THE IMPACT OF ROUTINE VITAMIN SUPPLEMENTATION ON SERUM LEVELS OF 25 (OH) D_3 AMONG THE GENERAL ADULT POPULATION AND PATIENTS WITH CHRONIC KIDNEY DISEASE

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Background: Vitamin D supplementation is recommended to maintain bone health in the general population and in particular in patients with chronic kidney disease (CKD). While the nutritional status of vitamin D is assessed by circulating levels of 25 (OH) D_3, it is not routinely measured to ensure the adequacy of vitamin D supplementation. Current recommendations require the maintenance of serum levels of 25 (OH) D_3 ≥70 nmol/L. The objective of this study is to assess the effect of routine vitamin supplements on the serum levels of 25 (OH) D_3 in the general population and among persons with CKD.

Method: Using data from the third National Health and Nutrition Examination Survey (NHANES III) we assessed the adequacy of routine vitamin supplementation by assessing serum levels of 25 (OH) D_3 among 15,390 adult participants, both with and without CKD.

Results: In the general population the participants with vitamin supplements had higher serum level of 25 (OH) D_3 (79.47 vs 74.38 nmol/L) and a lower prevalence of vitamin D deficiency (39% vs 48%) than participants not taking any supplements. In the CKD subgroup, the prevalence of vitamin D deficiency was lower with supplements (49%), while greater without supplements (59%). Vitamin D deficiency was higher among women, elderly, and minorities as previously reported. In an adjusted regression model the odds of severe vitamin D deficiency (<25 nmol/L) was 1.43 (P=.0032) among CKD patients, with a trend toward higher rates among patients not taking vitamin supplements (odds ratio 1.47, P=.0557).

Conclusion: Vitamin supplementation is associated with a lower prevalence of vitamin D deficiency and higher serum levels of 25 (OH) D_3. However, the current dose of vitamin D in routine vitamin supplements is still insufficient to maintain adequate serum 25 (OH) D_3 levels in a substantial portion of both the general and CKD populations. We must re-asses the dose of vitamin D in routine vitamin supplements in the United States. (*Ethn Dis*. 2005;15 [suppl 5]:S5-102–S5-106)

Key Words: Vitamin D, Chronic Kidney Disease, Vitamin D Supplementation

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INTRODUCTION

Disturbances in mineral and bone metabolism are common in patients with chronic kidney disease (CKD). Vitamin D supplementation is recommended for the maintenance of bone health in the general population and in particular for patients with CKD. The nutritional status of vitamin D is assessed by measuring circulating levels of 25 (OH) D_3.[1]

However, the serum level of 25 (OH) D_3 is not routinely measured to assess the adequacy of vitamin D supplementation. Current recommendations for adults are to maintain serum levels of 25 (OH) D_3 ≥70 nmol/L.[2,3] The objective of this study is to assess the effect of routine oral vitamin supplements on the serum levels of 25 (OH) D_3 in both the general population and in patients with CKD.

METHODS

Survey

We used data from the third National Health and Nutrition Examination Survey (NHANES III), a national probability survey conducted by the National Center for Health Statistics at 89 survey locations between 1988 and 1994. The survey is designed to estimate the prevalence of common chronic conditions and associated risk factors for disease control and prevention. The sample for the survey was obtained through a complex multistage cluster design with oversampling of persons ≥60 years of age, non-Hispanic Blacks, and Mexican Americans to enhance the precision of prevalence estimates in these groups.[4] Serum vitamin D levels were missing for 2937 participants. Supplements containing vitamin D were identified from the NHANES III. Participants receiving therapeutic doses of active vitamin D such as calcitriol, dihydrotachysterol, and ergocalciferol in vitamin D deficiency treatment doses (eg, 50,000 IU; n=4) were excluded. We also excluded pregnant women (they may receive special vitamin supplements; n=171), and participants with hypoalbuminemia (<3.0 g/L; n=99) and significant proteinuria (>3 g albumin/g creatinine; n=349) as surrogates of significant liver disease and nephrosis. We compared serum levels of 25 (OH) D_3 of participants receiving and not receiving routine vitamin D supplementation in the general population and among participants with CKD (defined as estimated glomerular filtration rate [GFR] <60 mL/min/1.73 m^2 or as GFR ≥60 mL/min/1.73 m^2 with proteinuria [30 mg albumin/g creatinine]) and without CKD (defined as GFR ≥60 mL/min/1.73 m^2 and no proteinuria).

Table 1. Characteristics of the analysis sample

	Number (%)	% Taking Vitamin Supplements	*P* value
Age			
<65	11,671 (75.83)	8.42	Reference
≥65	3,719 (24.17)	5.28	*P*<.0001
Gender			
Male	7,286 (47.34)	7.36	Reference
Female	8,019 (52.66)	8.39	*P*=.0008
Race			
White	6,688 (43.46)	8.07	Reference
Black	4,359 (28.32)	7.68	*P*=.001
Hispanic	4,393 (28.22)	5.64	*P*≤.0001

Study Sample

Our analysis used interview and laboratory data from the 15,390 adult participants ≥18 years of age within the NHANES data set with serum levels of 25 (OH) D_3. The number of participants receiving some form of vitamin D supplement was 1033 (6.7%), and 2072 (13.76%) of the participants have CKD. Serum levels of 25 (OH) D_3 were measured by using an INCSTAR 25 (OH) D_3 assay, with extraction of 25 (OH) D_3 followed by radioimmunoassay with a 25 (OH) D_3-specific antibody. The serum level of 25 (OH) D_3 was used to classify the participants as vitamin D deficient (<70 nmol/L) and severely vitamin D deficient (<25 nmol/L). Glomerular filtration rate (GFR) was calculated by using the abbreviated Modification of Diet in Renal Disease Study (MDRD) equation and adjusting the creatinine as previously reported.[5] [GFR (mL/min/1.73 m^2)=186.3 × SCr $^{-1.154}$ × Age$^{-0.203}$ × 0.742 (if female) × 1.210 (if African American)]

Statistical Analysis

The analysis sample was stratified by age, gender, and race/ethnicity. Mean levels of serum 25 (OH) D_3 were computed and compared between groups with the two-tailed Student *t* test. An adjusted logistic regression model was developed, with results expressed as odds ratios (OR) with 95% confidence intervals (95% CI). Data were weighted to account for oversampling, nonresponse bias, and poststratification population totals. Data analyses were conducted by using the Statistical Analysis System (version 8.0, 2000, SAS Institute, Cary, NC) and SUDAAN version 8.0 (Research Triangle Institute, Research Triangle Park, NC). Statistical hypotheses were tested with a *P* value <.05 as the level of statistical significance.

Table 2. Serum levels of 25 (OH) D3 (nmol/L) and prevalence of vitamin D deficiency (mild-moderate 25 ≤70 nmol/L and severe <25 nmol/L) in the general population among participants with and without vitamin supplementation in general population

	With Vitamin Supplements		No Vitamin Supplements	
	25 (OH) D3 (nmol/L) (±SE)	Prevalence of D Deficiency (%) (mild-moderate/severe)	25 (OH) D3 (nmol/L) (±SE)	Prevalence of D Deficiency (%) (mild-moderate/severe)
Total	79.47 (0.89)	39.16/1.41	74.38 (0.25)	48.27/1.90
White	83.34 (1.25)	33.28/0.56	78.81 (0.38)	41.82/0.93
Black	54.62 (1.30)	76.87/8.21	47.99 (0.32)	86.37/8.64
Hispanic	66.15 (1.46)	59.69/0.68	62.69 (0.36)	65.92/2.50
Age				
≥65	76.76 (2.00)	43.84/1.21	68.82 (0.44)	55.54/2.17
<65	79.82 (0.98)	38.57/1.44	75.54 (0.30)	46.76/1.84
Male	83.64 (1.31)	31.70/0.64	78.38 (0.35)	42.01/1.15
Female	76.07 (1.18)	45.26/2.05	70.61 (0.35)	54.19/2.60

RESULTS

A total of 7286 (47.34%) male and 8104 (52.66%) female participants were in the analysis sample. All three racial/ethnic groups examined were adequately represented in our analysis sample. The characteristics of the participants are shown in Table 1. In the general population the participants with vitamin supplements had a higher mean serum level of 25 (OH) D_3 (79.47 vs 74.38 nmol/L) and a lower prevalence of vitamin D deficiency (39% vs 48%) than participants who did not take supplements. Thus, a large percentage of each group was below the recommended serum level. Vitamin D deficiency was higher among women, elderly and minorities as previously reported (Table 2). Among patients who took vitamin supplements, Blacks had the highest prevalence (77%) of vitamin D deficiency (<70 nmol/L) followed by Hispanics (60%) and Whites (33%) (Table 2).

In an adjusted regression model to examine the likelihood of severe vitamin D deficiency (<25 nmol/L) no difference was seen by age (<65 years vs ≥65 years) or status of taking vitamin supplements (Table 3). However, the risk of having severe vitamin D deficiency was significantly higher across race/ethnicity (Black vs White OR 8.03, 95% CI 6.26–10.30; *P*<.0001; Hispanic vs White OR 2.32, 95% CI 1.73–3.11; *P*<.0001), gender (OR 2.47, 95% CI 2.02–2.99; *P*<.0001), and presence of CKD (OR 1.43, 95% CI 1.13–1.81; *P*=.0032) (Table 3).

Table 3. Determinants of severe vitamin D3 deficiency (<25 nmol/L) among the general population

	OR (95% CI)	*P*-value
Black (White)	8.03 (6.26–10.30)	<.0001
Hispanic (White)	2.32 (1.73–3.11)	<.0001
Female (Male)	2.47 (2.04–2.99)	<.0001
Age≥65 (<65)	1.17 (0.93–1.47)	.1708
Not taking vitamin supplements	1.47 (0.99–2.17)	.0557
Chronic kidney disease*	1.43 (1.13–1.81)	.0032

* GFR<60 mL/min/1.73 m^2 or GFR≥60 mL/min/1.73 m^2 with proteinuria.

In the CKD subgroup, the prevalence of vitamin D deficiency was also lower with vitamin supplements (49%) versus without supplements (59%). Gender differences were striking in the CKD group; >70% of men who took vitamin supplements had adequate vitamin D levels (mean 109 nmol/L), while only 40% of women who took supplements had adequate vitamin D levels (mean 70 nmol/L) (Table 4). Only among Hispanics were vitamin D levels similar among persons taking vitamin supplements with those not taking them. In the adjusted regression model the OR of severe vitamin D deficiency (<25 nmol/L) was 43% (*P*=.0032) for CKD patients versus non-CKD patients.

DISCUSSION

Our findings highlight the high prevalence of vitamin D deficiency in both the general and CKD populations, even in the presence of routine vitamin supplementation. We found a modest increase in mean serum vitamin D levels and the percentage of people with adequate vitamin D levels in the presence of routine vitamin supplementation. While the lower levels of vitamin D among women, minorities, and the elderly noted in our study are consistent with the existing body of literature,[6,7,8] these findings expand upon previous reports by using a large national database of a general and CKD population and more closely examining the role of vitamin supplementation on vitamin D levels. The high prevalence of vitamin D deficiency among elderly and women taking supplements is particularly worrisome given their high risk for osteoporosis. Approximately half of elderly women consume <137 IU/day of vitamin D, and nearly one quarter consume <65 IU/day (recommended intake 400 IU/day for people 51–70 years of age and 600 IU/day for people ≥71 years of age).[8]

Table 4. Serum Levels of 25 (OH) D3 (nmol/L) and prevalence of vitamin D deficiency (<70 nmol/L) among participants with chronic kidney disease (CKD) by vitamin supplementation status

	Serum levels of 25 (OH) D3 (nmol/L) (±SE)		Prevalence of 25 vitamin D deficiency (<70 nmol/L) (%)	
	Vitamin Supplements	No Vitamin Supplements	Vitamin Supplements	No Vitamin Supplements
Total	76.70 (2.64)	67.74 (0.67)	49.16	58.88
White	80.76 (3.42)	70.79 (0.93)	44.83	54.59
Black	57.63 (5.02)	48.87 (1.00)	70.59	85.07
Hispanic	59.00 (4.33)	57.88 (1.11)	62.22	73.51
Age				
≥65	80.20 (3.41)	66.54 (0.81)	45.26	59.34
<65	74.00 (4.10)	66.41 (2.33)	52.18	58.44
Male	90.66 (4.02)	73.13 (1.08)	30.04	50.69
Female	68.68 (3.12)	64.71 (0.85)	60.14	63.47

CKD: GFR<60 mL/min/1.73 m^2 or GFR≥60 mL/min/1.73 m^2 with proteinuria.

The serum level of 25 (OH) D_3 is an objective way to assess vitamin D nutritional status.[1] The issues around the recommended intake of vitamin D are complex. Vitamin D is acquired through diet and skin exposure to ultraviolet light. Ultraviolet light exposure and time spent outdoors appear to be better predictors of 25 (OH) D_3 levels than dietary vitamin D intake.[9] Also, dietary vitamin D intake may not correlate well with 25 (OH) D_3 levels.[10] Thus, vitamin D deficiency can occur as a result of reduced sun exposure. One limitation of our study is the lack of data on sun exposure by participants. However, the timing of blood collections for NHANES participants appears to minimize the effect of seasonal variation due to sunlight exposure on vitamin D levels as northern samples are collected during the warmer months when sunlight is more abundant, which suggests that the NHANES sampling method is appropriate for assessing vitamin D levels among the general population.[6]

Very few foods contain vitamin D (fatty fish and liver are the exceptions) and skin synthesis is the major source of the vitamin D production. Vitamin D is synthesized non-enzymatically in skin from 7-dehydrocholesterol during exposure to the ultraviolet rays in sunlight. This system is exceedingly efficient and brief casual exposure of the arms and face is estimated to be equivalent to ingesting 200 IU per day.[11] Blacks have been reported to have lower vitamin D production than do Whites under similar sun exposure and have lower 25 (OH) D_3 concentrations in winter and summer.[12,13] Matsuoka et al found that the absorptive characteristics for vitamin D were similar among Blacks and Whites, but the percentage changes in serum 25 (OH) D_3 were inversely related to the starting 25 (OH) D_3 concentrations.[14] Blacks also use dietary

supplements less frequently than do Whites, which could further contribute to the low vitamin D state, as noted in Table 1. Additional factors that may lead to vitamin D deficiency include decreased intake or malabsorption and hepatic disease. We attempted to address this factor by excluding patients with hypoalbuminemia, a marker of overt liver disease, malabsorption, or nephritic syndrome. In addition we also excluded participants with significant proteinuria, which may lead to loss of vitamin D binding protein and contribute to low vitamin D state.

With regard to CKD, the prevalence of vitamin D deficiency was increased in the CKD population that did not take vitamin supplements, while among those who took vitamin D supplements, the prevalence of vitamin D deficiency was lower than in the general population, particularly among women (Table 4).

A limitation of this study is the single assessment of proteinuria for determining CKD. The identification of patients with GFR <60 mL/min/1.73 m^2 should capture patients with true CKD, whereas those in NHANES with GFR ≥60 mL/min/1.73 m^2 with a one-time measurement of proteinuria may overestimate that subset by as much as 30% of patients with true CKD.[5]

Among patients with more severe stages of CKD, changes in bone and mineral metabolism are related to progressive renal failure and vitamin D deficiency, particularly 1,25 (OH) D_3, the active hormone generated from 25 (OH) D_3 metabolism that occurs primarily in the kidney.[15–17] Vitamin D deficiency, which is clinically represented by low 25 (OH) D_3 concentration, is frequently seen in CKD patients and may further contribute to reduced 1,25 (OH) D_3 levels. More than one third of participants with CKD who were taking vitamin D supplements and more than half not taking vitamin D supplements have serum vitamin D levels <70 nmol/L (Table 4), which may contribute to the progression of renal bone disease. The recent Kidney Disease Outcomes Quality Initiative has created guidelines for assessing vitamin D status and treatment, if necessary, in CKD patients. They recommend supplementation with vitamin D_2 (ergocalciferol) if the serum level of 25 (OH) D_3 is <70–75 nmol/L.[17]

A secondary analysis of a random sample of 15 of the nearly 200 vitamin supplements identified from the NHANES medication list revealed that the average dose of vitamin D was 297 IU. This dose would only increase serum 25 (OH) D_3 levels by an average of 7 nmol/L,[18,19]and would not substantially affect the prevalence of vitamin D deficiency in the general population. Recommendations for adult vitamin D intake in North America range from 5–15 μg/day (200–600 IU), depending on age.[3] However vitamin D intake of ≈1000 IU/day (>25 μg) is usually needed to maintain an average level of 25 (OH) D_3 >70 nmol/L.[20] Serum 25 (OH) D_3 concentration >70 nmol/L is suggested to be beneficial to various aspects of human health beyond osteoporosis, including preventing hypertension, cancer, autoimmune diseases, type 1 diabetes, and multiple sclerosis.[20–24] Our data revealed that serum levels of 25 (OH) D_3 are below recommended levels in many persons, even those taking vitamin D supplements.

In conclusion, the current levels of vitamin D in routine vitamin supplementation are inadequate to maintain adequate serum 25 (OH) D_3 levels in both the general and CKD populations. Severe vitamin D deficiency is particularly high among minorities, women, and CKD patients, even in the presence of routine vitamin supplementation. Our data suggest the need to monitor vitamin D status in patients more often and to reassess the dose of vitamin D in standard multivitamins in the United States to reduce the high rates of vitamin D deficiency.

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