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Low Dietary Vitamin D Predicts 34-Year Incident Stroke: The Honolulu Heart Program

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Abstract

Background and Purpose—Vitamin D deficiency has been reported to contribute to the risk of cardiovascular disease, especially stroke. We examined the relationship between dietary vitamin D intake and 34-year incident stroke.

Methods—The Honolulu Heart Program is a prospective population-based cohort study of 8,006 Japanese-American men in Hawaii who were 45-68 years old at the baseline examination in 1965-68. Dietary vitamin D intake was calculated using the Nutritionist IV v3 software from a 24-hour dietary recall. Subjects with prevalent stroke were excluded, leaving 7,385 men followed through 1999 for incident stroke. Subjects were divided into quartiles of dietary vitamin D for analyses.

Results—During 34 years of follow-up, 960 subjects developed stroke. Age-adjusted rates of incident stroke were significantly higher in the lowest dietary vitamin D quartile compared to the highest (all stroke: 6.38 vs. 5.14 per 1,000 person-years follow-up, p=0.030; thromboembolic stroke: 4.36 vs. 3.30, p=0.033). Using Cox regression, adjusting for age, total kilocalories, BMI, hypertension, diabetes mellitus, pack-years smoking, physical activity index, serum cholesterol, and alcohol intake, those in the lowest quartile had a significantly increased risk of incident stroke (all stroke HR=1.22, 95% CI=1.01-1.47, p=0.038; thromboembolic stroke HR=1.27, 95% CI=1.01-1.59, p=0.044), with the highest as reference. We found no significant associations between dietary vitamin D and hemorrhagic stroke.

Conclusions—Low dietary vitamin D intake was an independent risk factor for 34-year incidence of all stroke and thromboembolic stroke in Japanese-American men. Additional research is needed on vitamin D supplementation to prevent stroke.

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Keywords

dietary vitamin D intake; incident stroke; Japanese-American men; longitudinal cohort study

Introduction

The role of vitamin D in bone metabolism and calcium homeostasis is well known. There is a growing body of evidence that vitamin D deficiency is associated with many conditions including hypertension, insulin resistance, diabetes mellitus, cancers, infections, autoimmune diseases, heart failure, cardiovascular diseases, and stroke.[1-3] Vitamin D deficiency is prevalent in many regions around the world, especially in elderly populations.[4-8] The Institute of Medicine has recently increased the Recommended Dietary Allowance of vitamin D to 15 micrograms (600 IU) daily for ages 1 to 70 years. An even higher dose of 20 micrograms (800 IU) is recommended for those aged 71 years and older.[9]

Stroke is a leading cause of morbidity and mortality in the U.S. and many other countries. Although some studies have found vitamin D deficiency is associated with incident stroke, most of these were based on serum 25-hydroxyvitamin D (25(OH)D) concentration, the major circulating form of vitamin D and a good indicator of overall vitamin D status. Less is known about the association between dietary vitamin D intake and risk of stroke. To our knowledge, there have been no large longitudinal population-based studies of vitamin D and incident stroke in Asians. Our purpose was to determine the relationship between dietary vitamin D intake and development of subsequent stroke over 34 years of follow-up in a population-based cohort of Japanese-American men in Hawaii.

Methods

Study Design and Population

The Honolulu Heart Program (HHP) is a prospective population-based cohort study of coronary heart disease (CHD) and stroke in Japanese-American men which began in 1965. Participants were 8,006 men of Japanese ancestry and living on the island of Oahu, Hawaii. Subjects were initially identified using World War II Selective Service Registration files and details on the selection process have been published previously.[10] Subjects were 45 to 68 years old at the time of the first examination in 1965-68. Participants have been followed with serial examinations and continuous hospital surveillance for selected morbidities and all mortality. The study was approved by the Institutional Review Board of Kuakini Medical Center, and written informed consent was obtained at each examination. Details regarding study design have been described elsewhere.[11]

Data Collection

Predictor Variable – Dietary Vitamin D Intake—Trained dieticians conducted a 24-hour dietary recall interview at exam 1 (1965-68), using standardized methods to gather detailed information on dietary intake during the previous 24 hours. Food models and serving utensils were used to help subjects identify portion sizes accurately. Only data from individuals who reported "fairly typical" diet in the previous 24 hours were used in this analysis. Data on macro and micronutrient intake was calculated from the 24 hour dietary recall using the modified Nutritionist IV (version 3.0; N-Squared Computing) program (Salem, Oregon). Food items specific to Hawaii and the Japanese population but not listed in the Nutritionist IV database were either added directly from data provided by the Cancer Research Center of Hawaii and Japanese Food Tables of Food Composition, or assessed based on recipes from the USDA Recipe File or Hawaii cookbooks using the Nutritionist IV

program.[12, 13] Accuracy of the 24-hour dietary recall data were confirmed by comparison with a 7-day dietary record from 329 participants from the cohort, with no significant differences between these 2 methods.[14] We excluded 514 subjects from this analysis because of missing dietary data or because the 24-hour recall was not their "**fairly** typical" diet. In addition, dietary data of six food items were collected using a 7-day recall questionnaire 6 years later and were shown to support the reproducibility of long-term dietary frequency data in this cohort.[13]

Outcome Variable - Incident Stroke—Since the beginning of the HHP, there has been continuous, comprehensive surveillance for all mortality and selected morbidity including cardiovascular diseases. All hospital discharges on the island of Oahu, death certificates, and autopsy records were reviewed. Only 5 subjects could not be located after matching through the national death index at exam 4 (1991-93), the first of the late-life examinations. Surveillance for this cohort is considered essentially complete.

One hundred and seven subjects with prevalent stroke at baseline were excluded from the analysis. We defined incident stroke as acute onset of a neurological deficit for 2 weeks or until death, confirmed by either blood in the cerebrospinal fluid or evidence on brain tomography or magnetic resonance imaging. Possible strokes, defined as neurological deficits persisting for at least 24 hours but less than 2 weeks or unknown duration, were not included as stroke events because of diagnostic uncertainty. Strokes were classified as thromboembolic, hemorrhagic, or unknown type based on clinical information and findings of imaging studies, surgery or autopsy. Thromboembolic stroke was diagnosed when a focal neurological deficit developed usually without prolonged unconsciousness, nuchal rigidity, fever, pronounced leukocytosis, or bloody spinal fluid. Hemorrhagic stroke was diagnosed if a focal neurological deficit was associated with loss of consciousness, headache, and blood in the spinal fluid from atraumatic lumbar puncture or based on neuroimaging, surgical or autopsy findings. Subjects with focal neurological findings from other causes such as blood dyscrasias, neoplastic disease, head injury, surgical accident, meningoencephalitis, fat embolism, epilepsy, or cardiac arrest were excluded. Further details on the diagnosis of stroke are described elsewhere.[15] All **stroke** diagnoses were confirmed by a study neurologist and the HHP Morbidity and Mortality Review Committee using standardized research criteria **(ICD-8 codes 430-438)**.

Covariates—Total kilocalories and alcohol intake were measured by the same dietary interview as vitamin D intake. We also adjusted for potential confounders including age and cardiovascular risk factors. Body mass index (BMI) was defined as weight in kilograms divided by square of height in meters. Hypertension was defined as systolic or diastolic blood pressures   140 and   90 mmHg, respectively, or use of medication. Diabetes was defined by medical history or use of insulin or oral hypoglycemic medication. Smoking was defined as self-reported pack years. The physical activity index (PAI) quantified overall metabolic output during a typical 24-hour period, by multiplying a weighting factor by the number of hours spent in five activity levels (no activity=1.0, sedentary=1.1, slight=1.5, moderate=2.4, and heavy=5.0).[16] Serum cholesterol was measured using nonfasting blood.

Statistical Analysis

After excluding subjects with prevalent stroke at baseline and those with missing data on dietary vitamin D intake (defined as not "**fairly** typical" dietary intake or missing data), the final sample for this analysis included 7,385 subjects. Incident stroke data were available for up to 34 years of follow-up, from the baseline examination in 1965-68 through December 1999. The study population was divided into quartiles of dietary vitamin D intake for analysis, and general linear models compared age-adjusted baseline risk factors across

quartiles. Incidence rates of all strokes, thromboembolic and hemorrhagic strokes were calculated per 1,000 person-years of follow-up by quartiles of dietary vitamin D intake. Cox regression models calculated hazards ratios for incident stroke in each quartile, using the highest quartile as reference. We also assessed test for trend across hazard ratios by quartiles. Separate Cox regression analyses were performed for incident thromboembolic and hemorrhagic stroke. The analyses were adjusted for baseline age, total kilocalories, BMI, hypertension, diabetes, pack-years smoking, PAI, cholesterol, and alcohol intake. All analyses used SAS software package (version 9.2; SAS Institute, Cary, North Carolina). All statistical tests were 2-tailed, and $p < 0.05$ was considered significant.

Results

At the time of study enrollment, the average intake of dietary vitamin D was 3.62 micrograms/day (range 0.00-211.60). In the subsequent 34 years, 960 developed stroke, with 651 (68%) thromboembolic, 269 (28%) hemorrhagic and 40 (4%) unknown type.

Baseline characteristics by dietary vitamin D intake quartiles are summarized in Table 1. Those in the lower quartiles were significantly more likely to be older, have higher BMI, higher rates of hypertension, more smoking pack-years and higher alcohol intake. Those in the lower quartiles consumed fewer total kilocalories, had lower rates of diabetes and lower PAI.

Table 2 shows age-adjusted rates of incident stroke per 1,000 person-years of follow-up by quartiles of dietary vitamin D intake, with separate analyses for thromboembolic and hemorrhagic stroke. Incidence rate of stroke was inversely related to quartiles, with highest rates seen in the lowest quartile (p for trend = 0.030). A similar association was found for thromboembolic stroke, with highest rates in the lowest quartile (p for trend = 0.033). There was no correlation with hemorrhagic stroke.

Cox regression analyses calculated hazards ratios for 34-year incident stroke among quartiles, using the highest quartile as reference (Table 3). In unadjusted models, those in the lowest quartile had significantly higher risk of incident stroke. For incident thromboembolic stroke, the unadjusted risk was also significantly higher in the lowest quartile. These associations remained significant after adjusting for age, kilocalories, BMI, hypertension, diabetes, pack-years smoking, PAI, cholesterol, and alcohol intake (all stroke HR=1.22, 95% CI=1.01-1.47, p=0.038; thromboembolic stroke HR=1.27, 95% CI=1.01-1.59, p=0.044). No association was found for incident hemorrhagic stroke.

Discussion

In this prospective population-based study of Japanese-American men in Hawaii, low dietary vitamin D intake was independently associated with higher incidence of all stroke and thromboembolic stroke during 34 years of follow-up. The lowest quartile of dietary vitamin D intake had the highest incidence rates for all stroke and thromboembolic stroke, and also had higher baseline prevalence of cardiovascular risk factors. After adjustment, the significant relationships persisted. As demonstrated previously[17], we found no association with incident hemorrhagic stroke.

Although epidemiologic studies have found that inadequate vitamin D status is associated with risk of stroke, most have focused on serum vitamin D levels; few examined dietary vitamin D. To our knowledge, there was only one previous longitudinal cohort study of dietary vitamin D intake in 755 elderly subjects in Finland; high dietary vitamin D was associated with decreased 10-year incident stroke.[18] This study also found that risk of incident stroke was inversely associated with 1,25-dihydroxyvitamin D levels, but not with

25(OH)D levels. Our study cohort was much larger (n=7,385) and had 34 years of follow-up for incident stroke.

There have been several cross-sectional and longitudinal observational studies demonstrating that low serum levels of vitamin D were associated with increased incident stroke and stroke death.[8, 17-21] The Framingham Offspring Study (n=1,739) found that lower 25(OH)D levels were associated with higher 5-year incidence of cardiovascular diseases.[19] This study did not present data separately for incident stroke. A German study of 3,316 men and women referred for coronary angiography found an inverse relationship between vitamin D levels and stroke death over 7.7 years.[20] The Mini-Finland Health Survey examined 25(OH)D levels in more than 6,000 subjects (mean age 49 years) and found lower risk of stroke death in the highest quintile over 27 years.[17]

One potential limitation is our unique population of Japanese-American men living in Hawaii, which may limit generalizability to other ethnic groups or females. However, this is a genetically homogenous group with less variety in skin color. No data were available on sunlight exposure and the presence of kidney or liver diseases, which are closely related to vitamin D synthesis and metabolism. The consistent year-round sunny weather in Hawaii decreases the likelihood of inadequate sun exposure. Another limitation is that many of the stroke events happened before the advent of neuroimaging. Thus some misclassification of stroke, particularly thromboembolic and hemorrhagic stroke, may be possible. The single 24-hour dietary recall provides an approximation of food intake, however, errors are likely to be minimal because only subjects who reported "fairly typical" diets were included. In this cohort, accuracy of the 24-hour dietary recall was comparable to a 7-day dietary record[14], and dietary patterns were stable over time.[13, 22] Though data on vitamin D supplementation are lacking, regular use of supplements was uncommon in the 1960s. Vitamin D deficiency is associated with several cardiovascular risk factors, which could increase risk of stroke. We adjusted for these factors to minimize confounding.

A major strength of this study is the large prospective population-based design in a homogeneous sample of Asian-Americans, a previously unstudied group. Another strength is the long follow-up of 34 years. Additional strengths include excellent follow-up rates, completeness and thoroughness of stroke surveillance, and our ability to adjust for multiple cardiovascular risk factors. Our study is also unique because we examined incident stroke in relation to dietary vitamin D intake, whereas most studies have focused on serum concentration of vitamin D. Previous studies have found that vitamin D intake from diet and/or supplementation is positively correlated with serum vitamin D levels in a dose-response manner.[23-25]

Vitamin D is mainly synthesized when skin is exposed to sunlight, and dietary sources are generally not considered very significant in younger people. However, the ability of skin to produce vitamin D is markedly diminished by aging[26] as well as sunscreen use, protective clothing, lack of outdoor activities or institutionalization. Thus dietary sources are more important for the elderly. In our study population, the major source of dietary vitamin D was milk (r=0.78) and there was an extreme high correlation between dietary calcium and vitamin D intake (r=0.75). The relationship of low dietary vitamin D intake to all stroke and thromboembolic stroke became insignificant when additionally adjusted for milk intake **or calcium intake** (data not shown). It was not possible to completely separate the effects of dietary vitamin D, dietary calcium and milk intake, because of the extremely high correlations between these three variables. A previous analysis using data from 3,150 subjects aged 55 years or older among the HHP cohort demonstrated twice the risk of incident thromboembolic stroke in non-milk drinkers compared with those who consumed 16 oz/day or more over 22 years of follow-up.[27] However, that analysis did not control for

total caloric intake. Other studies of dietary vitamin D have not addressed the possible confounding effects of milk intake. This is an unresolved issue that warrants further studies.

Vitamin D deficiency is known to be associated with cardiovascular risk factors, including hypertension, insulin resistance, diabetes mellitus and systemic inflammation. Most tissues and cells in humans express vitamin D receptors, and vitamin D influences hundreds of genes regulating cellular proliferation, differentiation, apoptosis and angiogenesis.[1] Vitamin D deficiency and/or secondary hyperparathyroidism predispose to inappropriate upregulation of the renin-angiotensin system.[28] All of these conditions could lead to accelerated atherosclerosis and subsequent cardiovascular events.

In summary, our study confirmed that low dietary vitamin D intake was associated with increased risk of stroke. Based on the results of this and other epidemiological studies, higher vitamin D intake or vitamin D supplementation may be beneficial for stroke prevention. Large prospective placebo-controlled randomized studies are needed to confirm this relationship.

We await the results of VITAL, the Vitamin D and Omega-3 Trial, the first large randomized clinical trial of vitamin D supplementation with/without fish oil launched in 2010 to study cardiovascular diseases, cancer and other chronic diseases.[29]

Acknowledgments

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Table 1

Baseline characteristics by quartiles of dietary vitamin D intake (N=7,385): The Honolulu Heart Program.

	Dietary vitamin D intake quartiles (microgram/day)				
	Q 1 (0-1.12 µg)	Q 2 (1.12-2.23 µg)	Q 3 (2.23-4.13 µg)	Q 4 (4.13-211.60 µg)	p for trend
N	1847	1845	1847	1846	
Age (years)	54.80 ± 5.66	54.60 ± 5.61	54.37 ± 5.49	53.92 ± 5.47	<0.0001
Total kilocalories [*]	1999.6 ± 630.93	2197.0 ± 642.79	2267.1 ± 639.16	2419.9 ± 644.42	<0.0001
BMI (kg/m2) [*]	24.22 ± 3.12	23.90 ± 3.14	23.67 ± 2.95	23.45 ± 3.00	<0.0001
Hypertension (%) [*]	0.45.68 ± 0.49.34	0.44.40 ± 0.49.50	0.38.34 ± 0.48.04	0.36.13 ±0.47.42	<0.0001
Diabetes Mellitus (%) [*]	0.08.79 ± 0.28.42	0.07.54 ± 0.26.52	0.09.46 ± 0.29.15	0.11.33 ± 0.31.34	0.002
Pack-years smoking [*]	24.83 ± 25.14	23.67 ± 24.09	23.83 ± 23.85	22.77 ± 24.15	0.019
Physical activity index [*]	32.62 ± 4.36	32.91 ± 4.54	32.81 ± 4.41	33.04 ± 4.63	0.012
Serum cholesterol (mg/dl) [*]	218.65 ± 37.94	216.71 ± 39.66	218.58 ± 37.89	219.96 ± 36.65	0.146
alcohol intake (oz/month) [*]	16.74 ± 27.09	14.98 ± 25.00	12.32 ± 22.47	10.32 ± 21.39	<0.0001

[*] Adjusted for age at baseline

Table 2

Age-adjusted incidence rates of all stroke, thromboembolic and hemorrhagic stroke (per 1,000 person-years follow-up).

Type of stroke	dietary vitamin D intake quartiles				p for trend
	Q1 (n=1847)	Q2 (n=1845)	Q3 (n=1847)	Q4 (n=1846)	
All stroke (number of events)	6.38 (276)	5.03 (216)	5.72 (246)	5.14 (222)	0.030
Thromboembolic (number of events)	4.36 (190)	3.35 (145)	3.99 (172)	3.30 (144)	0.033
Hemorrhagic (number of events)	1.54 (69)	1.37 (61)	1.58 (71)	1.49 (68)	0.977

Table 3

Hazards ratios for incidence of all stroke, thromboembolic and hemorrhagic stroke according to dietary vitamin D intake quartiles.

	All stroke			Thromboembolic			Hemorrhagic		
Model	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Unadjusted									
Q1 vs Q4	1.33	1.12-1.59	0.001	1.41	1.13-1.75	0.002	1.08	0.77-1.51	0.663
Q2 vs Q4	1.03	0.85-1.24	0.751	1.07	0.85-1.35	0.573	0.95	0.67-1.34	0.761
Q3 vs Q4	1.15	0.96-1.38	0.127	1.24	0.99-1.54	0.059	1.08	0.78-1.51	0.636
p for trend			0.007			0.011			0.862
Adjusted [*]									
Q1 vs Q4	1.22	1.01-1.47	0.038	1.27	1.01-1.59	0.044	0.97	0.68-1.38	0.853
Q2 vs Q4	0.97	0.80-1.18	0.782	0.99	0.78-1.26	0.957	0.89	0.62-1.28	0.529
Q3 vs Q4	1.13	0.94-1.37	0.186	1.19	0.95-1.49	0.133	1.08	0.77-1.52	0.659
p for trend			0.130			0.142			0.610

[*]
adjusted for age, total kilocalories, BMI, hypertension, diabetes mellitus, pack-years smoking, PAI, serum cholesterol, and alcohol intake