L	(Sun et al., 2012)

CVD, cardiovascular disease; MI, myocardial infarction; CHF, chronic heart failure; LAA, large artery atherosclerosis; SAO, small artery occlusion; CE, cardioembolism; ICH, intracerebral hemorrhage; NA, not applicable. [a]including data from UK Biobank, EPIC-CVD, and two Copenhagen studies. [b]Median.

et al., 2017), while others concluded null results (Blondon et al., 2013). Notably, one study reported a non-linear positive association between serum 25OHD levels and carotid intima media thickness among populations with serum 25OHD ≥ 50 nmol/L (van Dijk et al., 2015). Intracranial atherosclerotic stenosis (ICAS) confers a substantial risk of first and recurrent ischemic stroke, which is highly prevalent in Asian (Ornello et al., 2018; Wang et al., 2014). Whether vitamin D holds a key function in the development of ICAS is an outstanding question that deserves further investigation.

3.2. MR studies

Despite overwhelming observational evidence advocating the association between serum 25OHD and incident ischemic stroke, MR analyses revealed inconclusive conclusions for causality of association (Table 2). Multiple previous MR studies assumed a linear relationship between genetically predicted 25OHD and CVD and concluded no causality (Afzal and Nordestgaard, 2017; Huang et al., 2019; Larsson et al., 2018). Notably, linear MR analysis violates the genuine non-linear association that prevails among vitamin D-deficient subjects. By non-linear MR analysis, the causal effect of low serum 25OHD (<50 nmol/L) on CVD risk has been demonstrated (Zhou et al., 2021), whereas this effect is absent specifically on stroke risk (Navale et al., 2022). However, one latest stratified MR analysis has criticized the shortcomings of non-linear MR analyses and suggested a lack of causal association for 25OHD with both cardiovascular and mortality outcomes at all strata of 25OHD, thus calling the previous positive finding into question (Sofianopoulou et al., 2024).

As for recurrent cardiovascular events, Chan et al. has revealed that genetically predicted decrease in 25OHD is causal for the recurrence of ischemic stroke and myocardial infarction combined among Southern Chinese participants. Though employing linear analysis, prevailing vitamin D deficiency/insufficiency (>90 %) in the study population enabled adequate power to detect relative effect sizes of increased 25OHD exposure (Chan et al., 2021). The causal association of serum 25OHD with combined cardiovascular events also holds true among hypertensive-diabetic participants, among which vitamin D deficiency is highly prevalent (Chan et al., 2022).

The etiologies and clinical features of ischemic stroke subtypes vary substantially and the proportions of stroke etiological subtypes vary among populations of different ethnic origins. For instance, the prevalence of LAA stroke and the etiological ICAS is higher in Asians (Ornello et al., 2018; Wang et al., 2014). However, information on stroke subtypes in the UK Biobank is not available, and thus subgroup analysis on stroke subtypes could not be performed. As a result, data are currently scarce regarding the causal effect of genetically low 25OHD on the risk of individual ischemic stroke subtypes. Through linear MR analysis using summary-level data of ischemic stroke from genome-wide association studies, one study performed subtype analysis but suggested null association with any subtypes (Larsson et al., 2018). Notably, limited amounts of vitamin D-deficient subjects among the study population could significantly reduce the likelihood to unveil the potential causality (if any).

Taken together, the association of vitamin D with the risk of ischemic stroke warrants further MR investigation. Whether the association differs with ischemic stroke subtypes and in distinct races has yet to be explored. Stratified MR analysis by serum 25OHD strata, non-linear MR approaches, and adequate sample sizes of vitamin D-deficient population will help increase the statistical power to detect a potential causality.

3.3. Randomized clinical trials (RCTs)

Calling into question the cardioprotective role of vitamin D, current RCTs (Manson et al., 2019; Neale et al., 2022; Scragg et al., 2017; Virtanen et al., 2022) and several meta-analyses of clinical trials (Autier et al., 2017; Barbarawi et al., 2019; Ford et al., 2014) have revealed that vitamin D supplementation confers no benefits on CVD outcomes, including stroke, which substantially challenges the findings observed from population-based studies. Yet, a critical reappraisal of views from observational studies raises potential shortcomings of current RCTs in investigating this association (Pilz et al., 2022). Notably, the framework for clinical studies evaluating nutrient effects has long been presented by Heaney, which deserves to be learned for future RCTs (Heaney, 2014).

First, baseline 25OHD levels of trial participants are mostly >50 nmol/L. Though subgroup analysis in vitamin D-deficient participants still reported null results, the power to detect potential effect sizes of vitamin D was rather limited owing to the small proportion of vitamin D-deficient subjects (Neale et al., 2022; Scragg et al., 2017; Virtanen et al., 2022). Several small RCTs and meta-analyses of clinical trials that focused on vitamin D-deficient subjects otherwise give promising results (Dibaba, 2019a; Lerchbaum et al., 2019; Wenclewska et al., 2019). As

Table 2
MR evidence indicating the association between vitamin D levels and stroke risk.

Stroke subtypes	Design	Samples	Country	Finding	Study
Stroke, ischemic and hemorrhagic stroke	Stratified analyses by 25OHD levels	386,406	Europe (UK Biobank, EPIC-CVD, and two Copenhagen studies)	Non-significant association with stroke in any 25OHD stratum	(Sofianopoulou et al., 2024)
CVD, including CAD, PAD, and stroke	Non-linear and linear	295,788	Europe (UK Biobank)	Non-linear association with CVD risk at 25OHD <50 nmol/L by non-linear analysis; Null association suggested by linear analysis	(Zhou et al., 2021)
Stroke and dementia	Non-linear and linear, as well as stratified analyses	294,514	Europe (UK Biobank)	Null association with stroke risk by either analysis; Non-linear association with dementia risk at 25OHD <50 nmol/L by non-linear analysis	(Navale et al., 2022)
Ischemic stroke	Linear	116,655	Europe	No association	(Afzal and Nordestgaard, 2017)
Cause-specific vascular disease and mortality[a]	Linear	99,012 Chinese and 106,911 Danish adults	China and Europe	No association	(Huang et al., 2019)
Ischemic stroke subtypes	Linear	GWAS summary statistics	Europe	No association	(Larsson et al., 2018)
Recurrent ischemic stroke and/or MI	Linear	441 subjects who had prior first ischemic vascular events	Hong Kong	Association with recurrent ischemic stroke/MI, any recurrent or de novo ischemic stroke/MI, and recurrent MI alone	(Chan et al., 2021)

MR, mendelian randomization; CVD, cardiovascular disease; CAD, coronary artery disease; PAD, peripheral artery diseases; MI, myocardial infarction; [a] Ischemic stroke was included as one of vascular outcomes.

discussed above, vitamin D supplementation appears to benefit vitamin D-deficient subjects, but not those who are sufficient. It has been increasingly recognized that clinical trials of vitamin D supplementation are unlikely to corroborate observational evidence among participants who are mostly vitamin D-replete (Bouillon et al., 2022). Moreover, it takes many years for RCTs to observe potential cardiovascular effects of vitamin D repletion owing to the long natural history of CVD. Leaving vitamin D deficiency uncorrected in such a long follow-up period is increasingly considered unethical.

Second, whether a proper 25OHD concentration range was achieved during the trial was mostly unknown. No screening for vitamin D deficiency at baseline and the lack of serial monitoring of 25OHD levels may lead to improper 25OHD levels that deviate from the optimal range. Growing observational evidence indicates that both low and high 25OHD levels are associated with increased all-cause mortality (Dai et al., 2021; Durup et al., 2012; Sempos et al., 2013; Zittermann et al., 2012), CVD mortality (Dror et al., 2013; Durup et al., 2015), CVD risk (Wang et al., 2019, 2008), and specifically stroke risk (Leung et al., 2017; Navale et al., 2022; Shi et al., 2020; Sofianopoulou et al., 2024). Accordingly, both inadequate and excessive vitamin D supplementation may conceal the potential cardiovascular benefits of vitamin D. Furthermore, serum 25OHD concentration is a highly confounded variable affected by genetic variations, seasonal variation, a spectrum of health behaviors, body mass index, sociocultural factors, and education levels (Gospodarska et al., 2023). Statistical adjustment for potential confounding variables is demanding to be accomplished in current RCTs.

Third, whether the impact of vitamin D supplementation varies by ischemic stroke subtypes remains uninvestigated. Given observational evidence that the correlation between vitamin D levels and ischemic stroke differs by stroke subtypes (Chaudhuri et al., 2014; De Silva et al., 2013; Judd et al., 2016; Manouchehri et al., 2017; Sun et al., 2012), whether vitamin D supplementation confers protection on specific subtypes deserves much more attention from future RCTs. Further, it is revealing to determine whether reversing vitamin D deficiency is an effective strategy to reduce the occurrence and recurrence of ischemic episodes among subjects at high risk of AIS (such as those with hypertension, diabetes mellitus, and ICAS) and with prior atherothrombotic events, respectively.

Considering the null MR finding that genetically predicted decrease in 25OHD is not causal for CVD risk even in the lowest 25OHD strata (Sofianopoulou et al., 2024), it seems futile to devote any more effort in this filed. Nonetheless, the above defects in the trial design have been recognized as the major obstacles to testing the cardiovascular effects of vitamin D, which hinders definite interpretation from the null data. To enable genuine causal effect estimation, it is wise for future RCTs to achieve sufficient sample sizes, focus on vitamin D-deficient populations, exploit efficient vitamin D replacement strategies, serially monitor vitamin D status during follow-up, and address racial and ethnic disparity.

3.4. Mechanisms

Vitamin D is involved in the development of CVD via multifactorial indirect (e.g., acting on blood pressure, insulin signaling, and lipid metabolism) and direct (e.g., acting on the cardiovascular system itself and the immune arm) mechanisms. From the former perspective, vitamin D deficiency has been demonstrated to be causally associated with increased risks of hypertension and diabetes mellitus (Afzal and Nordestgaard, 2017; Liu et al., 2021a). In a large meta-analysis of RCTs, vitamin D supplementation improved serum lipid profiles, particularly among vitamin D-deficient subjects (Dibaba, 2019b). Moreover, vitamin D signaling is involved in attenuating islet β-cell dysfunction and insulin resistance (Morró et al., 2020; Wei et al., 2018).

It is known that the pathological etiologies vary substantially among ischemic stroke subtypes. Here, we mainly discuss the mechanisms accounting for the impact of vitamin D on LAA subtype and its underlying atherosclerotic causes (Fig. 2). Atherosclerosis develops as an intricate interplay between endothelial dysfunction, lipid accumulation, and inflammation. Notably, VDR is expressed on almost all kinds of cells within the vasculature. Despite discrepancy concerning the efficacy of vitamin D in curbing atherosclerosis, ever-growing experimental studies have demonstrated the anti-atherogenic effects of vitamin D/VDR axis.

Endothelial dysfunction is an antecedent pathogenic event that initiates atherosclerosis. Mounting epidemiological data have shown an association between vitamin D deficiency and endothelial dysfunction (Al Mheid et al., 2011; Chitalia et al., 2012; Jablonski et al., 2011; Yiu et al., 2011; Zhang et al., 2015). Several small RCTs and meta-analyses supported the benefit of vitamin D supplementation on endothelial function (Hussin et al., 2017; Mazidi et al., 2017; Wolf et al., 2020; Zhang et al., 2018), while others concluded null effects (Beveridge et al., 2018; Witham et al., 2013). Experimental evidence showed that endothelial VDR acted to ameliorate oxidative stress and increase nitric oxide bioavailability (Andrukhova et al., 2014; Kanikarla-Marie and Jain, 2016; Ni et al., 2014; Polidoro et al., 2013).

Accumulating experimental evidence has illustrated the integral role of monocyte/macrophage vitamin D signaling in suppressing cholesterol uptake and foam cell formation (Kumar et al., 2021; Oh et al., 2015, 2009; Riek et al., 2014; Szeto et al., 2012; Yin et al., 2015). Vitamin D signaling is proposed to restrain atherosclerosis progression by curtailing sustained inflammation within the arterial wall, including leukocyte-endothelium interaction, leukocyte recruitment (Bozic et al., 2015; Kanikarla-Marie and Jain, 2016; Kose et al., 2022; Takeda et al., 2010), and cytokine/chemokine secretion (Bozic et al., 2015; Chen et al., 2016b; Jablonski et al., 2011; Martinez-Moreno et al., 2016; Ojaimi et al., 2013).

Vitamin D has also been suggested to play antithrombotic effects via alleviating cytokine-mediated dysregulation of tissue factor and thrombomodulin in a number of experimental studies (Aihara et al., 2004; Martinez-Moreno et al., 2016; Ohsawa et al., 2000; Wu-Wong et al., 2006). Vitamin D supplementation has been suggested to improve the prothrombotic profile, including platelet activation, platelet immune cell aggregates, and serum circulating inflammatory cytokine levels, in vitamin D-deficient individuals (Blondon et al., 2019; Johny et al., 2022).

Although rarely seen in the general population, supra-physiological levels of vitamin D can cause vascular calcification, another risk factor for atherosclerosis (Zittermann and Koerfer, 2008). In this line, it was observed that carotid intima media thickness increased in elderly populations with serum 25OHD $>$ 50 nmol/L (van Dijk et al., 2015). However, it is worth mentioning that whether carotid intima media thickness is an appropriate surrogate for the risk of CVD continues to be debated. Alternatively, carotid plaque assessment, specifically the presence/absence of carotid plaque and carotid plaque size and phenotype, may be superior to carotid intima media thickness for predicting CVD risk (Mathiesen et al., 2011; Shah, 2020). Experimental studies support the detrimental impact of both vitamin D deficiency and excess on atherosclerosis progression (Ellam et al., 2014). This biphasic effect of vitamin D might partially account for its non-linear association with mortality and CVD outcomes.

4. Vitamin D and ischemic stroke outcomes

4.1. Experimental studies

Several preclinical studies revealed that vitamin D deficiency exacerbated ischemic brain injury and stroke severity through excessive neuroinflammation and oxidative stress, and increased blood-brain barrier (BBB) leakage following experimental stroke (Balden et al., 2012; Sayeed et al., 2019; Yousuf et al., 2021). By contrast, another study suggested no discernible impact of vitamin D deficiency on stroke progression (Evans et al., 2018a). The difference may lie in the duration

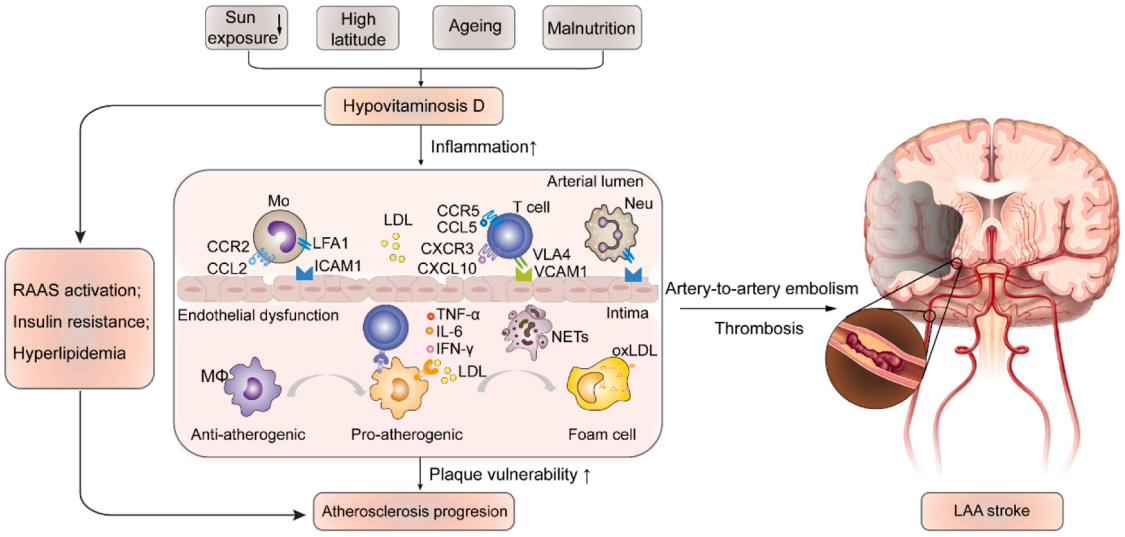

Fig. 2. Proposed mechanisms of hypovitaminosis D in potentiating ischemic stroke. Hypovitaminosis D has been identified as a potential promoter for ischemic stroke, proposedly via indirect and direct pathogenic factors. The former involves activation of the renin-angiotensin-aldosterone system (RAAS), insulin resistance, and hyperlipidemia. The latter refers to exacerbated inflammation, enhanced cholesterol deposition, and accelerated foam cell formation, principally contributing to atherosclerotic lesions. Eventually, atherosclerotic plaques of main cerebral arteries become destabilized, prone to thrombus formation, thromboembolism, and ensuing large artery atherosclerotic (LAA) stroke. Mo, monocyte; Mø, macrophage; Neu, neutrophil; NETs, neutrophil extracellular traps; ox-LDL, oxidized low-density lipoprotein; CCL5, C–C motif ligand 5; CCR5, CC chemokine receptor 5; CXCR3, CXC chemokine receptor 3; CXCL10, C-X-C motif ligand 10; ICAM1, intercellular adhesion molecule 1; VCAM1, vascular cell adhesion molecule 1; VLA4, very late antigen-4; TNF-α, tumor necrosis factor α; IFN-γ, interferon γ; IL-6, interleukin 6.

of the vitamin D-deficient diet. The latter study only performed a 4-week diet intervention (Evans et al., 2018a), in comparison to a 8-week one in the former (Balden et al., 2012; Sayeed et al., 2019; Yousuf et al., 2021).

Emerging evidence shows that vitamin D exerts therapeutic benefits in stroke animal models. Noteworthy, the therapeutic efficacy of vitamin D differs by its regimens, including its dosage, biological forms (parent vitamin D3 or bioactive $1,25(OH)_2D_3$), duration, and importantly, treatment timing. Most animal studies with positive results leverage pretreatment strategy or initiate vitamin D treatment immediately after cerebral ischemia, and adopted $1,25(OH)_2D_3$ that is the very bioactive form and can immediately exert biological actions following administration (Atif et al., 2013; Evans et al., 2018b; Fu et al., 2013; Guo et al., 2018; Kajta et al., 2009; Sadeghian et al., 2019; Velimirović et al., 2018; Wang et al., 2000; Yousuf et al., 2021; Zhang et al., 2022). One study suggested that poststroke administration of vitamin D3 failed to exert any treatment benefits, even though a preceding vitamin D-deficient diet exacerbated ischemic brain injury (Balden et al., 2012).

Presumably, the conversion process from low 25OHD levels to sufficient $1,25(OH)_2D_3$ concentrations in the CNS might have exceeded the optimal time window for strangling stroke-induced inflammatory episodes. However, prior administration of $1,25(OH)_2D_3$ represents a considerable translational gap between animals and humans. Furthermore, considering its detrimental side effects, such as hypercalcemia and renal stones, $1,25(OH)_2D_3$ is generally not recommended in clinical practice for non-skeletal diseases.

4.2. Observational studies

Vitamin D deficiency is highly prevalent in AIS patients (Alfieri et al., 2017; Tu et al., 2014) and affects approximately 70–80 % of AIS patients in Asia (Kim et al., 2020; Park et al., 2015; Tu et al., 2014; Yue et al., 2014). Several studies reported that the distribution of ischemic stroke subtypes differed according to 25OHD levels, with an increased proportion of LAA subtypes in the lowest tertile (Chaudhuri et al., 2014; Daubail et al., 2013; De Silva et al., 2013; Manouchehri et al., 2017). Overwhelming observational studies have revealed a significant association between lower 25OHD levels and larger infarct volumes, greater stroke severity, early neurological deterioration, stroke recurrence, worse short- and long-term functional outcomes, and increased mortality in AIS patients (Alfieri et al., 2017; Alharbi et al., 2022; Daubail et al., 2013; Hu et al., 2019; Huang et al., 2016; Kim et al., 2020; Liu et al., 2020; Nie et al., 2017; Park et al., 2015; Tu et al., 2014; Zeng et al., 2021). One study found the association between serum 25OHD and functional outcomes was significant only in patients with AIS, but not in those with hemorrhagic stroke (Zeng et al., 2021).

It was also suggested that low levels of vitamin D were associated with poststroke cognitive impairment (Chen et al., 2018b; Park et al., 2022) and poststroke depression (He and Ruan, 2022; Wang et al., 2018; Yue et al., 2014). Notably, the causality between genetically lower 25OHD levels and a higher risk of dementia has been established (Navale et al., 2022).

4.3. Clinical trials

So far, there are no recommendations for vitamin D supplementation to treat AIS patients. Owing to limited clues from clinical trials, there remain considerable knowledge gaps as to the efficacy, safety, optimal dosage, therapeutic timing, and optimal clinical benefit/risk balance for vitamin D medication among AIS patients. Several small pilot trials suggested the efficacy and safety of a single intramuscular bolus of 600,000 IU vitamin D3 in treating AIS patients with baseline 25OHD $<$75 nmol/L (Table 3) (Gupta et al., 2016; Hesami et al., 2022; Narasimhan and Balasubramanian, 2017). All these trials gave this medication in the acute phase and suggested improved functional outcomes months after ictus, as well as no significant adverse events in patients receiving vitamin D3.

Considering the relatively low 25OHD levels among AIS patients, a large bolus dose of vitamin D3 might be required to rapidly achieve sufficient concentrations of 25OHD and $1,25(OH)_2D_3$ in the ischemic brain to counter excessive neuroinflammation and forestall the progression of acute brain injury in the critically acute phase. A single dose of $\geq$300,000 IU vitamin D3 was suggested to be necessary to yield a rapid and sustained increase to 25OHD $>$75 nmol/L within a few days in vitamin D-deficient/insufficient individuals (Amrein et al., 2011; Chen

Table 3
Clinical interventional evidence indicating the impact of vitamin supplementation on stroke risk and outcomes.

Sample	Country	25OHD levels (nmol/L mean±SD)		Intervention (vitamin D *versus* placebo)	Duration of follow-up	Primary outcomes	Finding	Study
		Baseline	Final[a]					
25,871	USA	77.0 ±25	77.0 ±25	Oral 2000 IU/d	5.3 years	Cancer and CVD[b]	Null findings	(Manson et al., 2019)
5108	New Zealand	66.3 ±22.5	135.0 ±40	One oral dose of 200,000 IU and 100,000 IU/month later	3.3 years	CVD and death[b]	Null findings	(Scragg et al., 2017)
21,235	Australia	77 ±25	115 ±30	Oral 60,000 IU/month	5 years	All-cause mortality and mortality from cancer, CVD, and other causes	Null findings	(Neale et al., 2022)
2495	Finland	75.5	100.2 and 120.4[c]	Oral 1600 IU/d or 3200 IU/d	5 years	CVD and cancer	Null findings	(Virtanen et al., 2022)
5292	UK	38.0 ±16.3	62.3 ±21.8	Oral 800 IU/d	6.1 years	Cardiac failure, MI, and stroke	Benefits in cardiac failure but null impact on both MI and stroke	(Ford et al., 2014)
53[d]	India	45.0 ±14.5	90.0 ±37.5	600,000 IU (im.)	6 months	Functional outcome and mortality	Benefits in both outcomes	(Gupta et al., 2016)
41[d]	Iran	58.0 ±10.4	NA	600,000 IU (im.)	3 months	Neural damage, stroke severity at baseline, and functional outcomes	Benefits in all evaluated outcomes	(Hesami et al., 2022)
60[d]	India	45.0 ±9.5	NA	600,000 IU (im.)	3 months	Functional outcomes	Better outcomes in vitamin D-deficient (25OHD <50 nmol/L) subgroup but not in the insufficient subgroup (50–75 nmol/L)	(Narasimhan and Balasubramanian, 2017)
72[d, e]	Turkey	34.8 ±11.5	NA	300,000 IU (im.)	3 months	Functional outcomes	Benefits in partial evaluated outcomes	(Sari et al., 2018)
97 [f]	Japan	NA	NA	Oral 2000 IU/d	2 months	Functional outcome	Null findings	(Momosaki et al., 2019)

CVD, cardiovascular disease; MI, myocardial infarction; NA, not available; im., intramuscular injection. [a]Final serum 25OHD levels in the vitamin D-treated groups only. [b]Stroke was included as one of secondary outcomes. [c]100.2 nmol/L and 120.4 nmol/L in the 1600 IU/d and 3200 IU/d arms, respectively. [d] Patients with acute ischemic stroke and 25OHD <75 nmol/L. [e]Ischemic stroke patients at least 2 months after ictus with 25OHD <75 nmol/L. [f]Stroke patients during rehabilitation.

et al., 2016a; Cipriani et al., 2010; Kearns et al., 2014; Tellioglu et al., 2012). Yet, adverse events may arise at high supraphysiological levels of 25OHD, mostly resulting from hypercalcemia and hypercalciuria. The upper safety limit of 25OHD levels has been defined by an expert consensus as 250 nmol/L (Galoppin et al., 2022; Souberbielle et al., 2010). Despite the fairly broad safety range, there exists considerable cautiousness to medicate such high dose of vitamin D3 in AIS patients.

Several RCTs concluded negative results on stroke prognosis by administrating either a single dose of 300,000 IU vitamin D3 (Sari et al., 2018) or 8–12-week vitamin D3 (2000 IU/d) in the rehabilitation phase of ischemic stroke (Momosaki et al., 2019; Torrisi et al., 2021). Similarly, according to a post-hoc analysis on the Vitamin D and Omega-3 trial study, daily doses of 2000 IU vitamin D prior to stroke also did not improve functional outcomes either in total stroke or AIS patients (Rist et al., 2021). These null results might lie in the treatment timing of the chronic phase. Experimental findings have indicated that vitamin D treatment initiated only ahead of or early after stroke could mitigate ischemic brain injury and functional impairments (Evans et al., 2018c; Fu et al., 2013; Guo et al., 2018; Kajta et al., 2009; Velimirović et al., 2018; Wang et al., 2000; Zhang et al., 2022). Hypothetically, a critical period might exist to allow for the therapeutic efficacy of vitamin D for augmenting functional restoration after AIS. On the other hand, screening for vitamin D deficiency at baseline could be a critical issue determining the therapeutic efficacy of vitamin D. Most stroke patients in the Vitamin D and Omega-3 trial study are vitamin D-replete at baseline. This shortcoming in the study design was underpowered to detect the potential effects in stroke prognosis, and thus limited its interpretation.

4.4. Mechanisms

Emerging data support the concept that the brain constitutes a target tissue for vitamin D. In situ synthesis of $1,25(OH)_2D_3$ has been widely identified in neurons and glial cells by virtue of brain vitamin D metabolizing enzymes (Landel et al., 2018; Liu et al., 2021b; Smolders et al., 2013). Furthermore, VDR is widely distributed within the brain, the expression of which is relatively low in the homeostatic neural cells (Anwar et al., 2023).

Presumably, vitamin D could act on pathological events throughout the clinical course after AIS (Fig. 3). Following the initial ischemic insult, neuroinflammatory episodes are immediately elicited and play central roles in causing secondary brain injury (Cui et al., 2021). As discussed above, a wealth of preclinical evidence has elucidated the treatment efficacy of $1,25(OH)_2D_3$ in relieving infarct lesions, oxidative stress, neuroinflammation, BBB permeability, and neurological deficits in ischemic stroke animal models (Evans et al., 2018b; Fu et al., 2013; Guo et al., 2018; Kajta et al., 2009; Sadeghian et al., 2019; Velimirović et al., 2018; Wang et al., 2000; Zhang et al., 2022).

Cerebral ischemia pronouncedly induces VDR expression in the ischemic brain of both stroke models and patients (Cui et al., 2023b; Evans et al., 2018b; Ridder et al., 2009; Sayeed et al., 2019). However, limited data exist regarding the cellular expression patterns of brain VDR and the molecular mechanism of vitamin D/VDR axis in ischemic stroke. Recently, we have demonstrated a substantial time-dependent increase of VDR expression in peri-infarct microglia/macrophages following acute cerebral ischemia. Mechanistically, vitamin D/VDR axis contributes to orchestrating microglia/macrophage phenotype switch, the drastic neuroinflammatory responses and secondary brain injury following acute cerebral ischemia (Cui et al., 2023b).

Circulating IL-6 and C-reactive protein (CRP) have been widely

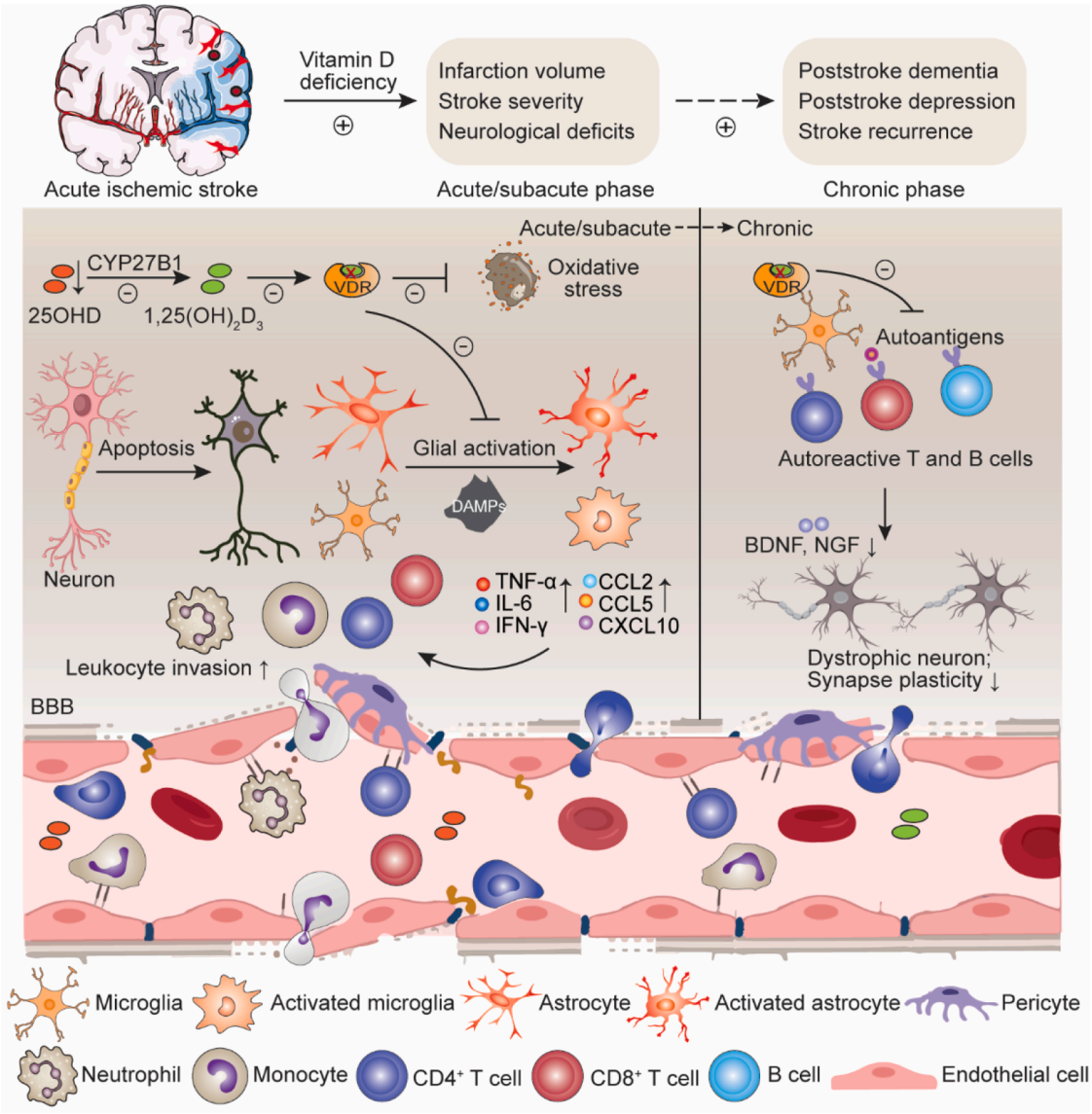

Fig. 3. Regulatory mechanisms of vitamin D on disease progression after acute ischemic stroke. Impaired vitamin D signaling due to either vitamin D deficiency or vitamin D receptor (VDR) dysfunction promotes infarction expansion, greater stroke severity, and worse neurological deficits in the acute/subacute phase of ischemic stroke, as well as the onset of neuropsychiatric sequelae in the long term. The former results from exaggerated oxidative stress, aggravated neuroinflammation, and increased blood-brain barrier (BBB) leakage. The latter might involve enhanced autoreactive immune responses mediated by autoreactive T and B cells in response to autoantigens released by damaged brain tissues, as well as hampered biosynthesis of neurotrophic factors, such as brain-derived growth factor (BDNF) and nerve growth factor (NGF). CCL5, C-C motif ligand 5; CXCL10, C-X-C motif ligand 10; TNF-α, tumor necrosis factor α; IFN-γ, interferon γ; IL-6, interleukin 6.

indicated as independent predictors of prognosis following AIS (Smith et al., 2013). Several lines of evidence pointed to an inverse relationship between the levels of 25OHD and that of IL-6 and high sensitivity CRP among AIS patients (Alfieri et al., 2017; Wang et al., 2018). In an experimental model mimicking poststroke infection via systemic lipopolysaccharide administration, a vitamin D-deficient diet exacerbated systemic inflammation and immunosuppression, as well as ischemic brain injury in stroke animals (Yousuf et al., 2021).

In the chronic phase of ischemic stroke, neuropsychiatric sequelae, including depression and cognitive decline, represent a particular pressing issue with a high incidence (Endres et al., 2022). The underlying mechanisms have not been elucidated, yet with autoreactive immune mechanisms emerging as a probably involved aspect (Cui et al., 2021). Vitamin D is suggested to be involved in the regulation of biosynthesis of neurotrophic factors (e.g., brain-derived neurotrophic factor and nerve growth factor) and neurotransmitter (Cui and Eyles, 2022). Hypothetically, such biological signals, as well as its potential roles in counteracting maladaptive chronic central inflammation, could aid postischemic neural repair, thereby restraining the development of chronic sequelae after stroke.

5. Conclusions

Vitamin D deficiency, a highly prevalent condition worldwide, has been receiving long-standing debate on its association with CVD. The review provides comprehensive evidence regarding the roles of vitamin D in the etiology, development, and progression of ischemic stroke. Convincing biological support from preclinical studies established the impact of vitamin D/VDR axis on the development and progression of ischemic stroke. However, due to large inconsistencies in the study design, outcomes assessed, and conclusions of current clinical studies, vitamin D supplementation is not recommended for the prevention/treatment of stroke. Nevertheless, it appears to be reasonable to prescribe vitamin D therapy among subjects with 25OHD levels <50 nmol/

L, particularly among those afflicting with AIS or at high risk.

Confronting the rising tide of ischemic stroke and its associated mortality and morbidity with ageing, it merits further investigation whether vitamin D supplementation, a feasible, safe, and cost-effective strategy, could be a potential preventive and therapeutic approach of ischemic stroke. It is reasonable for future clinical trials to address stroke etiological subtypes for investigating the efficacy of vitamin D in the prevention of AIS. Whether vitamin D supplementation could open promising avenues for immunomodulating and neuroprotective therapeutics among ischemic stroke patients merits further mechanistic insights from the preclinical setting and decisive evaluation from well-designed clinical trials. Mining this attractive target via concerted effort by both basic and clinical research promises to bridge gap between experimental and clinical findings and between observational and interventional findings.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Acknowledgements

This review was supported by the National Natural Science Foundation of China (Grant U1904207 and 91849115 to Yuming Xu) and the Nonprofit Central Research Institute Fund of Chinese Academy of Medical Sciences (Grant 2020PT31001 to Yuming Xu).

Author contributions

The central concept of this review was proposed by Yuming Xu and Pan Cui. Pan Cui and Zongping Xia outlined the manuscript. Pan Cui was responsible for the comprehensive literature search for references and creating the figures. Pan Cui and Haiman Hou contributed to drafting the manuscript and organizing the tables. Bo Song were involved in the critical revision of the manuscript. Yuming Xu and Zongping Xia were responsible for the final revision and overall content. The submission was approved by all authors.

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