ORIGINAL RESEARCH

Comparisons of Serum Vitamin D Levels, Status, and Determinants in Populations With and Without Chronic Kidney Disease Not Requiring Renal Dialysis: A 24-Hour Urine Collection Population-Based Study

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Objective: Vitamin D deficiency is frequent in the general population and might be even more prevalent among populations with kidney failure. We compared serum vitamin D levels, vitamin D insufficiency/deficiency status, and vitamin D level determinants in populations without chronic kidney disease (CKD) and with CKD not requiring renal dialysis.

Design and Methods: This was a cross-sectional, multicenter, population-based study conducted from 2010 to 2011. Participants were from 10 centers that represent the geographical and cultural diversity of the Swiss adult population (≥15 years old).

Intervention: CKD was defined using estimated glomerular filtration rate and 24-hour albuminuria. Serum vitamin D was measured by liquid chromatography-tandem mass spectrometry. Statistical procedures adapted for survey data were used.

Main Outcome Measure: We compared 25-hydroxy-vitamin D (25(OH)D) levels and the prevalence of vitamin D insufficiency/deficiency (serum 25(OH)D < 30 ng/mL) in participants with and without CKD. We tested the interaction of CKD status with 6 a priori defined attributes (age, sex, body mass index, walking activity, serum albumin-corrected calcium, and altitude) on serum vitamin D level or insufficiency/deficiency status taking into account potential confounders.

Results: Overall, 11.8% (135 of 1,145) participants had CKD. The 25(OH)D adjusted means (95% confidence interval [CI]) were 23.1 (22.6-23.7) and 23.5 (21.7-25.3) ng/mL in participants without and with CKD, respectively ($P = .70$). Vitamin D insufficiency or deficiency was frequent among participants without and with CKD (75.3% [95% CI 69.3-81.5] and 69.1 [95% CI 53.9-86.1], $P = .054$). CKD status did not interact with major determinants of vitamin D, including age, sex, BMI, walking minutes, serum albumin-corrected calcium, or altitude for its effect on vitamin D status or levels.

Conclusion: Vitamin D concentration and insufficiency/deficiency status are similar in people with or without CKD not requiring renal dialysis.

Introduction

ADVANCED KIDNEY FAILURE is associated with a decline in the 1-α-hydroxylation of 25-hydroxy-vitamin D (25(OH)D) and with a reduction in the metabolically active form 1,25-hydroxy-vitamin D [1,25(OH)D].[1] Kidney failure is also associated with an increase urinary loss of vitamin D and vitamin D binding protein.[2] Renal retention of phosphorus and increased fibroblast growth factor-23 in kidney failure may also contribute to vitamin D deficiency in kidney failure.[3] Compared with individuals without chronic kidney disease (CKD), patients with CKD might also have decreased sunlight exposure

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and suboptimal vitamin D intake from the diet.[4] As a result, patients with advanced CKD, such as those requiring dialysis, tend to have lower serum levels of vitamin D and higher levels of vitamin D deficiency.[5] Accordingly, the 2003 Kidney Disease Outcomes Quality Initiative and 2009 Kidney Disease Improving Global Outcomes Clinical Practice Guidelines recommend the evaluation of vitamin D status in patients with Stage 3 or higher CKD by measuring 25(OH)D levels.[4,6] Supplementation is recommended if 25(OH)D is less than 30 ng/mL, which is also a definition of vitamin D insufficiency for the general population.[7,8]

Although an inverse association of vitamin D levels with proteinuria has been observed in the early stage of CKD,[9-11] the associations of vitamin D levels and glomerular filtration rate (GFR) in earlier stages of CKD have been inconsistent.[12-16] Some studies have reported that vitamin D deficiency is more prevalent among populations with mild kidney failure than in the general population.[17,18] In contrast, other studies suggest that 25(OH)D levels are relatively stable in the earlier stages of CKD and only decrease in later stages of CKD (estimated GFR [eGFR] < 30 mL/minute per 1.73 m^2),[16] and yet other investigations have reported an inverse correlation between 25(OH)D levels and GFR.[12-16]

A previous analysis of the Swiss Study on Salt Intake (SSS) showed a high prevalence of vitamin D insufficiency and deficiency in the Swiss general adult population.[19] Factors associated with vitamin D status were also identified.[19] This study extends these observations to assess the association between early stages of CKD and the prevalence of vitamin deficiency. Further, we determined the degree to which risk factors associated with vitamin D levels differed by CKD status.

Methods

SSS

We used the data from the 2010 to 2011 SSS,[20] a population-based study that recruited participants from 10 centers that represent the geographical and cultural diversity of the Swiss adult population (≥15 years old). Its main objective was to estimate dietary salt/sodium intake using 24-hour urine collection in the Swiss population. The SSS complied with the Declaration of Helsinki and was approved by the local institutional ethics committees. All participants gave written informed consent. For participants younger than 18 years of age, written consent from 1 parent or a legal representative was obtained.

Sampling Strategy

Sampling strategy and recruitment have been described elsewhere.[19] In brief, sampling was stratified using 8 age (15-29 years, 30-44 years, 45-59 years, ≥60 years) and sex strata. The Italian-speaking region was oversampled to allow for a meaningful comparison with the 2 other major linguistic regions (i.e., French- and German-speaking regions). Recruitment began in January 2010 and ended in August 2011. Information letters were followed by phone calls.

Subjects were identified by means of the Swiss Federal Office Statistics phone directory, which is regularly updated by the major Swiss phone provider and covers 95% of the noninstitutionalized inhabitants in Switzerland. We performed a 2-stage sampling strategy. In the first stage, we contacted households by phone after having sent a letter of invitation to participate in the survey. A single person per household was randomly selected to respond to a first questionnaire by phone. In the second stage, the selected person came to the study center on 2 consecutive mornings for measurements by a trained health professional from the survey team and for urine collection. The following efforts were made to minimize the nonresponse rate: (1) multiple attempts to contact participants were made, including outside of regular working hours (e.g., during evenings and weekends); (2) home visits were made to provide and collect urine bottles; and (3) participants received a small reward at the end of the study (e.g., 30 Swiss franc CHF gift card, 1 CHF ≈ $1 in January 2014). Because of difficulties in recruiting young participants, we had to complete the study sample (aged 15-20 years old) by recruiting volunteers from schools and universities. The participation rate was low (10%).

Assessment Process and Clinical Data

Kidney function was calculated using the following Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.[21]

For females with serum creatinine (SCr) levels of 62 μmol/L or less: $eGFR = 144 \times (SCr/62)^{-0.329} \times (0.993)^{\text{age in years}}$

For females with SCr levels greater than 62 μmol/L: $144 \times (SCr/62)^{-1.209} \times (0.993)^{\text{age in years}}$

For males with SCr levels of 80 μmol/L or less: $141 \times (SCr/80)^{-0.411} \times (0.993)^{\text{age in years}}$

For males with SCr greater than 80 μmol/L: $141 \times (SCr/80)^{-1.209} \times (0.993)^{\text{age in years}}$

CKD-EPI (functional marker of the kidney lesion) and albuminuria (structural marker of the kidney lesion) measured through 24-hour urine collection were used to stage CKD. CKD Stages 1 to 5 were defined as recommended in the Kidney Disease Outcomes Quality Initiative guidelines (i.e., stage = 0 if eGFR > 60 mL/min/1.73 m^2 and 24-hour albuminuria ≤ 30 mg/24 hours, stage = 1 if eGFR > 90 and 24-hour albuminuria > 30 mg/24 hours, stage = 2 if eGFR 60-90 and 24-hour albuminuria > 30 mg/24 hours, stage = 3 if eGFR 30-60, stage = 4 if eGFR 15-30, and stage = 5 if eGFR < 15).[18] Given the few participants with CKD Stages 4 and 5, CKD Stages 3 or greater were combined. All urine samples were analyzed centrally in the laboratory of Lausanne University Hospital.

Blood pressure (BP) was measured 5 times at each visit on the left arm after at least 5 minutes of rest in the seated position using a clinically validated automated oscillometric device (Omron® HEM-907, Matsusaka, Japan) with a standard cuff or with a large cuff if arm circumference was 33 cm or larger.[22] The average of 10 BP readings was used for analyses. Hypertension was defined as a mean systolic BP (SBP) of 140 mmHg or greater or a mean diastolic BP (DBP) of 90 mmHg or greater or the presence of antihypertensive medication.

Weight and height were measured, and body mass index (BMI) was calculated as weight divided by height in square meters. Waist circumference was measured using standard procedures. Diabetes was considered as present whenever the use of antidiabetic drug treatment was reported. Postmenopausal status, use of oral contraceptives or hormone replacement therapy, ethnicity, and smoking status were self-reported.

Information on diet (e.g., fish, wine, and beer consumptions) and daily exercise (minutes of walking) was collected using questionnaires. Participants were asked to report their medications and supplements. This list of reported medications/supplements was compared to the original Compendium® of Switzerland medicine database (http://www.compendium.ch/) to identify vitamin D supplements and treatments.

Biologic Data

Total serum calcium was measured by *O*-cresolphtalein, and albumin was measured by bromocresol green; albumin-corrected calcium was then calculated. Creatinine was measured using the Jaffe kinetic compensated method (Roche Diagnostics, Switzerland). Twenty-four-hour urinary sodium, urea, and potassium excretions were used to estimate their respective consumptions. Because of lack of information on parathyroid hormone (PTH), we used 24-hour urinary calcium excretion as a proxy of PTH activity.

Altitude and Sunshine Hours Data

Participants were geocoded by merging information on the participant's private address with latitude, longitude, and altitude information using Python programming and Google Maps Find Altitude software (https://developers.google.com/maps/documentation/elevation/). Data on sunshine hours were obtained from Meteoswiss, which collects sunshine hours using meteorological stations distributed throughout Switzerland (http://www.meteoswiss.admin.ch/web/en.html). For each participant, data on sunshine hours collected in the station nearest to the participant's address were used. The exposure period in the month before the participant's day of blood collection was used to estimate the monthly mean sunshine hours.

Vitamin D

Total 25(OH)D serum concentration, including 25(OH)D_3 and 25(OH)D_2, was measured by liquid chromatography-tandem mass spectrometry in the laboratories of the Swiss Federal Office of Public Health. An in-house validated method with hexadeuterated 25(OH)D_3 as the internal standard was developed.[23,24] Reference material[25] was used during validation of the method and again every 6th month during the study. The limits of quantification of the method were 1.5 ng/mL (conversion factor: 1 ng/mL = 2.496 nmol/L) for 25(OH)D_3 and 1.0 ng/mL for 25(OH)D_2. Intra- and interassay coefficients of variation for 25(OH)D_3 were 4% and 8%, respectively. If 1 of the reference sera showed more than 15% deviation from the target value, then the results were discarded and the assay was repeated.

Vitamin D Status

To describe the cohort, we used customary definitions of vitamin D status as sufficient, insufficient, and deficient for 25(OH)D levels of 30 ng/mL or greater, 20 to 29.9 ng/mL, and less than 20 ng/mL, respectively.[7,8]

Vitamin D Month-Specific Tertiles

The 25(OH)D concentrations fluctuate because of seasonal variation in sun exposure. Thus, the use of a single blood sample to estimate the long-term 25(OH)D average may lead to misclassification bias. When considering 25(OH)D as a categorical variable, it has been shown that month-specific tertiles of 25(OH)D are preferable to adjusting for seasonal variation.[26] Therefore, we used month-specific tertiles of 25(OH)D as the dependent variable. For each month of the study period, the distribution of 25(OH)D was used to define the specific tertiles of 25(OH)D.

Statistical Analyses

Statistical analyses were performed using Stata 12.0 (Stata Corporation, College Station, TX) and SAS 9.3 (SAS Institute, Cary, NC). To account for the complex sampling, design estimates and variances were calculated using design-based and Taylor expansion method procedures,[26] and design-based test statistics (design-based Student *t*, *F*, or Rao-Scott tests and design-based Wald χ^2 or generalized design-based Wald χ^2 tests)[27] were used for statistical inference.

As outcome variables, we used the 25(OH)D) level (model 1) and the month-specific tertile 25(OH)D levels (model 2). When considering 25(OH)D as a continuous outcome, failure to adjust for date of sample collection has been shown to create a bias toward the null. Therefore, we included the month of sample collection (11 dummy variables) as a covariate in linear models when vitamin D was entered as a continuous variable. To satisfy the linearity assumption, serum 25(OH)D levels were transformed using the square-root transformation.

Vitamin D month-specific tertiles were then considered as inherently ordered categories, and cumulative logit models were used. In this approach, the odds of the vitamin D upper tertile is equal to the probability of the vitamin D upper tertile divided by the probability of the lower or middle vitamin D tertiles. In the cumulative logit models, we assume that the odds ratio (OR) is invariant to where the outcome categories are dichotomized (e.g., between lower and middle/upper or between lower/middle and upper tertiles). We tested the proportional odds assumption using a design-based Score test for survey data implemented in Stata.[26] The null hypothesis of proportional odds fails to be rejected whenever the Score test is not significant. In all of our models the score test was not significant, which suggests that the use of a cumulative logit model was appropriate.

For our first hypothesis (the prevalence of vitamin D sufficiency, insufficiency, and deficiency are different in participants with and without CKD), we compared vitamin D levels and prevalences of sufficient, insufficient, and deficient vitamin D status by CKD status. We also tested the first hypothesis among participants without vitamin D supplement or treatment.

Our second hypothesis was that the associations of determinants of vitamin D levels and status were different in patients with and without CKD as well as across CKD stages. In these analyses, we hypothesized that CKD modified the effect of attributes on vitamin D. We considered 6 specific attributes of vitamin D: age, sex, BMI, walking activity, serum albumin-corrected calcium, and altitude. These attributes were a priori selected based on biological and epidemiological evidence.[28–31] Product terms of CKD status (no CKD vs. CKD Stage 1 or greater) and the 6 attributes were integrated in models adjusting for potential confounders and ensuring that the models were hierarchically well formulated. We considered only first-degree interaction terms (e.g., a 2-factor product such as attribute × CKD) in our models. We used the SAS Collin macro (Emory University, Kleinbaum et al.) for assessing collinearity. Significance for tests, including the interaction test, was set at a P value less than .05.

For the purpose of this analysis, BMI was categorized into less than 25.0 kg/m^2, 25.0 to 29.9 kg/m^2, and 30 kg/m^2 or greater; self-described ethnicity was defined as Caucasian versus non-Caucasian; smoking status was defined as never, current, and ex-smokers; high wine and fish consumptions were both defined as consumption of these items 3 or more days per week; and tertiles of the reported daily average minutes of walk were used.

Results

Participants' Characteristics

A total of 1,145 subjects were included in the multivariate analysis, 11.8% (135 of 1,145) of who had CKD with CKD stages as follows: 48 of 1,145 (4.2%) Stage 1 or 2 and 87 of 1,145 (7.6%) Stage 3 or 4. No participant had CKD Stage 5. Compared with patients without CKD, the mean 24-hour albuminuria was higher among patients with CKD (5.8 vs. 57.3 mg/24 hours, $P < .001$). Characteristics for all participants and by CKD status are detailed in Table 1. In addition to the eGFR, participants with and without CKD statistically differed by several means, including use of oral contraceptive or hormonal replacement therapy, BMI, waist circumference, calcium and urea urinary excretions, and vitamin D supplementation. SBP but not DBP differed between participants with and without CKD (SBP: 124.8 vs. 133.0 mmHg, $P < .001$; DBP: 75.5 vs. 74.9 mmHg, $P = .554$, respectively).

The mean 25(OH)D levels by CKD status and CKD stages are presented in Figure 1. The unadjusted and adjusted 25(OH)D means were not significantly associated with either CKD status or CKD stages. The 25(OH)D adjusted means (95% confidence interval) were 23.1 (22.6-23.7) and 23.5 (21.7-25.3) ng/mL in participants without and with CKD, respectively. In participants without CKD, CKD Stages 1 or 2, and CKD Stage 3 or greater, the 25(OH)D adjusted means were 23.1 (22.5-23.7), 23.4 (22.3-24.5), and 23.7 (21.6-25.9) ng/mL, respectively. We found no association between 25(OH)D and CKD status or stages in analyses restricted to participants without vitamin D supplement or treatment ($n = 1{,}100$) (Fig. 1).

The prevalence of vitamin D insufficiency (20-29.9 ng/mL) or deficiency (<20 ng/mL) was high but similar in participants with and without CKD (75.3% [95% confidence interval {CI} 69.3-81.5] and 69.1% [95% CI 53.9-86.1], respectively, $P = .054$; Table 2). In both participants with and without CKD, prevalence of vitamin D insufficiency and deficiency was higher during the October-March period than the April-September period. Prevalence of vitamin D status (adequate, insufficiency, deficiency) restricted to participants without vitamin D supplement ($n = 1{,}100$) overall and by periods are presented in Table S1. No difference was found in participants with and without CKD.

Determinants of Vitamin D Tertiles

In multivariate analyses, none of the 6 a priori interaction terms used in linear and ordinal logistic models were statistically significant. Multivariate associations of characteristics with vitamin D month-specific tertiles on the basis of the full model are reported in Table 3. CKD was not associated with vitamin D status in the multivariable model (OR: 0.92, 95% CI 0.61-1.38). Compared with the French-speaking region and after adjustment, the Italian-speaking regions were associated with a higher likelihood of being in a higher vitamin D tertile (OR: 1.68, 95% CI 1.09-2.58). Compared with non-Caucasians, Caucasians were more likely to be in

Table 1. Characteristics of the Swiss Study on Salt Intake Participants by CKD Status (N = 1,145)

	All (N = 1,145)		No CKD (n = 1,010)		CKD (n = 135)		
Attributes	Mean or %	95% CI	Mean or %	95% CI	Mean or %	95% CI	P
Male gender (%)	48.9	47.3-50.5	49.0	47.0-50.9	48.5	40.7-56.4	.710
Age (y)	48.5	47.9-49.2	46.4	45.6-47.1	64.7	61.7-67.8	<.001
Higher education (university degree or higher) (%)	42.4	39.5-45.3	43.5	40.4-46.6	34.1	26.5-42.7	.043
Linguistic regions (%)							.791
French-speaking	26.8	24.2-29.6	27.0	24.3-30.0	25.1	18.3-33.5	
German-speaking	66.8	64.0-69.5	66.5	63.5-69.4	68.9	60.5-76.1	
Italian-speaking	64.1	55.0-74.6	6.5	5.5-7.6	6.0	3.8-9.4	
Swiss citizenship (%)	85.4	83.2-87.3	85.1	82.8-87.2	87.2	80.2-92.0	.536
Caucasian ethnicity (%)	98.5	97.5-99.1	98.5	97.4-99.1	98.4	97.4-99.1	.261
Smoking status (%)							.081
Never smokers	53.6	50.6-56.5	53.6	50.5-56.7	53.2	44.6-61.7	
Smokers	17.1	15.0-19.5	18.0	15.6-20.5	11.1	6.8-17.9	
Former smokers	29.3	26.7-32.0	28.4	25.7-31.3	35.6	27.8-44.2	
Tertiles of daily average minutes of walking							.312
Lower tertile	54.8	51.8-57.7	55.6	52.4-58.7	48.5	40.0-57.2	
Middle tertile	24.6	22.1-27.2	24.2	21.6-27.0	27.3	20.3-35.7	
Upper tertile	20.6	18.3-23.1	20.2	17.7-22.8	24.1	17.4-32.4	
Hypertension (%)	31.1	28.6-33.6	27.2	24.7-29.9	59.9	51.2-67.9	<.001
Diabetes (%)	2.8	2.0-3.9	2.6	1.0-2.7	11.2	6.8-17.9	<.001
Menopause (among women) (%)	44.6	41.8-47.5	41.4	38.2-44.7	68.9	57.1-78.6	<.001
Oral contraceptive use (among women) (%)	35.0	31.2-39.0	33.3	29.4-37.6	47.2	35.4-59.2	.003
Estimated glomerular filtration rate*	89.8	88.8-90.7	92.8	91.9-93.7	67.4	63.1-71.7	<.001
24-h albuminuria (mg/24 h)	11.9	8.3-15.7	5.8	5.5-6.1	57.3	27.4-87.2	<.001
Overt proteinuria† (%)	0.3	0.1-0.9	0.0	0.0-0.0	2.7	1.0-7.3	<.001
Body mass index (kg/m^2)	25.2	25.0-25.5	25.1	24.9-25.4	26.2	25.3-27.1	.032
Waist circumference (cm)	90.2	89.5-90.9	89.7	88.9-90.4	94.0	91.3-96.8	.003
Systolic blood pressure (mmHg)	125.8	124.9-126.6	124.8	124.0-125.7	133.0	129.7-135.7	<.001
Diastolic blood pressure (mmHg)	75.4	74.8-76.0	75.5	74.9-76.1	74.9	73.1-76.7	.554
Albumin-corrected calcium	2.31	2.30-2.31	2.31	2.30-2.31	2.32	2.31-2.34	.100
Urinary excretion (mmol/24 h)							
Sodium	158.4	154.5-162.3	159.3	155.3-163.4	151.3	137.9-164.8	.269
Potassium	67.4	66.0-68.8	67.8	66.3-69.0	64.5	59.7-69.2	.195
Calcium	4.05	3.91-4.18	4.18	4.04-4.33	3.02	2.60-3.45	<.001
Urea	365.9	358.6-373.3	370.5	362.7-378.4	331.8	307.2-356.4	.004
High fish‡ (%)	5.8	4.6-7.4	5.9	4.5-7.6	5.7	2.7-11.4	.929
High wine‡ (%)	35.4	32.7-38.2	35.8	32.9-38.8	32.4	24.8-40.9	.447
High beer‡ (%)	16.1	14.1-18.3	16.9	14.7-19.3	10.0	5.9-16.6	.049
Use of vitamin D supplements (%)	4.1	3.1-5.4	3.2	2.2-4.5	10.8	6.5-17.5	<.001
Altitude (m)	468.6	460.1-477.0	470.0	460.5-478.7	460.8	438.5-483.2	.476
Latitude (°)	47.0	47.0-47.1	47.0	47.0-47.1	47.1	47.0-47.1	.423
Mean monthly sunshine hours	5.41	5.28-5.55	5.45	5.31-5.59	5.16	4.79-5.52	.136

CI, confidence interval; CKD, chronic kidney disease.
*Estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.
†Defined as 24-h albuminuria ≥ 300 mg/24 h.
‡Defined as consumption of these items ≥3 d/wk.

a higher vitamin D tertile (OR 3.21, 95% CI 1.08-9.47). Waist circumference but not BMI was negatively associated with vitamin D month-specific tertiles; each unit increase of waist circumference was associated with a 2% decreased likelihood of being in a higher vitamin D month-specific tertile. Participants in the middle, but not in the upper, tertile of daily average minutes of walk were more likely to be in higher vitamin D tertiles than participants in the lower tertile. Oral contraceptive or hormonal replacement therapy, altitude, urinary excretion of urea, use of vitamin D supplement or treatment, and high wine consumption were positively associated with vitamin D month-specific tertiles.

Discussion

In this population-based study, we found that the prevalence of vitamin D deficiency was high in people with CKD not requiring dialysis, but not higher than in people without CKD. Vitamin D status and vitamin D levels (25(OH)D) did not differ by CKD status or stages. We also found no evidence that vitamin D major determinants are different in subjects with and without

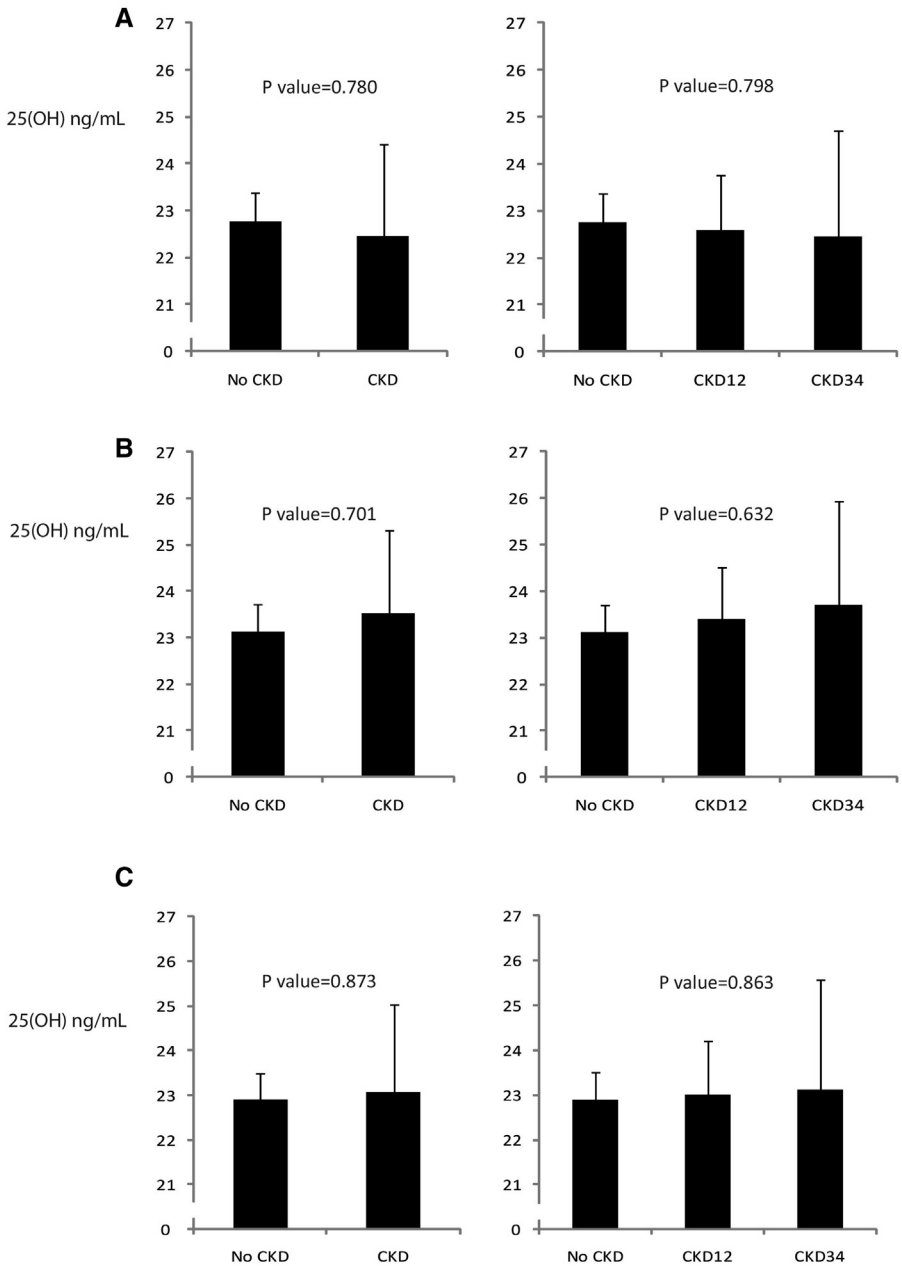

Figure 1. Vitamin D levels and CKD: (A) unadjusted, (B) fully adjusted*, and (C) restricted to participants without vitamin D supplements or therapy. *Adjusted for sex; age; albumin-corrected calcium; body mass index; waist circumference; daily minutes of walking; altitude; education; monthly mean hours of sunshine; latitude; smoking status; vitamin D supplement or treatment (when appropriate); linguistic region; wine and beer consumption; oral contraceptive or hormonal replacement therapy; menopause; hypertension; diabetes; nationality; ethnicity; sodium, potassium, urea, and calcium urinary excretion; and month of sampling. CKD, chronic kidney disease; 25(OH)D, 25-hydroxy-vitamin D.

CKD (i.e., CKD does not modify the effect of major attributes on vitamin D).

Using 25(OH)D levels, we found a high prevalence of vitamin D insufficiency or deficiency in participants with and without CKD not requiring dialysis. Our results are in line with previous reports that found either no association of 25(OH)D level and eGFR[12,13] or a decrease in 25(OH)D level only in participants with an advanced decrease in eGFR (Stage 3+).[14,16] Our results contrast with a previous study from Mehrotra and colleagues showing that individuals with CKD had a higher prevalence of 25(OH)D deficiency.[17] In this previous study, the adjusted odds of vitamin D deficiency was 1.39 (1.09-1.77), higher among patients with CKD than patients without CKD, whereas vitamin D insufficiency was not associated with CKD.[17] Differences in the population

Table 2. Raw Numbers and Weighted Prevalences of Sufficient (≥30 ng/mL), Insufficient (20-29.9 ng/mL), and Deficient (<20 ng/mL) Vitamin D Status by CKD Status and Period of the Year (N = 1,145)

		April-September		October-March		All Periods (April-March)	
CKD Status	Vitamin D Status	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)
No CKD	Vitamin D sufficiency	190/577	31.2 (27.5-35.2)	73/433	16.6 (13.4-20.4)	263/1,010	24.7 (22.1-27.5)
	Vitamin D insufficiency	242/577	43.3 (39.1-47.5)	215/433	31.8 (27.5-36.5)	387/1,010	38.1 (35.1-41.2)
	Vitamin D deficiency	145/577	25.5 (22.0-29.3)	215/433	51.6 (46.9-56.4)	360/1,010	37.2 (34.2-40.3)
CKD	Vitamin D sufficiency	31/75	40.8 (29.9-52.7)	12/60	20.2 (11.9-32.3)	43/135	30.9 (23.6-39.3)
	Vitamin D insufficiency	24/75	28.9 (19.6-40.5)	16/60	25.9 (16.4-38.4)	40/135	27.5 (20.5-35.7)
	Vitamin D deficiency	20/75	30.3 (20.4-42.3)	32/60	53.9 (41.2-66.1)	52/135	41.6 (33.4-50.4)
Rao-Scott χ^2 test comparing participants with and without CKD by periods: P value			.0712		.598		.0537

CI, confidence interval; CKD, chronic kidney disease.

Rao-Scott χ^2 test across periods among participants without CKD: $P < .0001$; Rao-Scott χ^2 test across periods among participants with CKD: $P = .009$.

studied and methods used may explain some variation in findings. For example, we used 24-hour urine collection to define albuminuria whereas Mehrotra and colleagues relied on a single urinary spot. In addition, we measured vitamin D using the gold standard method and considered 25(OH)D month-specific tertiles to adjust for seasonal variation and avoid bias away from the null.

The absence of difference in 25(OH)D levels—and thereby vitamin D deficiency prevalence—in participants with and without CKD could be attributed, in part, to a decrease in 25(OH)D catabolism. Recent studies have reported no correlation or even an inverse correlation between 25(OH)D levels and GFR despite decreased levels of $1,25(OH)2D_3$[12-16]; the level of 25(OH)D could paradoxically be higher among people with early stages of CKD (i.e., inverse correlations between GFR and 25(OH)D) than in people with adequate kidney function. Indeed, the product of 25(OH)D catabolism (24,25(OH)D) seems to be decreased in CKD, leading to a state of stagnant vitamin D metabolism. Information on 24,25(OH)D levels would be needed to further explore this hypothesis in the study presented here.[32]

Few studies explored whether the determinants of vitamin D deficiency in populations with and without CKD are the same. In multivariate analyses, we assessed this by testing 6 a priori formulated interactions. CKD status did not interact with age, sex, BMI, walking minutes, serum albumin-corrected calcium, or altitude for its effect on vitamin D status or levels. This is consistent with a previous study that assessed these interactions.[10] Thus, the major determinants of vitamin D seemed to be similar in populations with and without CKD not requiring dialysis. In addition, we found that the associations between factors and vitamin D levels in the general adult population (linguistic regions, Caucasian ethnicity, daily average minutes of walk, oral contraceptive or hormonal replacement, waist circumference, vitamin D supplementation or therapy, high wine consumption, and altitude)[18] are independent of kidney function.

Vitamin D insufficiency or deficiency is very high in the general population. In a recent study using the same source population, we showed that vitamin D insufficiency or deficiency were as high as 75% in the general population.[19] Although the high prevalence of suboptimal vitamin D is of concerns in general, it remains to be determined whether it is of even more concern among the CKD population. In a recent meta-analysis of prospective studies (10 studies, N = 6,853), higher 25(OH)D levels were associated with significantly improved survival in patients with CKD.[33] Of note, several meta-analyses have shown that higher 25(OH)D levels were also associated with significantly improved survival in the general population.[34,35] Whether treatment of low 25(OH)D levels using vitamin D supplementation improves survival in patients with or without CKD (not requiring dialysis) remains to be shown in randomized controlled trials.

Strengths and Limitations

With respect to exploring the association between 25(OH)D levels and kidney function, this is a large population-based study using 24-hour urine collection; measuring 25(OH)D by the gold standard technique (liquid chromatography-tandem mass spectrometry); and taking into account geographical, meteorological, and nutritional information. Another strength is the use of a single laboratory for centralized urine and blood analyses. Information on major known potential confounders was available, but despite these efforts, information is still incomplete. For example, we lack information on PTH and on the darkness of the skin. PTH is closely related to the metabolism and homeostasis of vitamin D, calcium, and phosphorus via the intestine, kidney, and bone. In the kidney, PTH enhances the distal tubular reabsorption of calcium and stimulates the 1-α-hydroxylation of 25(OH)D leading to the formation of 1,25(OH)2D.[36] An increase in free ionized calcium reduces PTH release by a negative feedback loop, which in turn decreases vitamin D activation in the kidney. A low level of 1,25(OH)2D is associated with reduced

Table 3. Multivariate Association (Ordinal Logistic Regression, Full Model) of Characteristics With Month-Specific Tertiles of 25(OH)D: OR of Being in a Higher Tertile of 25(OH)D (N = 1,145)

Attributes	Ordinal OR	95% CI	P
CKD (vs. no CKD)	0.92	0.61-1.38	.673
Male gender	0.90	0.63-1.29	.576
Age (y)	1.00	0.99-1.01	.596
Education superior (university, diploma superior)	1.03	0.81-1.31	.791
Linguistic regions			
French-speaking	Reference	–	–
German-speaking	1.68	0.83-13.36	.146
Italian-speaking	1.68	1.09-2.58	**.019**
Swiss citizenship	1.03	0.73-1.44	.880
Caucasian ethnicity	3.21	1.08-9.47	**.035**
Smoking status			
Never smokers	Reference	–	–
Smokers	1.05	0.76-1.45	.782
Former smokers	1.02	0.77-1.34	.901
Tertiles of daily average minutes of walk (min)			
Lower tertile	Reference	–	–
Middle tertile	1.37	1.02-1.84	**.035**
Upper tertile	1.18	0.88-1.59	.266
Hypertension	0.94	0.69-1.28	.697
Diabetes	0.63	0.27-1.48	.291
Menopause	1.11	0.72-1.71	.643
Oral contraceptive	1.91	1.31-2.79	**.001**
Body mass index (kg/m^2)	0.97	0.91-1.03	.306
Waist circumference (cm)	0.98	0.96-0.99	**.028**
Corrected calcium	3.20	0.82-12.5	.095
Vitamin D supplements or treatment	5.06	2.56-10.0	**<.001**
Urinary excretion of sodium, (mmol/24 h)	0.99	0.99-1.00	.858
Urinary excretion of potassium, (mmol/24 h)	0.99	0.99-1.00	.765
Urinary excretion of calcium (mmol/24 h)	1.06	1.00-1.12	.054
Urinary excretion of urea (100 mmol/24 h)	1.12	1.00-1.28	.056
High wine*	1.37	1.06-1.77	**.015**
High beer*	0.86	0.63-1.17	.338
Altitude (per 100-m increase)	1.09	1.01-1.18	**.021**
Latitude (°)	0.90	0.45-1.79	.761
Mean monthly sunshine hours	1.02	0.97-1.07	.456

25(OH)D, 25-hydroxy-vitamin D; CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio.

Approximate likelihood-ratio test of proportionality of odds across response categories: P = .5369 (Score test, Parallel Lines test).

Bold indicates statistically significant ($P < 0.05$).

*Defined as consumption of these items ≥3 d/wk.

intestinal absorption of calcium, which in turn leads to increased PTH production with resulting increased bone resorption. In patients with CKD, vitamin D supplementation decreases PTH.[37] These tight physiological relationships translate into the well-described negative correlation between 25(OH)D and PTH in cross-sectional analyses of population-based studies.[38] Thus, PTH is an important factor to consider when looking at the association between vitamin D status and kidney function.

We did not use a comprehensive food frequency questionnaire. However, diet contains only small amounts of vitamin D and information on fish consumption was collected, which is the major dietary source of vitamin D in humans. We did not take air pollution, ozone, time of the day, and cloud cover into account. These weather-related factors may influence radiation from the Sun and thus vitamin D photosynthesis,[31] although the effect is likely to be minor. We did not use para-aminobenzoic acid to check the completeness of urinary collection. However, the ratio of urinary creatinine excretion-to-kilograms of body weight over 24 hours and urine volumes suggested a good quality of most urine collections.

We used definitions of vitamin D deficiency and insufficiency that have been proposed by experts. This definition has been used in most epidemiological studies, but different definitions exist.[8] Although the definition of vitamin D deficiency and insufficiency is debated, this would not bias our results because we used the same definition when comparing people with and without CKD. GFR and CKD stages were based on the CKD-EPI equation and albuminuria. More accurate measurements (including inulin clearance, iothalamate clearance, cystatin C) exist.

The low participation rate limits the external validity of our findings. We explain this low participation rate by the unattractiveness of 24-hour urine collection together with the 2-stage sampling strategy, which implies that the person we contacted by phone was not automatically the one selected to enter the study. Blood collection was not mandatory to participate in the original study, and we cannot exclude that this could have potentially introduced a bias. Among participants excluded from the analyses for other missing data than blood values, age, sex, the levels of 25(OH)D, eGFR, and albuminuria did not differ. Also, some households were dropped from being included in the target population if certain household characteristics did not meet specific criteria.

Of note, our results are based on data collected from the general population in which potential factors influencing the relationship between vitamin D and kidney function are less prevalent than in patients selected from clinical settings. For example, the urinary loss of vitamin D binding protein observed in advanced kidney failure increases the urinary loss of vitamin D, but only a few participants (0.3%) had overt proteinuria in this population-based study. Also, previous studies have reported an inverse association between obesity and vitamin D level.[39] There are several mechanisms by which vitamin D levels could be negatively associated with obesity, including the decrease of outdoor physical activity, the inadequate diet, and the sequestration of vitamin D in the cutaneous fat among people.[40] The reason for the increasing prevalence of vitamin D deficiency observed in the United States could be in part due

to the increase of obesity.[29] Our study population did not have high BMI, which may explain, at least in part, the absence of an independent association of BMI or obesity with vitamin D status (data for obesity not shown).

Practical Application

People with CKD have similar prevalence of vitamin D deficiency and levels of 25(OH)D than people without CKD. CKD status does not modify the effect of major vitamin D determinants on vitamin D levels or status. Although the high prevalence of suboptimal vitamin D is of concern in general, it remains to be determined whether it is of even more concern among the CKD population.

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Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1053/j.jrn.2014.04.005.

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