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Low Dietary Vitamin D in Mid-Life Predicts Total Mortality in Men with Hypertension: The Honolulu Heart Program

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Abstract

BACKGROUND—Vitamin D deficiency was associated with total mortality in previous epidemiological studies. Little is known about effects of dietary vitamin D intake on mortality. We examined the association between mid-life dietary vitamin D intake and 45-year total mortality.

METHODS—The Honolulu Heart Program is a longitudinal cohort study of 8,006 Japanese-American men in Hawaii aged 45–68 at baseline (1965–68). Mid-life dietary vitamin D intake was calculated from 24-hour dietary recall using Nutritionist IV v3 software. We divided subjects into quartiles of dietary vitamin D. Total mortality data were available over 45 years through 2010.

RESULTS—Age-adjusted total mortality rates were higher in the lower quartiles of dietary vitamin D intake compared to the highest (p for trend=0.011). Using Cox regression, low dietary vitamin D was significantly associated with total mortality; quartile (Q) 1 hazard ratio (HR)=1.14, 95% CI=1.07–1.22, $p<0.001$; Q2 HR=1.11, 95% CI=1.04–1.18, $p=0.002$; and Q3 HR=1.08, 95% CI=1.01–1.15, $p=0.027$; Q4= reference. After adjusting for age, kilocalories, cardiovascular risk factors and prevalent chronic diseases, only Q2 remained significant (HR=1.08, 95% CI=1.00–1.15, $p=0.037$). Among hypertensive subjects only, those in lower 2 quartiles had higher total mortality; Q1 HR=1.12, 95% CI=1.01–1.25, $p=0.039$; and Q2 HR=1.13, 95% CI=1.02–1.26, $p=0.025$; compared to Q4. There was no significant relationship in subjects without hypertension.

CONCLUSIONS—Low dietary vitamin D intake in mid-life was a weak predictor of total mortality over 45 years of follow-up. We found a significant association between low dietary

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CONFLICT OF INTEREST

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vitamin D intake and higher total mortality only among hypertensive subjects. Vitamin D may have cardioprotective effects.

Keywords

vitamin D; mortality; hypertension; Japan/ethnology; Asian Americans

INTRODUCTION

Besides its classical roles in skeletal health, vitamin D has recently been studied extensively in association with other organ systems. It is now known that vitamin D deficiency is a highly prevalent condition worldwide and affecting more than 40% of the U.S. general population in the National Health and Nutrition Examination Survey (NHANES) 2005-2006.¹ This cross-sectional study showed a strong association between vitamin D deficiency, defined as serum 25-hydroxyvitamin D (25(OH)D) level of less than 50nmol/L (20 ng/ml), with cardiovascular risk factors such as hypertension, low high-density lipoprotein cholesterol level, and obesity.¹ Several other studies have demonstrated that vitamin D deficiency is an underrecognized independent risk factor for cardiovascular diseases (CVD), cancer, and mortality.² The NHANES III followed subjects for over 8 years and found significantly higher total mortality among subjects in the lowest quartile of serum vitamin D levels compared to the highest.³ Furthermore, a Cochrane systematic review and meta-analysis including 50 studies found that vitamin D supplementation decreased total mortality.⁴

Although there have been several epidemiologic studies showing an association between low serum vitamin D and higher mortality⁵⁻¹⁰, they were all based on relatively short follow-up periods, mostly about 10 years, with the longest being 28 years.⁷ In addition there was only 1 previous study in an Asian population, which was postmenopausal women in Japan.¹⁰ Moreover, to our knowledge, no previous population-based study has examined the impact of dietary intake of vitamin D on total mortality. The purpose of this study was to determine the relationship between mid-life dietary vitamin D intake and subsequent total mortality over 45 years of long-term follow-up among Japanese-American men living in Hawaii.

METHODS

Study Design and Population

The Honolulu Heart Program (HHP) is an ongoing longitudinal epidemiological cohort study of cardiovascular diseases, which began in 1965 with 8,006 Japanese-American men living on the island of Oahu, Hawaii. The original participants were initially identified through World War II Selective Service Registration files.¹¹ They were born between 1900 and 1919, and were 45 to 68 years old at the first examination in 1965-68. The entire cohort has continuously been followed since the beginning of the study with serial examinations, and by monitoring selected morbidities and all mortality. The study design has been described in detail elsewhere.¹² This study was approved by the Institutional Review Board of Kuakini Medical Center. Written informed consent was obtained from all participants at each examination.

Data Collection

Predictor Variable - Dietary Vitamin D Intake—Dietary information was obtained by trained dietitians with a 24-hour dietary recall interview at the first examination in 1965-68, using standardized methods to gather detailed information on dietary intake of food and beverages consumed during the previous 24 hours. Food models and serving utensils were used to help subjects identify portion sizes more accurately. In this analysis, we only used data from individuals who reported a “fairly typical” diet in the last 24 hours. All dietary records were analyzed using the modified Nutritionist IV program (version 3.0; N-Squared Computing, Salem, Oregon) to obtain intake of macro- and micronutrients. Since some food items specific to Hawaii or the Japanese population were not listed in the Nutritionist IV database, they were either added 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 by the Nutritionist IV program.^{13,14} We excluded 514 men from the analysis because of missing dietary data, or because data were not representative of a typical diet.

Outcome Variable - Total Mortality—Data on total mortality were available from the beginning of the study (1965-68) through December 2010. There has been continuous monitoring for medical outcomes with a comprehensive hospital surveillance system since 1965. We obtained medical records from all hospital discharges on the island of Oahu for selected morbidities and all mortality. In addition, study staff reviewed all obituaries in local newspapers, and obtain death certificates, autopsy records, and reports from the family, primary physicians, and medical examiners.¹⁵ Because this is an island population, out-migration rates have been very low (less than 1 per 1,000 per year). After matching through the national death index at the fourth examination in 1991-93, only 5 subjects could not be located, and surveillance of this study was considered essentially complete.

Covariates—Baseline covariates were selected for potential confounding due to associations with both vitamin D intake and total mortality. Intake of total kilocalories was assessed at the time of the 24-hour dietary recall data collection. Body mass index (BMI) was defined as weight (kg) divided by height (m) squared. Hypertension was defined as systolic blood pressure 140 mm Hg or greater, or diastolic blood pressure 90 mm Hg or greater, or if the participant was taking antihypertensive medications. Diabetes mellitus was defined by medical history, or using insulin and/or oral hypoglycemic medications. Smoking was defined as self-reported pack-years. Physical activity was measured using the physical activity index (PAI). This index was calculated by multiplying the approximate oxygen consumption of five different activity levels (no activity=1.0, sedentary=1.1, slight=1.5, moderate=2.4, heavy=5.0) with self-reported usual numbers of hours per day engaged in performing those activities. This index is a reliable indicator of overall energy consumption in middle and late life and has been used in the Framingham Study.¹⁶ Serum cholesterol was measured on non-fasting blood specimen.

Statistical Analyses

We identified 7,492 subjects as the final sample for this analysis, after excluding those who had missing dietary data or did not have “fairly typical” diet. The participants were divided

into 4 groups based on dietary vitamin D intake (Quartile [Q] 1: 0.0-1.12, Q2: 1.12-2.23, Q3: 2.23-4.12, Q4: 4.12-211.6 µg/day). Age-adjusted baseline risk factors were estimated by covariance analysis methods, comparing risk factor levels in the quartiles of vitamin D intake by general linear models. We calculated age-adjusted total mortality rates per 1,000 person-years of follow-up according to dietary vitamin D intake quartiles. Multivariate analyses were performed using Cox regression models to examine the relationship between quartiles of dietary vitamin D intake and subsequent total mortality, with the participants in the highest quartile as a reference group. Crude hazard ratios (HRs) were then adjusted for baseline age, total kilocalories, cardiovascular risk factors (BMI, hypertension, diabetes mellitus, pack-years smoking, PAI and serum cholesterol level), and prevalent coronary heart disease (CHD), stroke and cancer. To assess the effect of hypertension on the correlation between dietary vitamin D intake and total mortality, we divided the whole cohort into 2 groups based on their hypertension status and performed stratified analyses using Cox regression models. In Cox regression, test for trend across quartiles was calculated using dietary vitamin D intake quartile as an ordinal variable. SAS software package (version 9.2; SAS institute, Cary, North Carolina) was used for all the analyses. All statistical tests were based on 2-tailed of significance and $p < 0.05$ was considered statistically significant.

RESULTS

Table 1 displays aged-adjusted mean levels of baseline demographics, risk factors and prevalent diseases by quartiles of dietary vitamin D intake. Subjects in the higher vitamin D intake quartiles had significantly better health status and healthier lifestyle; they were younger, consumed more total kilocalories, had higher PAI, lower BMI, lower pack-years of smoking, and lower rates of hypertension. Diabetes mellitus was the only exception and its prevalence was higher with higher quartiles of dietary vitamin D intake. Serum cholesterol level and prevalent CHD, stroke, and cancer were not significantly associated with quartiles of dietary vitamin D.

There were 6,972 deaths (93.1% of the final sample) during the 45 years of follow-up from the baseline examination in 1965-68 through December 2010. As shown in Table 2, the age-adjusted total mortality rates were higher in the lower 3 quartiles of dietary vitamin D intake; Q1=36.31, Q2=36.42, Q3=35.75, and Q4=34.84 per 1,000 person-years of follow-up, p for trend=0.011.

In Table 3, we present the results of Cox regression analyses, with unadjusted and adjusted HRs by quartiles of dietary vitamin D intake, using the highest quartile Q4 as reference. We found a significant dose-response relationship between low dietary vitamin D intake and total mortality; Q1 HR=1.14, 95%CI=1.07-1.22, $p < 0.001$; Q2 HR=1.11, 95%CI=1.04-1.18, $p = 0.002$; and Q3 HR=1.08, 95%CI=1.01-1.15, $p = 0.027$; using Q4 as reference. However, after adjustment for age, total kilocalories, BMI, hypertension, diabetes mellitus, pack-years smoking, PAI, serum cholesterol, and prevalent CHD, stroke and cancer, only Q2 remained significant (HR=1.08, 95%CI 1.00-1.15, $p = 0.037$). The assumption of proportionality was checked, but showed no violation in our models.

In stratified analyses, we found a significant relationship between low dietary vitamin D intake and higher total mortality only among those with hypertension (Q1 HR=1.12, 95%CI=1.01-1.25, $p=0.039$; and Q2 HR=1.13, 95%CI=1.02-1.26, $p=0.025$, compared to Q4, p for trend=0.022) in the fully adjusted model (Table 4). In contrast, dietary vitamin D intake was not a predictor of total mortality among those without hypertension. There was no significant interaction effect observed between hypertension and dietary vitamin D intake (data not shown, p for interaction>0.1).

DISCUSSION

In this longitudinal, cohort study of Japanese-American men in Hawaii, dietary vitamin D intake in mid-life was a weak predictor for total mortality over 45 years of follow-up. After stratifying the cohort into two groups based on prevalent hypertension, we found a significant association between low dietary vitamin D intake and higher total mortality only among those with hypertension, while there was no such relationship observed in those without hypertension.

Although this is the first study focusing on dietary vitamin D intake as a predictor for risk of total mortality, previously there have been several prospective observational studies examining the relationship between serum vitamin D levels and total mortality. Most of them showed that lower vitamin D levels were associated with higher total mortality,^{3,5,6,8-10} however, a few studies found no correlation.^{17,18} The literature provides conflicting information about the definition of vitamin D deficiency, and studies have used different cut-points of serum vitamin D levels. According to data from the U.S. general population aged 65 years or older in NHANES III (N=3,408), 25(OH)D levels of less than 25 nmol/L and 25-50 nmol/L were associated with significantly higher total mortality (HR=1.83, 95%CI=1.14-2.94, and HR=1.47, 95%CI=1.09-1.97, respectively) compared to levels of more than 100nmol/L, over 7 years of follow-up.⁵ InCHIANTI, an Italian prospective population-based study, followed 1,006 men and women for 6.5 years and observed that those in the lowest quartile of serum 25(OH)D level had more than twice the risk of total mortality than those in the highest quartile (HR=2.11, 95%CI=1.22-3.64).⁶ A recent Cochrane meta-analysis combined 50 interventional articles of vitamin D supplementation (N=94,148) and found 3% decrease in total mortality risk among supplemented groups (pooled HR=0.97, 95%CI=0.94-1.00).⁴ There have been multiple randomized clinical trial studies examining the effects of vitamin D supplementation on various cardiovascular outcomes, with negative results. No significant changes in blood pressure were observed with calcium and vitamin D supplementation among postmenopausal women in the Women's Health Initiative Calcium/Vitamin D trial,¹⁹ and with selective vitamin D receptor activator (paricalcitol) among patients with type 2 diabetes and albuminuria who were on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the Selective Vitamin D Receptor Activator for Albuminuria Lowering (VITAL) Study.²⁰ In the PRIMO randomized controlled trial, paricalcitol supplementation failed to show significant changes in left ventricular mass index or diastolic function among chronic kidney disease patients.²¹

A limitation of this study was our unique population consisting of Japanese-American men living in Hawaii. Further research is needed to examine whether our findings can be

generalized to the other ethnic groups or females. Another limitation was the lack of information on sunlight exposure, kidney and liver diseases, serum vitamin D levels, and vitamin D supplement use, all of which may have a significant impact on vitamin D status. However, Hawaii's year-round sunny weather makes the likelihood of inadequate sunlight exposure unlikely. Although the major source of vitamin D is from cutaneous synthesis and only a small amount comes from diet, positive correlation between dietary vitamin D intake and serum vitamin D levels have been shown in other studies.²²⁻²⁴ Also, less than 1.5% of people in the same age groups among the U.S. population used vitamin D supplementation regularly in the 1970s and before²⁵, making it unlikely that we missed data on supplement use. Although data from a single 24-hour dietary recall might have been affected by recall bias, day-to-day variation, and possible changes in dietary habits over the follow-up period, errors were considered to be minimal because well-trained dietitians performed comprehensive interviews covering foods specific to Hawaii and Japan, and only subjects reporting "fairly typical" diet were included. Furthermore, 7-day dietary frequency surveys conducted 2 and 6 years later among the same cohort supported significant reproducibility in long-term dietary patterns.^{14,26} In this cohort, higher vitamin D intake was associated with higher prevalence of diabetes mellitus, which is contrary to previous findings in the literature.² Prevalence of diabetes mellitus at the baseline examination in 1965-68 was defined only by history or use of insulin and/or oral hypoglycemic medications, and did not include objective measures such as fasting glucose level or hemoglobin A1c. This may have led to some misclassification of diabetes, and may be partly related to this inconsistent finding.

One of this study's major strengths is its robust study design; a large population-based observational study among a homogeneous group of Japanese-American men with serial comprehensive examinations and thorough surveillance, as well as a lengthy and complete follow-up for up to 45 years. We were also able to adjust for a wide range of potential confounders. Little data are available on this topic in Asian populations, and only one previous study investigated Japanese postmenopausal women in Japan.¹⁰ All previous studies have examined serum 25(OH)D level as a predictor for total mortality, and this study is, to the best of our knowledge, the first study to examine the relationship between dietary intake of vitamin D and total mortality.

In the United States, milk has been fortified with vitamin D since the 1930s, as are cereals, yogurts, cheeses, and orange juice.²⁷ The main dietary source of vitamin D in this cohort was milk (correlation coefficient, $r=0.78$). Overall, the vitamin D intake of this population was extremely low and only the fourth quartile had vitamin D intake within the recommended daily intake for this age group. This may partly be explained by low milk intake in this population.^{28,29} Previous prospective observational studies of milk intake and mortality have shown mixed results. Some found that higher milk intake was associated with lower risk of total mortality, while others did not find any associations.^{30,31} In this study, the lower 2 quartiles of vitamin D intake demonstrated higher total mortality compared to the highest quartile in hypertensive subjects, after full adjustment for confounders. This protective effect of dietary vitamin D on total mortality may have resulted from the fact that vitamin D intake was a surrogate marker of milk intake, and milk intake, rather than vitamin D, was associated with lower risk of mortality. However, even after further adjusting the

final Cox models for milk intake (oz/day), dietary vitamin D remained significantly associated with total mortality (Q1; HR=1.17, 95% CI=1.00-1.36, $p=0.045$, Q2; HR=1.17, 95% CI=1.02-1.36, $p=0.030$). This suggests that the association between vitamin D and total mortality was independent of milk.

The possible pathophysiological mechanisms underlying an association between vitamin D and total mortality are not completely understood. In this study, low dietary vitamin D intake was significantly associated with higher total mortality among hypertensive subjects while no association was found in non-hypertensive. Those who had hypertension were at higher risks of atherosclerosis and cardiovascular diseases and vitamin D might have been protective against those conditions.

There is a body of evidence which supports the hypothesis that activated vitamin D (1,25-dihydroxyvitamin D) exerts cardiovascular protective effects. Serum vitamin D levels are inversely associated with vascular calcification, which is a marker of atherosclerosis.^{32,33} Vitamin D receptors are known to be widely distributed in various human cells, including endothelial cells, vascular smooth muscle cells, cardiomyocytes³⁴, macrophages, and activated T-lymphocytes³⁵, and vitamin D regulates gene expression via these receptors. Vitamin D may prevent atherosclerogenesis by suppressing endothelial cell activation, adhesion molecule expression and subsequent monocyte and lymphocyte migration into the vessel walls, vascular smooth muscle cell proliferation and migration, and foam cell formation.^{34,36} It has also been suggested that vitamin D possesses anti-inflammatory properties by decreasing release of pro-inflammatory molecules such as TNF- α and IL-6.³⁴

In addition to its direct interactions with cardiovascular tissues and leukocytes, vitamin D appears to have a cardioprotective effect by down-regulating the renin-angiotensin system (RAS).³⁷ Angiotensin II (AT II), a potent vasoconstrictive peptide and the primary effector of RAS, is implicated in various levels of pathogenesis of atherosclerosis. AT II activates endothelial cells and increases reactive oxygen species and decreases nitric oxide, which induces endothelial dysfunction leading to increased expression of cellular adhesion molecules and increased release of chemotactic and pro-inflammatory cytokines. Vascular smooth muscle cells express AT II type 1 receptors, and AT II facilitates smooth muscle cell proliferation and migration through the receptors.³⁸ Additionally, AT II seems to be associated with coagulation and fibrinolysis by increasing expression of tissue factor and plasminogen activator inhibitor type 1, both of which promote thrombogenicity.³⁹

Hypertension is one of the strongest traditional cardiovascular risk factors.⁴⁰ The hypertensive subjects in this cohort, compared to those without hypertension, were probably more predisposed to atherosclerosis and cardiovascular morbidity and mortality. Higher dietary intake of vitamin D may have effectively prevented atherosclerosis or thrombosis formation by the aforementioned possible cardioprotective mechanisms, which may have resulted in decreased total mortality in this study. This hypothesis is further supported by a previous analysis from the same HHP cohort, which found that lower dietary vitamin D in mid-life was associated with higher incidence of overall and thromboembolic strokes over 34 years of follow up.⁴¹

These results need to be replicated in other population based cohort studies, and should also examine cause-specific mortality related to dietary vitamin D intake. Future studies should focus on increasing dietary vitamin D intake or vitamin D supplementation, which may be potentially promising interventions to decrease mortality in subjects with hypertension or at a high risk of cardiovascular diseases.

In this study, we found that low dietary vitamin D intake in mid-life was a significant independent predictor of subsequent total mortality over 45 years of follow-up, only among hypertensive subjects. This association was not found in non-hypertensive subjects.

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Table 1

Baseline characteristics by quartiles of dietary vitamin D intake (N=7,492): The Honolulu Heart Program.

Mean Values	Dietary vitamin D intake quartiles (microgram/day)				p for trend
	Q 1 (0-1.12)	Q 2 (1.12-2.23)	Q 3 (2.23-4.12)	Q 4 (4.12-211.60)	
N	1874	1873	1872	1873	
Age (years)	54.84 ± 5.68	54.65 ± 5.64	54.43 ± 5.52	54.00 ± 5.51	<0.0001
Total kilocalories ^a	1997.0 ± 631.0	2191.1 ± 645.1	2257.6 ± 639.8	2412.7 ± 645.8	<0.0001
Body mass index (kg/m ²) ^a	24.23 ± 3.12	23.90 ± 3.14	23.67 ± 2.97	23.46 ± 3.00	<0.0001
Prevalent Hypertension (%) ^a	46.14 ± 49.32	44.75 ± 49.53	39.21 ± 48.17	36.58 ± 47.52	<0.0001
Prevalent Diabetes Mellitus (%) ^a	8.7 ± 28.3	7.9 ± 27.0	9.8 ± 29.5	11.5 ± 31.5	0.0007
Pack-years smoking ^a	24.84 ± 25.19	23.71 ± 24.00	23.88 ± 24.02	22.95 ± 24.32	0.0307
Physical activity index ^a	32.62 ± 4.39	32.86 ± 4.54	32.78 ± 4.45	32.99 ± 4.62	0.0260
Serum cholesterol (mg/dl) ^a	218.65 ± 37.88	217.06 ± 40.31	218.42 ± 37.85	219.88 ± 36.72	0.2008
Prevalent coronary heart disease (%) ^a	4.41 ± 20.67	4.40 ± 20.52	4.39 ± 20.44	3.51 ± 18.17	0.1886
Prevalent stroke (%) ^a	1.21 ± 11.23	1.36 ± 11.67	1.82 ± 13.31	1.32 ± 10.94	0.5256
Prevalent cancer (%) ^a	0.90 ± 9.71	1.20 ± 11.02	1.02 ± 9.95	1.04 ± 9.72	0.8365

Q = quartile.

^a Adjusted for age at baseline

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Table 2

Age-adjusted incidence rates of total mortality per 1,000 person-years follow-up (N=7,492).

	dietary vitamin D intake quartiles				p for trend
	Q1 (n=1874)	Q2 (n=1873)	Q3 (n=1872)	Q4 (n=1873)	
incidence rates	36.31	36.42	35.75	34.84	0.011
number of events	1762	1749	1741	1720	

Q = quartile.

Table 3

Hazards ratios for total mortality according to dietary vitamin D intake quartiles.

Model	unadjusted			adjusted ^a		
	HR	95% CI	p value	HR	95% CI	p value
whole cohort						
Q1 vs. Q4	1.14	1.07-1.22	<0.001	1.05	0.98-1.12	0.210
Q2 vs. Q4	1.11	1.04-1.18	0.002	1.08	1.00-1.15	0.037
Q3 vs. Q4	1.08	1.01-1.15	0.027	1.03	0.96-1.10	0.376
p for trend			<0.001			0.117

CI = confidence interval; HR = hazard ratio; Q = quartile.

^aadjusted for baseline age, total kilocalories, body mass index, hypertension, diabetes mellitus, pack-years smoking, physical activity index, serum cholesterol, coronary heart disease, stroke and cancer.

Table 4

Hazards ratios for total mortality, stratified for hypertensive vs. non-hypertensive.

Model	unadjusted			adjusted ^a		
	HR	95% CI	p value	HR	95% CI	p value
hypertensive						
Q1 vs. Q4	1.15	1.04-1.27	0.008	1.12	1.01-1.25	0.039
Q2 vs. Q4	1.08	0.97-1.20	0.142	1.13	1.02-1.26	0.025
Q3 vs. Q4	1.10	0.99-1.22	0.084	1.06	0.95-1.18	0.302
<i>p</i> for trend			0.017			0.022
non-hypertensive						
Q1 vs. Q4	1.07	0.98-1.17	0.142	0.99	0.90-1.08	0.756
Q2 vs. Q4	1.08	0.99-1.18	0.093	1.03	0.94-1.13	0.489
Q3 vs. Q4	1.05	0.97-1.15	0.244	1.02	0.93-1.11	0.693
<i>p</i> for trend			0.105			0.879

CI = confidence interval; HR = hazard ratio; Q = quartile.

^a adjusted for baseline age, total kilocalories, body mass index, diabetes mellitus, pack-years smoking, physical activity index, serum cholesterol, coronary heart disease, stroke and cancer.