Original Article

# Factors Related to Hypovitaminosis D in Persons with Ischemic Stroke

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***Background***: Low Vitamin D level can be related to malfunction of various organs. Information on prevalence of hypovitaminosis D and related factors is important to improve quality of stroke management including rehabilitation.

***Objective***: To evaluate the prevalence of hypovitaminosis D and related factors in acute stroke patients.

***Materials and Methods***: Cross sectional study was conducted at Srinagarind Hospital, Khon Kaen, a tertiary referral center of the acute stroke patients, admitted between January and June 2017.

***Results***: Ninety-six acute stroke patients were included in the present study. Most were males (n=61, 64%) with mean age of 65±12 years. The prevalence of hypovitaminosis D was 54.17% (95% CI 44.23 to 64.14). Factors related to hypovitaminosis D were female, indoor activities, duration of sunlight exposure less than 30 minute a day, frequency of sunlight exposure less than two times a week, regular sunscreen use, and area of application. In addition, vitamin D levels were negatively correlated with the severity of stroke (National Institutes of Health Stroke Scale, NIHSS) (r=–0.227, p=0.026), and positively correlated with ability to perform daily activities (Barthel index, r=0.242, p=0.017). There was no significant correlation between hypovitaminosis D and other factors such as age, body mass index, co-morbidities, Thai Mental State Examination (TMSE) score, and high vitamin D diet consumption.

***Conclusion***: Hypovitaminosis D was found to be highly prevalent in acute stroke patients. Main factors that significantly affected vitamin D levels were female and inadequate sunlight exposure. Vitamin D levels should be routinely evaluated in stroke patients.

***Keywords***: Cerebrovascular accident, Functional outcome, Prevalence, Vitamin D deficiency

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Vitamin D is one of the important factors in regulating calcium and bone metabolism. It is also important for most vital systems in the body such as neuromuscular, cardiovascular, immune, and endocrine systems(1). Vitamin D2 (ergocalciferol) and D3 (cholecalciferol) are the two main forms of vitamin D found in nature. The source of these is mainly derived from the skin's synthesis after exposure to sunlight (about 90%) and from food supplements (about 10%)(2).

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The major cause of vitamin D deficiency is from vitamin D synthesis reduction in the skin due to less sun exposure and more indoor activity and use of sun blocking materials like sunscreen and clothing(3). Other factors include inadequate vitamin D intake and gastrointestinal disorders such as post gastrectomy, celiac disease, inflammatory bowel syndrome, and pancreatic insufficiency(4). Further, vitamin D deficiency was reported in patients with chronic kidney disease or liver disease and patients taking medications affecting vitamin D metabolism such as anticonvulsants or glucocorticoids(5).

Vitamin D deficiency is an important cause of various conditions, including osteoporosis, muscle weakness, hypertension, coronary heart disease,

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and stroke. The Third National Health and Nutrition Examination Survey (NHANES III) demonstrated that hypovitaminosis D was associated with major cardiovascular and coronary events, diabetes (odds ratio [OR] 1.98), hypertension (OR 1.30), overweight (OR 2.29), and dyslipidemia (OR 1.47)(6). Sun et al in a cohort study found significant association of low vitamin D level and the risk of stroke (OR 1.49, 95% confidence interval (CI) 1.01 to 2.18)(7). The authors also conducted meta-analysis (n=6 prospective cohort studies) and found an increased risk of stroke associated with low vitamin D (pooled relative risk 1.52, 95% CI 1.20 to 1.85)(7).

Previous studies have reported the associated link between the Vitamin D deficiency and stroke severity, and its impact on rehabilitation outcomes. Wang et al found significant positive relationship between low vitamin D level and severity of stroke measured by the National Institutes of Health Stroke Scale (NIHSS) (r=–0.389, p<0.001)(8). Kienreich et al in another study found vitamin D deficiency had a significant effect on reduction of neuroprotective factors that affect stroke severity, cognitive function, and poor rehabilitation response(9). Wei and Kuang also reported association of vitamin D deficiency with poor recovery of stroke at one-year post stroke (OR 3.2, 95% CI 1.7 to 4.2)(10).

The prevalence of vitamin D deficiency and positive correlation to cardiovascular disease was reported in many countries in both Western and Eastern regions including USA, Finland, Nepal, Singapore, and India(11-15). However, to date there is no report on prevalence of vitamin D deficiency in stroke population in Thailand. Therefore, the present study aimed to evaluate the prevalence of vitamin D deficiency and causal factors of vitamin D deficiency in acute stroke patients admitted to a tertiary hospital in Thailand.

## Materials and Methods

### *Participants and setting*

The present study was a cross-section conducted at Srinagarind Hospital, a tertiary referral center in Khon Kaen, Thailand and included all acute stroke patients consecutively admitted to the stroke unit during a 6-months period between January and June 2017. The inclusion criteria were acute stroke patients within 15 days after diagnosis confirmed by computer tomography (CT) or magnetic resonance imaging (MRI), aged 18 years and above, and able to provide a written informed consent before commencing the study. The exclusion criteria included patients with chronic liver disease, chronic kidney disease, bone cancer, and digestive disorder that affected vitamin D absorption, and patients who received or are currently on vitamin D supplement, thyroid, parathyroid, estrogen, progesterone, steroids, thyroid hormones, or anticonvulsants 90 days before stroke.

### *Data collection and measurement*

Participants' socio-demographic data (age, sex, occupation, etc.) and clinical data (stroke type, related symptoms and treatments, co-morbid conditions, etc.) were collected. The participants' habits of consuming diets containing high levels of vitamin D and sun exposure in the last six months were also recorded.

Stroke severity was assessed using the NIHSS Thai version that include 11 items with score ranging from 0 to 42 (higher score indicates higher severity of stroke)(16). The functional level was evaluated by Barthel index score consisted of 10 items of activities of daily living with score ranging from 0 to100 (higher score indicates less impairment)(17). The severity of cognitive impairment was assessed by the Thai Mental State Examination (TMSE) modified from the Mini-Mental State Examination (MMSE)(18). TMSE is a questionnaire with total score of 30 (lower score indicates higher cognitive impairment).

### *Laboratory investigation*

Blood sample was collected from the cubital fossa for vitamin D [25-hydroxyvitamin D, 25(OH) D] analyses. The blood sample was collected around 8.00 am kept in clot blood gel and sent to the hospital laboratory within one hour. The blood sample was analyzed by electrochemiluminescence immunoassay (ECLIA)(19). Based on this test, hypovitaminosis D was defined as 25(OH)D level less than 30 ng/ml [25(OH)D level range of 20 to 30 ng/ml for vitamin D insufficiency, and 25(OH)D level less than 20 ng/ml for vitamin D deficiency](14).

The present study was approved by the Human Research Ethics Committee of the Khon Kaen University (IE number: HE 591387).

### *Statistical analysis*

The sample size estimation for prevalence study was calculated based on a type I error ($\alpha$)=0.05, precision of estimation(e)=0.1 and p=0.488 from Chaudhuri et al study(15). The number of stroke patients required using this calculation was 96.

All data were analyzed using Stata v.10.1 statistical program. The descriptive statistic of various demographic and clinical variables were presented as mean and standard deviation. The prevalence of low

**Table 1.** Demographic data, sunlight exposure and consuming of diet with high vitamin D (n=96)

| Characteristics | n (%) | Characteristics | n (%) |
|---|---|---|---|
| Age (years), Mean±SD | 65±12 | Other symptoms (can have more than 1 symptom) | 21 (21.9) |
| Weight (kg), Mean±SD | 63.96±12.85 | Underlying diseases | |
| Height (cm), Mean±SD | 162.80±8.48 | Diabetes | 32 (33.3) |
| BMI (kg/m$^2$), Mean±SD | 24.06±4.2 | Hypertension | 58 (60.4) |
| Sex | | Heart disease | 11 (11.5) |
| Male | 61 (63.5) | Dyslipidemia | 22 (22.9) |
| Female | 35 (36.5) | Others (can have more than 1 disease) | 10 (10.4) |
| Occupation | | Physical activities | |
| Civil service | 31 (32.3) | Indoor | 58 (60.4) |
| Farmers | 16 (16.7) | Outdoor | 38 (39.6) |
| Business | 8 (8.3) | Duration of sunlight exposure | |
| Employer | 6 (6.2) | ≥30 minutes a day | 68 (70.8) |
| Others | 4 (4.2) | <30 minutes a day | 28 (29.2) |
| No occupation | 31 (32.3) | Frequency of sunlight exposure | |
| Residence | | ≥2 times a week | 43 (44.8) |
| Urban | 52 (54.2) | <2 times per week | 53 (55.2) |
| Rural | 44 (45.8) | Sunscreen protection | |
| Types of stroke | | No | 78 (81.3) |
| Large vessel infarction | 22 (22.9) | Yes | 18 (18.7) |
| Lacunar infarction | 49 (51.1) | Area applied | |
| Transient ischemic attack | 8 (8.3) | Only face | 9 (50.0) |
| Recurrent stroke | 17 (17.7) | Both face and body | 9 (50.0) |
| Neurological manifestation | | SPF in sunscreen | |
| No hemiplegia | 28 (29.2) | SPF 30 to 50 | 5 (27.8) |
| Hemiparesis | 52 (54.2) | SPF 15 to 30 | 3 (16.6) |
| Dysarthria | 44 (45.8) | Unknown | 10 (55.6) |
| Hemiparesthesia | 22 (22.9) | | |

SD=standard deviation; SPF=sun protection factor

vitamin D was presented as a percentage and 95% confidence intervals. The factors related low vitamin D level was analyzed by univariate analysis. The univariate analysis was performed by using binary logistic regression. The degree of association was presented as OR with 95% CIs. The p-value less than 0.05 was accepted as statistically significant.

## Results

The demographic and clinical characteristics of the participants are presented in Table 1. Of the 96 participants included, most (n=61, 64%) were males. The average age of the participants was 65±12 (range 37 to 91) years and mean body mass index (BMI) was 24.06±4.20 kg/m². Most participants (54.2%) lived in urban area. The most common comorbidity reported included hypertension (60.4%), followed by diabetes (33.3%), dyslipidemia (22.9%), heart diseases (11.5%), and other diseases (10.4%). There were variabilities in stroke pathology, with majority (51%) having lacunar infarction, followed by large vessel infarction (22.9%), transient ischemic attack (8.3%), and recurrent stroke (17.7%). Over half of the participants (54.2%) have hemiparesis, 45.8% reported dysarthria, 29.2% hemiplegia, 22.9% hemiparesthesia, and 21.9% other form of impairments.

The severity of stroke was measured using the NIHSS with average score of 7.76±7.51 (8.77±8.28

for those with hypovitaminosis D, and 6.57±6.37 for those with normal vitamin D level). The average Barthel index score was 55.86±29.24 (51.38±29.99 for those with hypovitaminosis D and 61.16±27.49 for those with normal vitamin D level). The average TMSE score was 19.25±9.22 (18.33±10.14 for those with hypovitaminosis D and 20.34±7.97 for those with normal vitamin D level).

***Exposure to sunlight***

Majority of the participants (60.4%) reported they spent their day doing indoor activities. Surprisingly, over half (55.2%) reported that they got exposed to sunlight between 10:00 and15:00 hours for 30 minutes or more, 41.7%, had less than 30 minutes sunlight exposure, and 3.1% did not have any sunlight exposure. Over half (52.1%) reported less than two times a week having exposure to sunlight. Most participants (81.3%) were not using any sunscreen at any times. Of those using sunscreens, 50% reported applying sunscreen on only face, while rest applied both on face and body. Most of patients (55.6%) did not know the meaning of sun protection factor (SPF) on sunscreen lotion, 27.8% applied sunscreen with SPF strength of 30 to 50, and 16.6% applied sunscreen with SPF 15 to 30.

***Food habits***

Most participants consumed eggs and cow's milk or soymilk one to four times a week, and canned fish, liver, meat, and mushrooms less than once a week. Most participants never consumed cod liver oil, fish, yogurt, and salmon as shown in Table 2.

**Table 2.** Consuming diet with high vitamin D (n=96)

| High vitamin D containing food | n (%) |
|---|---|
| Cod liver oil 15 ml | |
| Regularly | 0 (0.0) |
| Often | 2 (2.1) |
| Sometimes | 13 (13.5) |
| Never | 81 (83.4) |
| Salmon | |
| Regularly | 0 (0.0) |
| Often | 4 (4.1) |
| Sometimes | 23 (24.0) |
| Never | 69 (71.9) |
| Canned fish | |
| Regular | 0 (0.0) |
| Often | 14 (14.6) |
| Sometimes | 62 (64.6) |
| Never | 20 (20.8) |
| Liver/meat | |
| Regular | 2 (2.1) |
| Often | 20 (20.8) |
| Sometimes | 62 (64.6) |
| Never | 12 (12.5) |
| Eggs | |
| Regular | 30 (31.2) |
| Often | 43 (44.8) |
| Sometimes | 22 (22.9) |
| Never | 1 (1.1) |
| Mushrooms | |
| Regular | 4 (4.2) |
| Often | 34 (35.4) |
| Sometimes | 55 (57.3) |
| Never | 3 (3.1) |
| Cow's milk or soy milk | |
| Regular | 19 (19.8) |
| Often | 47 (49.0) |
| Sometimes | 25 (26.0) |
| Never | 5 (5.2) |
| Yogurt 240 ml | |
| Regular | 3 (3.1) |
| Often | 4 (4.2) |
| Sometimes | 32 (33.3) |
| Never | 57 (59.4) |

***Prevalence of low vitamin D***

The average vitamin D levels of the participants was 29.51±12.80 ng/ml. Based on the aforementioned defined criteria, prevalence of hypovitaminosis D amongst the participants was 54.17% (95% CI 44.23 to 64.14), vitamin D deficiency 23.96% (95% CI 21.9 to 41.7), and vitamin D insufficiency was 30.21% (95% CI 19.7 to 39.1).

***Factors related to low vitamin D level***

A series of univariate analyses were conducted to identify causal factors associated with participants' vitamin D deficiency. The factors related to vitamin D deficiency were female, performing indoor activities most of the times, duration of sunlight exposure of less than 30 minutes a day, frequency of sunlight exposure less than two times a week, and sunscreen applied on both face and body (Table 3). In addition, vitamin D levels were negatively correlated to severity of stroke (NIHSS; r=–0.227, p=0.026), and positively correlated to ability to perform daily activities (Barthel

**Table 3.** The relationship of related factors and vitamin D levels

| Factors | OR (95% CI) |
|---|---|
| Female | 3.15 (1.29 to 7.67) |
| Age ≥65 years | 1.28 (0.57 to 2.86) |
| Diabetes | 1.67 (0.70 to 3.97) |
| Hypertension | 0.93 (0.41 to 2.11) |
| Heart disease | 1.56 (0.42 to 5.71) |
| Dyslipidemia | 1.30 (0.49 to 3.40) |
| Indoor activity | 3.95 (1.66 to 9.38) |
| Duration of sunlight exposure | |
| <30 minutes a day | 2.81 (1.09 to 7.26) |
| Frequency of sunlight exposure | |
| <2 times a week | 93.60 (23.52 to 372.43) |
| Sunscreen used | 4.44 (1.36 to 14.53) |
| Area applied sunscreen | |
| Face only | 2.11 (0.49 to 9.02) |
| Both face and body | 8.42 (1.01 to 70.56) |
| SPF 30 to 50 | 4.21 (0.45 to 39.39) |
| SPF 15 to 30 | 2.11 (0.18 to 24.18) |
| Unknown SPF | 4.21 (0.84 to 21.10) |

OR=odds ratio; CI=confidence interval; SPF=sun protection factor

index; r=0.242, p=0.017). There was no significant correlation between low vitamin D levels and other factors evaluated including, age, BMI, co-morbidities, TMSE score, and consuming diets containing high levels of vitamin D.

## Discussion

To the authors' knowledge, the present study is the first study to report the prevalence of vitamin D deficiency and related potential causal factor in Thailand. The findings suggest high prevalence of vitamin D deficiency level in acute stroke patients. The significant related causal factors of this deficiency were being a female, spending most of daytime in indoor activity, severity of stroke, and less functional ability. The other factors including age, BMI, co-morbidities, cognitive ability, sunscreen use, and high vitamin D diet consumption did not have any significant association with vitamin D deficiency in the present patient cohort.

The prevalence of low vitamin D level in the present study cohort was significantly higher than normal population (aged 15 to 98 years) in the Northeast of Thailand (54.2% versus 25.1%)[20]. Remarkably, the prevalence of low vitamin D levels in acute stroke cohort found in the present study was lower than in stroke population in USA (73.4%)[11], Finland (67.6%)[12], Nepal (62%)[13], and Singapore (95%)[14], but slightly higher than in India (48.8%)[15]. This variance between countries may be due to location or latitude affecting seasoning or duration of sunlight exposure, diet, and culture.

The present study found female stroke patients were more likely to have lower vitamin D levels than male, which is consistent with the previous studies that surveyed the related factors in normal Thai population[20]. Thai women are more likely to avoid sun exposure than male due to various reasons. As expected, inadequate sunlight exposure including the patients who spent most of daytime in indoor activity, short duration and low frequency of sunlight exposure, and habit of applying sunscreen cream in both face and body was associated with low vitamin level. Adequate sunlight exposure combined with consumption of high vitamin D diet has been suggested for vitamin D deficiency prevention[19].

The high prevalence of low vitamin D level in stroke patients in the present study supported the previous evidences that suggested low vitamin D was one of the risk factors of stroke[7]. Experts in the field postulate that increase risk of stroke due to vitamin D deficiency may be related to process of atherosclerosis formation, reduced blood pressure by inhibited renin and angiotensin system[21], suppressed thrombotic formation[22,23], reduced atherogenic dyslipidemia[24], prevented intimal media thickness and arterial plaques[25], and reduced lymphocytes activation and the inflammatory cytokines[26,27]. Therefore, stroke guidelines recommend regular monitoring of vitamin D levels to prevent stroke or to prevent second attack.

Consistent with previous studies, the findings of the present study showed strong correlation of low vitamin D levels with severity of stroke and functional ability[8,28]. Wang et al found serum 25(OH) D levels in ischemic stroke was related to both severity of stroke at admission and functional outcome in patients[8]. Li et al also suggested low serum 25(OH) D levels was a factor to predict a larger amount of ischemic brain tissue and neurological deficit[28]. The suggested underlying mechanisms of vitamin D deficiency include involvement of vitamin D in increased inflammatory response and suppressed neuroprotective process[29,30].

Some potential limitations conducting the present study cannot be ruled out. Firstly, this was a cross sectional descriptive study and did not provide longitudinal information. Secondly, the stroke cohort was a selective cohort from a single tertiary hospital admitted for short duration (six months) and with strict inclusion criteria for patient who agreed to participate in research projects, which may limit the generalizability of these findings. However, as evaluation of the vitamin D level was routine clinical procedure in the hospital, all attempts were made to include all consecutive patients admitted within the defined study period. Further, the study was conducted in January to June, which included both winter and summer seasons in Thailand, as different seasons may affect the amount of sunlight and vitamin D synthesis in the body.

## Conclusion

Vitamin D deficiency is highly prevalent in stroke patients and associated with increased risk of stroke with significant negative consequences. Understanding the prevalence and impact of vitamin D deficiency is important for comprehensive patient management and should be routinely evaluated in stroke patients to reduce complications. Further, potential related factors associated with this deficiency identified in the present study have important implications for the treating clinicians and need to be explored in larger cohorts. Further study should compare the prevalence of vitamin D deficiency in different seasons. In addition, vitamin D levels should be monitored in longer-term in subacute and chronic stage of stroke, as this may have significant implication for rehabilitation interventions.

## What is already known on this topic?

The high prevalence of vitamin D deficiency and related factors in stroke patients have been reported in many countries.

## What this study adds?

In Thailand, the culture, lifestyle, and high vitamin D diet consuming may be different from other countries. This study revealed the high prevalence of vitamin D deficiency in acute stroke patients in Thailand, which suggests physicians to monitor regularly the vitamin D level in all stroke patients.


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## Conflicts of interest

The authors declare no conflict of interest.

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