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Vitamin D deficiency and osteoporosis in stroke survivors: an analysis of National Health and Nutritional Examination Survey (NHANES)

Derya Uluduz[*], **Malik M. Adil**, **Basit Rahim**, **Waqas I. Gilani**, **Haseeb Abdul Rahman**, **Sarwat I. Gilani**, and **Adnan I. Qureshi**

Zeenat Qureshi Stroke Institute, St. Cloud, MN, USA

[*]*Istanbul University Cerrahpasa School of Medicine, Department of Neurology, Istanbul, Turkey*

Abstract

Background and purpose—An inverse association between 25-hydroxyvitamin D (25[OH]D) levels and stroke was emphasized in recent studies. Our objective was to determine the rate of Vitamin D deficiency and risk of associated osteoporosis among stroke survivors in a nationally representative population.

Methods—Participants from the National Health and Nutritional Examination Survey (NHANES) from 2001 to 2006 were included. Stroke survivors were then divided into two groups depending on serum 25(OH)D levels: <30 ng/dl as Vitamin D deficiency and ≥30 ng/dl as normal. Comparisons of demographics and risk factors between two groups were performed using SAS software. Multivariate analysis was performed to determine the association between Vitamin D deficiency and osteopororis in stroke survivors after adjusting for potential confounding factors.

Results—There were 415 (4.0%) stroke survivors among 10,255 participants in NHANES. The mean age (±SD) of stroke survivors was 67.6 (±17.3) years and 211 (50.8%) were men. Mean 25(OH)D concentrations were not significantly different in patients with stroke (20.3 versus 21.8 ng/ml, $p = 0.65$) although the rate of osteoporosis was significantly higher among stroke survivors (17.9% versus 6.9%, $p < 0.0001$). Out of 415 stroke patients, Vitamin D deficiency was seen in 71.0% of patients. The rates of osteoporosis were similar between patients with or without Vitamin D deficiency. After adjusting for potential confounders, there was no association between Vitamin D deficiency and osteoporosis.

Conclusions—Vitamin D deficiency and osteoporosis are highly prevalent among stroke survivors; however, there does not appear to be a relationship between the two entities.

Keywords

Vitamin D deficiency; osteoporosis; stroke; National Health and Nutritional Examination Survey (NHANES); bone fractures

Introduction

Recent studies have focused on the role of indices of mineral metabolism in the pathogenesis of cardiovascular and cerebrovascular diseases (CVDs). The discovery that Vitamin D receptors have a wide tissue distribution including the vascular wall has provided new insights into the possible relationship between Vitamin D and CVD [1]. Several clinical studies have reported a high prevalence of Vitamin D deficiency in patients with coronary artery disease and stroke [2], suggesting that Vitamin D might play a role in the pathogenesis of arterial disease [1,3]. An inverse association was observed between 25 (OH)D levels and risk of incident stroke [2,4,5]. Despite the relationship between prior Vitamin D status and stroke occurence, studies have not ascertained the existence of Vitamin D deficiency among stroke survivors who may be particularly predisposed because of immobility, limited exposure to sunlight, and dietary changes subsequent to stroke. The clinical significance of Vitamin D deficiency in stroke survivors may be considerable given the risk of osteoporosis and fractures in such patients [6–8]. Low levels of serum 25(OH)D are common amongst women with osteoporo-

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Correspondence to: Derya Uluduz MD, Istanbul University Cerrahpasa School of Medicine, Department of Neurology, Istanbul, Turkey

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sis [9] and low bone mineral density (BMD) is frequent in patients with CVD supporting a potential cause effect relationship [10–15].

We examined the relationship between 25(OH)D levels and osteoporosis among stroke survivors in a nationally representative sample to avoid biases introduced by stroke characteristics and patients' socioeconomic status in limited sample studies.

Material and methods

The data sets used in this study were derived from the National Health and Nutrition Examination Survey (NHANES) with subsequent 2-year cycles (2001–2002, 2003–2004, 2005–2006). NHANES is a large, multistage, complex survey of the noninstitutionalized civilian US population 2 months of age and over conducted by the National Center for Health Statistics (NCHS). Detailed description of the survey design and data collection procedure is available in the online-only Data Supplement [16]. Briefly, the population was sampled with a complex, stratified, multistage probability cluster sampling design to provide data that are representative of the overall US population. The survey collected demographics, socioeconomic status, dietary, and health-related information, in addition to the examination and laboratory data obtained by highly trained medical professionals. Selected participants consent to a household interview followed by an examination in the NHANES Mobile Examination Center. NHANES was reviewed and approved by the NCHS ethics review board. Participants provided written informed consent before participation. We only included adults ages 18 and older in our analysis.

The NHANES data questions include the ascertainment of demographics such as gender, age, race/ethnicity, risk factors of CVD such as cigarette smoking, alcohol consumption, cardiac disease (congestive heart failure, heart attack, and coronary heart disease), diabetes mellitus (DM), hypertension, and body mass index (BMI). Presence of osteoporosis and laboratory results including lipid profile were assessed in all study participants according to protocols described in NHANES operating manual [16]. Age was defined as age at the time of the interview. Race/ethnicity, based on self-reported information, was classified into three categories as non-Hispanic Whites, African Americans, and others. Responses to the medical conditions section of the NHANES household interview were used to establish history of risk factors [16]. Smoking status was ascertained by responses to the smoking section of the household questionnaire and current smoker participants were classified as every day, some days, or not at all. Alcohol consumption was defined as persons who had drunk at least 12 alcohol drinks per year. BMI was calculated as weight in kilograms over height in meters squared (kg/m2). Serum 25(OH)D levels was measured using a 25-hydroxyvitamin D radioimmunoassay (Diasorin, Inc., Stillwater, MN, USA). As there is still some debate on the best classification of Vitamin D status, we used a currently proposed Vitamin D classification including clinical relevant cutoff values. Vitamin D deficiency was considered with serum 25(OH)D levels <30 ng/dl [1].

Fasting levels of triglycerides were measured enzymatically with a Hitachi 704 Analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). Total cholesterol and LDL-C concentrations were calculated using the Friedewald's equation (i.e., LDL-C = total cholesterol-HDLC — triglyceride/5).

The NHANES survey included a questionnaire where participants were specifically asked whether they had suffered a stroke. We considered participants to have had a stroke if they answered yes to the question "Has a doctor ever told you that you had a stroke?" A participant was defined as "diabetic" or "hypertensive" if they reported they had ever been told by a doctor that either they had diabetes or high blood pressure or were taking medications for these conditions. History of cardiovascular disease was determined by a positive response to any of the following conditions "Has a doctor or other health care professionals ever told you had; congestive heart failure, heart attack and coronary heart disease" [16]. Osteoporosis was defined by whether the participant had ever been diagnosed as having osteoporosis by a physician and/or whether s/he had been treated for osteoporosis.

Statistical analysis

All the data were descriptively presented using mean ± standard deviation (SD) for continuous data and frequencies for categorical data. For all tests, a *p*-value <0.05 (two-sided) was considered significant. We tested two hypotheses: 1) The proportion of patients with Vitamin D deficiency and/or osteoporosis is higher among stroke survivors compared with nonstroke patients after adjusting for potential confounders. 2) The risk of osteoporosis is higher among stroke survivors with Vitamin D deficiency compared with those with normal Vitamin D levels after adjusting for potential confounders. Multivariable logistic regression analysis was performed to test the above hypothesis. In the multivariate analysis, variables were selected based on prior studies to deter-

Table 1. Demographic and clinical characteristics of person in NHANES 2001-2006 with and without history of stroke

	Persons with history of stroke(*n* = 415)	Persons without history of stroke (*n* = 9824)	*p* value
Age (years)	67.56 ± 17.3	47.61 ± 20.3	<0.0001
Women	211 (50.84)	5095 (51.8)	0.684
Race/ethnicity			
Non-Hispanic Whites	242 (58.3)	5006 (50.9)	
African American	92 (22.1)	2079 (21.1)	
Others	81 (19.5)	2739 (27.9)	0.002
BMI (kg/m^2)	27.2 (7.1)	26.9 (7.1)	0.374
Medical conditions			
Cigarette smoking	237 (57.1)	4666 (47.5)	<0.0001
Congestive heart failure	112 (17.8)	465 (3.1)	<0.0001
Coronary heart disease	114 (18.1)	616 (4.2)	<0.0001
Myocardial infarction	123 (19.6)	645 (4.4)	<0.0001
Alcohol, drug or cocaine use	19 (26.0)	652 (20.6)	0.034
Diabetes mellitus	130 (31.3)	947 (9.6)	<0.0001
Hypertension	299 (72.5)	3056 (31.4)	<0.0001
Osteoporosis	38 (17.9)	337 (6.9)	<0.0001
Laboratory results			
Vitamin D levels (ng/dl)	20.3 (9.0)	21.8 (9.2)	0.657
Total cholesterol (mg/dl)	195.0 (47.2)	200.0 (43.7)	0.034
Triglycerides (mg/dl)	160.2 (99.6)	146.0 (131.7)	0.0008
LDL (mg/dl)	111.6 (39.2)	113.9 (36.7)	0.185

Abbreviations used: BMI: body mass index; LDL: low-density lipoprotein.

mine the association between confounding factors, Vitamin D deficiency and osteoporosis independently [1,3,4,12,17–20]. In the analysis with osteoporosis as the dependent factor, we adjusted for age, gender, smoking status, alcohol consumption, cardiovascular disease, and diabetes mellitus. In the analysis with Vitamin D deficiency as the dependent factor, we adjusted for age, gender, ethnicity, smoking status, hypertension, diabetes mellitus, and cardiovascular diseases. All variables were entered as categorical variables except age and BMI that were entered as continuous measurements. Statistical analysis was performed using the Statistical Analysis Systems (SAS) software package version 9.1 (SAS Institute, Inc., Cary, NC).

Results

Among 10,255 adult participants included in the analysis, there were 415 (4.0%) stroke survivors. Table 1 shows the baseline characteristics of participants with and without stroke such as age, gender, race/ethnicity, BMI, prevalence of cardiovascular risk factors and presence of osteoporosis, drug and cocaine use, and lipid levels. The mean age [±SD] of stroke survivors was significantly higher (67.5 [±17.3] years versus 47.6 [±20.3] years, p < 0.0001). The proportion of non-Hispanic Whites was significantly higher among those with stroke (58.3% versus 22.1%). The proportion of patients with hypertension, diabetes mellitus, and CVD were significantly higher among stroke survivors. The mean triglyceride levels in mg/dl [±SD] were significantly higher among stroke survivors (160.2 [±99.6] mg/dl versus 146.0 [±131.7] mg/dl, p = 0.0008). The mean total cholesterol levels in mg/dl [±SD] were significantly higher among stroke survivors (195.0 [±47.2] mg/dl versus 200.0 [±43.7] mg/dl, p = 0.034). BMI did not differ between the two groups. The average values of Vitamin D concentration were 20.3 [±9.0] ng/dl in stroke survivors and 21.8 [±9.2] ng/dl in nonstroke participants (p = 0.65), as presented in Table 1. The rate of osteoporosis was significantly higher among stroke survivors (17.9% versus 6.9%, p < 0.0001). The rate of Vitamin D deficiency was not significantly different among stroke survivors compared with nonstroke patients (OR 1.1, 95% CI 0.8-1.5 , p = 0.4) after adjusting for potential confounders. However, the rate of osteoporosis was significantly higher among stroke survivors (OR 1.2, 95% CI 0.6-2.0 , p = 0.5) even after adjusting for potential confounders. Addition of Vitamin D deficiency to the

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Table 2. Comparisons of demographic, clinical, and laboratory variables among stroke survivors in Nhanes 2001–2006 with and without Vitamin D deficiency

	Persons with Vitamin D deficiency (*n* = 295)	Persons without Vitamin D deficiency (*n* = 120)	*p* value
Age (years)	67.56 ± 17.0	67.57 ± 18.0	0.996
Women	148 (50.1)	63 (52.5)	0.666
Race/ethnicity			
Non-Hispanic Whites	176 (59.6)	66 (55.0)	
African American	69 (23.3)	23 (19.1)	
Others	50 (16.9)	31 (25.3)	0.215
BMI (kg/m^2)	27.6 (6.9)	26.1 (7.3)	0.084
Medical conditions			
Cigarette smoking	174 (58.9)	63 (52.5)	0.863
Congestive heart failure	53 (17.9)	59 (17.7)	0.861
Coronary heart disease	53 (17.9)	61 (18.3)	0.040
Myocardial infarction	61 (20.6)	62 (18.6)	0.497
Alcohol, drug or cocaine use	10 (24.3)	9 (28.1)	0.643
Diabetes mellitus	95 (32.2)	35 (29.1)	0.939
Hypertension	212 (72.6)	87 (72.5)	0.807
Osteoporosis	22 (17.1)	16 (19.0)	0.683
Laboratory results			
Vitamin D levels (ng/dl)	17.3 ± 6.4	34.6 ± 5.3	<0.0001
Total cholesterol (mg/dl)	193.6 ± 48.7	199.2 ± 42.4	0.331
Triglycerides (mg/dl)	163.0 ± 103.8	152.1 ± 85.7	0.908
LDL (mg/dl)	111.9 (40.8)	111.2 (35.2)	0.904

Abbreviations used: 25(OH)D: 25-Hydroxyvitamin D; BMI: body mass index; LDL: low-density lipoprotein.

model did not change the odds ratio (1.2 to 1.2) of the association.

Out of 415 stroke patients, Vitamin D deficiency was seen in 71.0% of the patients (mean concentration of 17.3 ± 6.4 ng/dl) and was normal in 29.0% patients (mean concentration of 34.6 ± 5.3 ng/dl) (Table 2). The mean age [±SD] of patients with and without Vitamin D deficiency was similar (67.56 [±17.0] and 67.57 [±18.0] years, p = 0.996). The gender and race/ethnicity were not different between each groups of stroke survivors with a higher proportion of non-Hispanic Whites in both groups (59.6% and 55.0%). The proportion of patients with hypertension, diabetes mellitus, cigarette smoking, alcohol consumption, and CVD were similar between patients with and without Vitamin D deficiency excluding coronary heart disease which was higher in patients with normal Vitamin D levels. Stroke patients with Vitamin D deficiency had a nonsignificantly higher BMI (27.6 [±6.9] versus 26.1 [±7.3] kg/m2, p = 0.084). The mean triglyceride, total cholesterol, and LDL levels in mg/dl [±SD] were similar in each group of stroke survivors (163.0 [±103.8] mg/dl and 152.1 [±85.7] mg/dl, p = 0.908, 193.6 [±48.7] mg/dl and 199.2 [±42.4] mg/dl, p = 0.331 and 111.9 [±40.8] mg/dl and 111.2 [±35.2] mg/dl, p = 0.904, respectively). The rates of osteoporosis were similar between patients with and without Vitamin D deficiency (17.1% and 19.0%, p = 0.683). After adjusting patients for potential confounders, no association was found between Vitamin D deficiency and osteoporosis (OR 1.2, 95% CI 0.4–3.6, p = 0.7) (Table 3).

Discussion

Our study found a significant higher rate of osteoporosis among stroke survivors even after adjusting of other factors that predispose to osteoporosis in the multivariate analysis consistent with previous studies [21–23]. Several explanations can be considered to explain the higher rate of osteoporosis among stroke survivors including (a) their age-related independent progression, (b) the presence of shared risk factors (such as cigarette smoking and physical inactivity), and (c) the presence of common pathophysiological mechanisms involving endogenous hormones or inflammatory cytokines. Other large observational studies have found an association between low bone density and either incident cardiovascular disease or subclinical atherosclerosis [23,24]. There might be an overlap between risk factors for atherosclerosis and osteoporosis [23]. Atherosclerosis, by

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Table 3. Association between history of stroke, Vitamin D deficiency and osteoporosis: Nhanes 2001–2006

Outcomes	Unadjusted		Adjusted for age and gender		Adjusted for age, gender, and risk factors[a]		Adjusted for age, gender, risk factors, and Vitamin D deficiency[b]	
	OR (95% C.I.)	*p* value	OR (95% C.I.)	*p* value	OR (95% C.I.)	*p* value	OR (95% C.I.)	*p* value
Osteoporosis	3.0 (2.0-4.3)	<0.0001	1.5 (0.1-2.1)	0.07	1.2 (0.6-2.0)	0.5	1.2 (0.6-2.2)	0.5
Vitamin D deficiency	1.0 (0.8-1.1)	0.9	1.0 (0.8-1.2)	0.9	1.1 (0.8-1.5)	0.4	Not applicable	

Vitamin D: 25-hydroxyvitamin D; OR: odds ratio.

[a]Osteoporosis as dependent variable-adjusted for cigarette smoking status, alcohol consumption, cardiovascular disease (congestive heart failure, heart attack, coronary heart disease), and diabetes mellitus.

[b]Vitamin D deficiency as dependent variable adjusted for ethinicity, cigarette smoking status, cardiovascular disease (congestive heart failure, heart attack, coronary heart disease), diabetes mellitus, and hypertension.

reducing blood flow to the lower extremities, could alter bone metabolism in the hip and result in osteoporosis as well.

Vitamin D deficiency could be another explanation for the high rate of osteoporosis in stroke survivors. A low level of Vitamin D decreases bone density, influences neuromuscular dysfunction, and increases the risk of falls and fractures [14,25]. In a long-term study of stroke survivors, there were associations between low Vitamin D, low bone density, and poststroke hip fractures [7]. However, in our study, we found a higher rate of osteoporosis in stroke survivors versus nonstroke participants and a higher rate of Vitamin D deficiency among stroke survivors, but no association between Vitamin D deficiency and osteoporosis could be demonstrated. Bone loss occurs early after stroke and increases over time with limited activity. The current data suggests alternate explanations such as inactivity for osteoporosis rather than Vitamin D deficiency [26]. The high proportion of patients with Vitamin D deficiency among stroke survivors is possibly related to malnutrition or sunlight deprivation and reduced cutaneous production. The clinical significance of Vitamin D deficiency in stroke survivors need to evaluated in further studies.

There are several issues that need to considered prior to interpretation of results. First, 25(OH)D levels were only measured once at baseline and may not be reflective of lifetime Vitamin D status. Second, there may be selection bias in stroke survivors. Presence of osteoporosis and low Vitamin D will be more prominent in long-term hospitalized or housebound patients. Excluding those patients might underestimate the rate of Vitamin D deficiency in stroke survivors. Third, this study is cross sectional and based on self-report whereby participants were notified by their physician of the diagnosis, with potential for misclassification bias and uncertainty of data accuracy. There are several studies demonstrating the reliability of self reported data and higher validity is noted with structured interviews or questionnaires [27–30]. NHANES used structured methods for data collection that increases the validity of our results.

Conclusion

In conclusion, this study demonstrates that Vitamin D deficiency and osteoporosis are highly prevalent among stroke survivors; however, there does not appear to be a relationship between the two entities.

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Contribution of authors:

Derya Uluduz MD, Malik M Adil MD, Basit Rahim MD, Sarwat I. Gilani MD, Haseeb Abdul Rahman MD, Waqas I. Gilani MD, Adnan I. Qureshi MD.Equally assisted in the synthesis and discussion of ideas, and

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share equal responsibility for the information written in the manuscript above.

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