

Vitamin D status and related factors among Korean stroke survivors: the Fourth and Fifth Korea National Health and Nutrition Examination Surveys

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Abstract

Background: The aim of this study was to investigate the vitamin D status and related factors in community-dwelling Korean stroke survivors. **Methods:** Data of 23,872 individuals ≥ 20 years who participated in the Korea National Health and Nutrition Examination Surveys (KNHANES) were analyzed. Participants who had ever been diagnosed with stroke by a doctor were defined as stroke survivors ($n = 431$). The serum 25-hydroxyvitamin D (25(OH)D) level was measured by radioimmunoassay, and vitamin D deficiency was defined as 25(OH)D < 20 ng/mL. The association between vitamin D and stroke status was analyzed using multivariable general linear models and logistic regression models adjusted for sociodemographic and clinical covariates. **Results:** The adjusted mean 25(OH)D level of stroke survivors was significantly lower than that of nonstroke controls; however, after adjustment for SBP level and use of antihypertensive medication, the difference was no longer statistically significant. The burden of 25(OH)D deficiency was not higher in stroke survivors than in nonstroke controls (adjusted OR = 1.14; 95% CI, 0.81-1.62). Current smoking was independently associated with 25(OH)D deficiency among stroke survivors (adjusted OR = 3.17; 95% CI, 1.33-7.55). **Conclusions:** These findings indicated that treatment of high blood pressure and smoking cessation may be important measures to control vitamin D levels in stroke survivors.

Background

Vitamin D is traditionally known for its function in bone metabolism, but it has recently emerged as a potential risk factor for other diseases such as diabetes, osteoarthritis, and cardiovascular disease [1-3]. Stroke, one of the cardiovascular diseases, is among the major healthcare burdens of modern society [4, 5]. Cigarette smoking, hypertension, diabetes, high total cholesterol, low high-density lipoprotein cholesterol, physical inactivity, and obesity are well-documented and modifiable risk factors for stroke [4]. Recent studies have indicated that vitamin D deficiency could be a novel risk factor for stroke [1, 6-8].

Although vitamin D has been suggested as a potential risk factor for stroke, the findings from epidemiologic studies of vitamin D status and stroke incidence and outcomes have been controversial because of differences in study participants and study design [7-12]. Nevertheless, researchers have found the association of a low serum vitamin D level measured before or at the onset of acute stroke with incident stroke risk and outcomes [7, 12, 13]. However, vitamin D status and its related factors in noninstitutionalized stroke survivors are not yet fully understood. Previous studies of vitamin D levels in community-dwelling stroke survivors have focused primarily on differences in bone mineral density of the affected and unaffected sides [14].

Although vitamin D deficiency affects over 60% of the South Asian and Southeast Asian population [15, 16], most previous studies of the association between vitamin D and stroke have focused on Caucasians and African Americans, and studies on Asian populations are relatively limited. Despite the potential beneficial roles of vitamin D and the high prevalence of vitamin D deficiencies, population-based studies investigating the association between vitamin D and stroke have rarely been conducted in Koreans.

Therefore, we performed the present study to investigate vitamin D status and risk factors for vitamin D deficiency among noninstitutionalized stroke survivors in Korea.

Methods

Study design and participants

A cross-sectional data from the Fourth and Fifth Korea National Health and Nutrition Examination Surveys (KNHANES) were used. A stratified, multistage, clustered probability sampling method was applied in KNHANES to build a representative database of the community-dwelling Korean population. The survey was organized into household health interviews, nutrition surveys, and health examination conducted at mobile examination centers.

A total of 10,533, 8,958, 8,518, and 8,058 individuals were participated in KNHANES in 2009, 2010, 2011, and 2012, respectively. Among a total of 36,067 participants, 23,872 individuals aged ≥ 20 years (10,278 men and 13,594 women) who were measured for 25-hydroxyvitamin D (25(OH)D) and answered the health interview questions for previous stroke history were included. Participants who answered “yes” to the question “Have you ever been diagnosed with stroke by a doctor?” were defined as ‘stroke survivors’.

Biochemical measurement

Blood samples collected after >8 hours of fasting were analyzed within 24 hours. The serum 25(OH)D level was assessed by radioimmunoassay with 25-Hydroxyvitamin D 125I RIA Kit (DiaSorin, USA) using a 1470 WIZARD Gamma-Counter (PerkinElmer, Finland). Among the many circulating metabolites of vitamin D metabolism, serum 25(OH)D is documented as the best indicator to assess nutritional vitamin D status, to diagnose vitamin D deficiency and insufficiency and to evaluate the effects of treatment [17]. Using the Institute of Medicine guidelines [18], we considered deficient 25(OH)D to be <20 ng/mL, which have been suggested to be sufficient for bone health in the Korean population [19]. Serum total and high-density lipoprotein cholesterol were evaluated using enzymatic methods on a Hitachi Automatic Analyzer 7600 (Hitachi, Japan). All analyses were performed at Neodin Medical Institute (Seoul, Korea).

Anthropometric measurement

The health interview questionnaire was used to obtain information regarding residence area, daily sun exposure time, smoking status, alcohol use, education level, physical activity level, diabetes and use of lipid-lowering and antihypertensive medication. Residence area was classified as urban and rural. Sun exposure time was categorized as ≥ 5 hrs/day or <5 hrs/day. Current smokers were defined as those who had smoked more than five packs of cigarettes during their lifetime and were smoking currently; all others were nonsmokers. The Korean Alcohol Use Disorders Identification Test (AUDIT) score was used to classify the alcohol use (low-risk, 0–7; intermediate-risk, 8–14; and high-risk, ≥ 15 points) [20]. Education

level was categorized as less than middle school graduation (≤ 9 years) and high school/college and more (> 9 years). Physical activity was categorized as high, moderate and low by the short form of the International Physical Activity Questionnaire [21].

Body mass index was calculated as the individual's weight divided by the square of the height (kg/m^2) and further divided into 3 categories: underweight ($< 18.50 \text{ kg}/\text{m}^2$), normal ($18.50\text{-}24.99 \text{ kg}/\text{m}^2$), and obese ($\geq 25.00 \text{ kg}/\text{m}^2$). The trained nurses measured blood pressure three times at 30-second intervals after the participant rested for 5 minutes using a mercury sphygmomanometer (Baumanometer; Baum, USA). The final systolic blood pressure (SBP) value was determined by averaging the values from the second and third measurements and was categorized as $< 140 \text{ mmHg}$ or $\geq 140 \text{ mmHg}$ [9].

Statistical analysis

Descriptive statistics for participant characteristics were obtained by determining frequency distributions of categorical data and the weighted means and standard errors of continuous variables. The mean 25(OH)D level according to stroke status was obtained using general linear models adjusting multiple confounders. Covariates were selected considering their documented associations with 25(OH)D and stroke in previous studies and based on their clinical applicability [7, 8, 10, 11, 22]. We made four models to progressively reduce confounding associations. To investigate the degree of 25(OH)D deficiency risk based on stroke status, odds ratios (OR) and 95% confidence intervals (95% CI) were obtained while controlling for covariates using multivariable logistic regression analyses. To further determine the risk factors for having 25(OH)D deficiency in stroke survivors, subgroup analyses involving univariable and multivariable logistic regression analyses were performed among the stroke survivors. We used SPSS software (version 24; IBM/SPSS, USA) to perform complex sample procedures applying weighted values of KNHANES. *P*-values less than 0.05 were taken as statistically significant.

Results

Among 23,872 participants, 431 individuals were stroke survivors. The weighted prevalence of stroke was 1.22% (SE = 0.08%) in the Korean population aged ≥ 20 years. The weighted mean age at diagnosis of stroke was 56.64 ± 0.78 years, and the mean time since diagnosis of stroke was 8.72 ± 0.47 years. Compared with the controls without a history of stroke ($n = 23,441$), the stroke survivors showed different demographic, lifestyle, and clinical characteristics, which are summarized in Table 1. The stroke survivors were more likely to be older and to have a higher body mass index, lower physical activity, and higher SBP than controls. The stroke survivors also showed an increased proportion of rural residence, nonsmoker, low-risk alcohol drinker, low education level, and diabetes than nonstroke controls.

Table 2 presents the comparison of mean 25(OH)D levels in both groups, adjusting for covariates affecting the 25(OH)D level. When adjusting for age and sex, the mean 25(OH)D levels of stroke survivors and nonstroke controls were not different (model 1; *P* = 0.078 in Table 2). After further adjustment for

other confounders, the adjusted mean 25(OH)D level in stroke survivors became significantly lower than that in controls (model 2; $P = 0.021$ and 3; $P = 0.039$ in Table 2). However, after additional adjustment for SBP level and use of antihypertensive medication, the difference in mean 25(OH)D levels between stroke survivors and controls was no longer statistically significant (model 4; $P = 0.091$ in Table 2).

The weighted prevalence of 25(OH)D deficiency (25(OH)D <20 ng/mL) was 71.19% (SE = 0.77%), which indicated a high prevalence of 25(OH)D deficiency in the noninstitutionalized Korean population. The weighted prevalence of 25(OH)D deficiency was 61.08% (SE = 2.91) in stroke survivors and 72.36% (SE = 0.75) in controls. As shown in Table 3, there was no significant association between past history of stroke and current 25(OH)D deficiency. We performed further logistic regression analyses to identify potential risk factors for 25(OH)D deficiency in noninstitutionalized stroke survivors. In the univariate analysis, current smoking and high total cholesterol levels (≥ 240 mg/dL) were significantly related to 25(OH)D deficiency (crude ORs in Table 4). Finally, the multivariable logistic regression analysis revealed that 25(OH)D deficiency was 3.17 times higher in current smokers than in nonsmokers among the participants previously diagnosed with stroke (adjusted OR in Table 4).

Discussion

The present study demonstrated that the adjusted mean 25(OH)D level of community-dwelling stroke survivors is significantly lower than that of nonstroke controls when high blood pressure was not adjusted. Decreased 25(OH)D levels in stroke survivors may be mediated by hypertension. However, 25(OH)D deficiency using a cut-off value of 20 ng/mL was not associated with the previous history of stroke. Current smoking was the only independent factor associated with vitamin D deficiency in stroke survivors. To our knowledge, this study is the first in Korea to investigate the mean vitamin D level and the burden of vitamin D deficiency among community-dwelling stroke survivors.

We found that multivariable adjusted 25(OH)D levels were significantly lower in stroke survivors than in controls (models 2 and 3 in Table 2). However, the significantly lower mean 25(OH)D level in stroke survivors was no longer statistically significant after further adjustment for SBP and the use of antihypertensive medication (model 4 in Table 2). Therefore, decreased 25(OH)D levels in stroke survivors may be mediated by the effect of vitamin D on hypertension. A cross-sectional study of 239 Indian ischemic stroke patients reported similar associations between vitamin D, hypertension and stroke with our study [8]. According to the results of the current study, hypertension may be an important mediator of low vitamin D levels in stroke survivors as well as a risk factor for the incident and recurrent stroke [4, 23]. Fortunately, the levels of vitamin D and blood pressure can be modified by medication and nutritional support. Therefore, monitoring and treating vitamin D levels and SBP would be important in stroke survivors.

Several hypotheses have been suggested regarding the underlying mechanism of the association between vitamin D and stroke. Vitamin D has been indicated to play an important role in the autocrine and paracrine regulation of brain function [2, 24]. Animal and human studies support this hypothesis by

confirming the expression of vitamin D receptors in specific brain regions such as the cerebellum and hypothalamus [1, 25]. Furthermore, vitamin D can exhibit neuroprotective attributes through antioxidation, neuronal calcium regulation, immunomodulation, enhanced nerve conduction, and detoxification mechanisms [26]. In addition, vitamin D has vasoprotective effects through modulating atheroma formation, endothelial function, and the renin–angiotensin–aldosterone system [1, 2]. Among the multiple functions of vitamin D in the human body, vitamin D can affect blood pressure [1, 2]. A possible mechanism is the effects of vitamin D on the renin-angiotensin system, which plays an important role in the regulation of blood pressure [27]. Another possible pathophysiology may be endothelium-dependent vascular relaxation [28] and/or anti-inflammatory effects [29] of vitamin D. The results of our study also support the role of blood pressure as a mediator in the association between vitamin D and stroke.

The present study found that 25(OH)D deficiency is not associated with the previous history of stroke, which is partially consistent with the previous cross-sectional study in the general US population (White, Black, and Hispanic race) [10]. The previous study concluded that 25(OH)D deficiency (defined as 25(OH)D <12 ng/mL) was significantly associated with an increased risk of stroke. Although this association was attenuated to be nonsignificant after adjustment for diabetes, SBP, diastolic blood pressure, and total cholesterol, there was no reasonable explanation for this attenuated association in the previous study. Furthermore, when vitamin D is measured in participants with the previous stroke, as in most epidemiological studies, it is inappropriate to interpret the results to mean that the vitamin D deficiency is associated with the increased risk of stroke.

The results of the current study suggest that stroke survivors do not have an increased burden of vitamin D deficiency compared with participants without a history of stroke. A possible explanation is that vitamin D deficiency in the Korean general population is too high to find any associations with a disease [15, 30]. We estimated that 71.19% of the adult Korean population were vitamin D deficient on the basis of the cutoff value of 20 ng/mL. Furthermore, the categorization of vitamin D levels into a binary variable can lead to losing information. Another explanation for the lack of association between previous stroke status and vitamin D deficiency is that it may be inappropriate to use the cut-off value of 25(OH)D defined by skeletal health. The optimal vitamin D level has been classically determined considering bone health and parathyroid hormone level [18, 19]. The various cut-off values across many previous studies may reflect the changing understanding of the roles of vitamin D beyond bone metabolism to include nonskeletal actions of vitamin D influencing chronic diseases such as cancer, autoimmune diseases and cardiovascular disease [2]. Future studies are needed to determine optimal levels for vitamin D in relation to cardiovascular disease, including stroke.

The independent adverse effect of cigarette smoking on vitamin D deficiency among stroke survivors should be highlighted. The logistic regression analyses in stroke survivors indicated that current smoking is an independent risk factor for vitamin D deficiency among individuals with a history of stroke. The prevalence of current smokers was significantly lower in stroke survivors than in the controls. However, among stroke survivors, vitamin D deficiency was 3.17 times higher in current smokers than in nonsmokers. Smoking is one of the most well-established risk factors for stroke [4]. Smoking may

increase stroke risk through both acute effects on thrombus generation in narrowed vessels and chronic effects related to an increased degree of atherosclerosis [31]. Smoking can also acutely increase mean blood pressure and heart rate [32] and is associated with the later development of atherosclerosis [33]. Therefore, the synergistic effects of smoking and vitamin D deficiency modulating atherosclerosis and blood pressure may explain the observed strong independent association between current smoking and vitamin D deficiency in stroke survivors.

The present study has several limitations. Due to the nature of cross-sectional studies, the direction of causality cannot be formally determined. Because of the established sets of variables in KNHANES, we did not know whether the stroke was hemorrhagic or ischemic. We were unable to adjust for seasonal variation due to limitations in access to individual data for the season. Therefore, we hypothesized a normal distribution of season in both stroke survivors and controls because the serum sampling of KNHANES was evenly distributed during each year. Although we included established confounders and added confounders stepwise into multiple models, some unknown conditional associations may have generated adjustment bias.

Conclusion

Mean vitamin D levels without adjusting for blood pressure are lower in stroke survivors than in nonstroke controls. High blood pressure may be a key factor mediating vitamin D level among stroke survivors. However, there is no association between stroke history and vitamin D deficiency using the commonly applied clinical cutoff value of <20 ng/ml. Among stroke survivors, current smoking, possibly influencing atherosclerosis and blood pressure, is the only independent risk factor for vitamin D deficiency.

Abbreviations

KNHANES: Korea National Health and Nutrition Examination Surveys; 25(OH)D: 25-hydroxyvitamin D; AUDIT: Alcohol Use Disorders Identification Test; SBP: systolic blood pressure; OR: odds ratios

Declarations

Funding

Not applicable.

Availability of data and materials

The KNHANES database is released for public use in Korean on a website (<http://knhanes.cdc.go.kr>).

Authors' contributions

YHK contributed to concept, design, literature search, data acquisition, data analysis, statistical analysis and manuscript preparation, manuscript editing and finalization. JSL contributed to data acquisition,

data analysis, statistical analysis and manuscript preparation, manuscript editing and finalization. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The Institutional Review Board at the Korea Centers for Disease Control and Prevention approved the protocol (IRB no. 2009-01CON-03-2C, 2010-02CON-21-C, 2011-02CON-06-C, and 2012-01EXP-01-2C), and all participants signed informed consent forms. Because this study analyzed public data, ethical approval from our hospital was waived.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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