Effect of Vitamin D Supplementation on Kidney Function in Adults with Prediabetes

A Secondary Analysis of a Randomized Trial

*Sun H. Kim,[1] Irwin G. Brodsky,[2] Ranee Chatterjee,[3] Sangeeta R. Kashyap,[4] William C. Knowler,[5] Emilia Liao,[6] Jason Nelson,[7] Richard Pratley,[8] Neda Rasouli,[9] Ellen M. Vickery,[10] Mark Sarnak,[11] Anastassios G. Pittas,[10] and the D2d Research Group**

Due to the number of contributing authors, the affiliations are listed at the end of this article.

Correspondence: Dr. Sun H. Kim, Division of Endocrinology, Gerontology and Metabolism, 300 Pasteur Drive, S-025, Stanford, CA 94305. Email: sunhkim@stanford.edu

Abstract

Background and objectives Low serum 25-hydroxyvitamin D (25[OH]D) concentration has been associated with higher levels of proteinuria and lower levels of eGFR in observational studies. In the Vitamin D and Type 2 Diabetes (D2d) study, we investigated the effect of vitamin D supplementation on kidney outcomes in a population with prediabetes.

Design, setting, participants, & measurements Overweight/obese adults with high risk for type 2 diabetes (defined by meeting two of three glycemic criteria for prediabetes) were randomized to vitamin D_3 4000 IU per day versus placebo. Median duration of treatment was 2.9 years (interquartile range 2.0–3.5 years). Kidney outcomes included (*1*) worsening in Kidney Disease: Improving Global Outcomes (KDIGO) risk score (low, moderate, high, very high) on two consecutive follow-up visits after the baseline visit and (*2*) mean changes in eGFR and urine albumin-to-creatinine ratio (UACR).

Results Among 2166 participants (mean age 60 years, body mass index 32 kg/m^2, serum 25(OH)D 28 ng/ml, eGFR 87 ml/min per 1.73 m^2, UACR 11 mg/g, 79% with hypertension), 10% had moderate, high, or very high KDIGO risk score. Over a median follow-up of 2.9 years, there were 28 cases of KDIGO worsening in the vitamin D group and 30 in the placebo group (hazard ratio, 0.89; 95% confidence interval [95% CI], 0.52 to 1.52]). Mean difference in eGFR from baseline was −1.0 ml/min per 1.73 m^2 (95% CI, −1.3 to −0.7) in the vitamin D group and −0.1 ml/min per 1.73 m^2 (95% CI, −0.4 to 0.2) in the placebo group; between-group difference was −1.0 ml/min per 1.73 m^2 (95% CI, −1.4 to −0.6). Mean difference in UACR was 2.7 mg/g (95% CI, 1.2 to 4.3) in the vitamin D group and 2.0 (95% CI, 0.5 to 3.6) in the placebo group; between-group difference was 0.7 mg/g (95% CI, −1.5 to 2.9).

Conclusions Among persons with prediabetes, who were not preselected on the basis of serum 25(OH)D concentration, vitamin D supplementation did not affect progression of KDIGO risk scores and did not have a meaningful effect on change in UACR or eGFR.

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Introduction

The American Diabetes Association (ADA) defines prediabetes not as a disease, but as a condition that increases risk for type 2 diabetes and cardiovascular disease (1). Individuals with prediabetes commonly have comorbidities, including hypertension, which mediate risk for patient-relevant outcomes, including kidney disease. In addition, low circulating 25-hydroxyvitamin D (25[OH]D) concentration has been suggested as a risk factor for both type 2 diabetes (2) and kidney disease (3–6).

Several lines of reasoning suggest a potential renoprotective role of activated vitamin D, 1,25$(OH)_2$D. Preclinical studies suggest that 1,25$(OH)_2$D helps regulate the renin-angiotensin system (7,8), enhances insulin sensitivity (9), and improves endothelial function (10), which can all affect BP and maintain vascular health (11) of the kidney. In addition, knockout of vitamin D receptors in mice can aggravate hyperglycemia-induced kidney injury leading to worsening albuminuria and glomerulosclerosis (8).

Human studies have shown that low circulating 25(OH)D concentration can predict all stages of kidney disease, from albuminuria to kidney failure (3–6), but some studies have found no association (12,13). In the Third National Health and Nutrition Examination Survey (NHANES III), prevalence of albuminuria increased with each decrease in quartile of blood 25(OH)D concentration (3). In an Australian population cohort, blood 25(OH)D concentration lower than 20 ng/dl was independently associated with prevalent albuminuria (4). In the same cohort, vitamin D deficiency (25[OH]D<15 ng/dl) was associated with incident albuminuria and reduced eGFR (eGFR<60 ml/min

per 1.73 m^2) (5); low circulating 25(OH)D concentration was also associated with progression to kidney failure in the NHANES III cohort (6).

Despite evidence for associations between low circulating 25(OH)D concentration and kidney disease, few clinical trials have evaluated the effect of vitamin D supplementation on kidney outcomes. The Vitamin D and Type 2 Diabetes (D2d) study was a randomized clinical trial of US adults with prediabetes to test the effect of vitamin D_3 supplementation versus placebo on diabetes risk (14). In the D2d study, vitamin D supplementation did not significantly decrease new-onset diabetes (hazard ratio, 0.88; 95% confidence interval [95% CI], 0.75 to 1.04); however, since publication of the main D2d results, aggregate meta-analyses have reported a significant 11%–12% reduction in diabetes risk with vitamin D supplementation among people with prediabetes (15,16). This study is a secondary analysis to determine prevalence of kidney dysfunction in the D2d prediabetes population and to examine the effect of vitamin D supplementation on incident kidney outcomes.

Materials and Methods

Overview of the D2d Study

This study is a secondary analysis of the D2d study focusing on kidney outcomes. The D2d study was a randomized, double-blind, placebo-controlled, multisite clinical trial to test whether vitamin D supplementation has an effect on new-onset diabetes in adults with prediabetes (clinicaltrials.gov NCT 01942694, registered 9/16/2013). Details of the protocol and results have been published (14,17). The institutional review board at each clinical site approved the protocol, and all participants provided written, informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Study Population

Participants were recruited from 22 medical centers across the United States (18). Eligible participants met at least two of three glycemic criteria for prediabetes as defined by the 2010 ADA guidelines: fasting plasma glucose 100–125 mg/dl (5.6–6.9 mmol/L); plasma glucose 2 hours after a 75-g oral glucose load 140–199 mg/dl (7.8–11.0 mmol/L); hemoglobin A1c 5.7%–6.4% (39–47 mmol/mol) (19). Other inclusion criteria were age greater than or equal to 30 years (25 years for American Indians, Alaska Natives, Native Hawaiians, or other Pacific Islanders) and body mass index (BMI) of 24–42 kg/m^2 (22.5–42 kg/m^2 for Asians). A low serum 25(OH)D level was not an eligibility criterion. Key exclusion criteria included: any glycemic criterion in the diabetes range; use of diabetes or weight-loss medications; history of hyperparathyroidism, nephrolithiasis, hypercalcemia, or bariatric surgery; or an eGFR—calculated by means of the Chronic Kidney Disease Epidemiology Collaboration equation (20)—of less than 50 ml/min per 1.73 m^2 of body-surface area. For a complete list of eligibility criteria, see Supplemental Table 1. The recruitment and screening process has been described previously (17,18,21).

Intervention and Procedures

Participants were randomized to take either a single softgel that contained 4000 IU of vitamin D_3 (cholecalciferol) or matching placebo once daily. Randomization was computer generated and block-stratified according to trial site, BMI (<30 or ≥ 30 kg/m^2), and race (White or non-White). Study staff used a web-based, interactive, D2d-specific study pill inventory and randomization system to enter the stratification information, and the system assigned the participant to vitamin D_3 or placebo. At randomization and every 6 months, the system generated a specific pill bottle number that study staff used to dispense study pills to participants in a blinded fashion. No unblinding took place during the study, and study staff and participants were notified of the assignment after the primary results were published. Participants were asked to limit the use of outside-of-study vitamin D to 1000 IU per day from all supplements and calcium supplements to 600 mg per day.

Follow-Up and Measurements

Follow-up visits occurred at month 3, at month 6, and twice per year thereafter. Blood and urine for kidney outcomes were collected after an 8-hour overnight fast at baseline, and at months 3 (blood only), 12, 24, 36, and 48. Serum for creatinine was analyzed on the same day of the visit at each site's clinical laboratory (see Supplemental Table 2). Other blood and urine specimens were processed locally and shipped to the central laboratory for long-term storage at $-80°C$ until analyses. Stored serum samples were used to measure 25(OH)D by liquid chromatography tandem mass spectrometry validated by a quarterly proficiency-testing program administered by the Vitamin D External Quality Assessment scheme (United Kingdom) (22,23). Stored urine was used to measure both albumin, using an immunoturbidimetric method, and creatinine, using an enzymatic-colorimetric method with calibration traceable to an isotope dilution mass spectrometry reference measurement procedure; both measurements were completed on the Cobas c311 analyzer (Roche Diagnostics, Indianapolis, IN).

Outcomes

We evaluated time to worsening in kidney function on the basis of the risk categories established by the Kidney Disease: Improving Global Outcomes (KDIGO) organization (Supplemental Figure 1) (24). The KDIGO risk classification has four levels on the basis of eGFR (ml/min per 1.73 m^2) and urine albumin-to-creatinine ratio (UACR, mg/g): (*1*) green—low risk (eGFR$\geq$60 and UACR$<$30); (*2*) yellow—moderate risk (eGFR$\geq$60 and UACR 30–300 or eGFR 45–59 and UACR$<$30); (*3*) orange—high risk (eGFR$\geq$60 and UACR$>$300 or eGFR 45–59 and UACR 30–300 or eGFR 30–44 and UACR$<$30); and (*4*) red—very high risk (eGFR 45–59 and UACR$>$300 or eGFR 30–44 and UACR$\geq$30 or eGFR$<$30 and any UACR). We defined worsening in kidney function as an increase by at least one KDIGO risk category from baseline on two consecutive visits (confirmed KDIGO worsening). Time to worsening in KDIGO risk category was chosen as a composite outcome in order to incorporate both eGFR and UACR, as prior studies have suggested an effect of vitamin D on both kidney measures (3–6), and KDIGO categories predict risk of cardiovascular disease,

progressive kidney disease, and mortality. In sensitivity analyses, we expanded the outcome to include any individual who had worsening in KDIGO classification at their last study visit only (unconfirmed KDIGO worsening).

We also examined the following kidney end points: change from baseline in eGFR and change from baseline in UACR (as continuous variables); time to meeting eGFR<60 ml/min per 1.73 m^2 (among participants with eGFR≥60 ml/min per 1.73 m^2 at baseline); and time to meeting UACR≥30 mg/g (among participants with UACR<30 mg/g at baseline).

Covariates

Age, race, and ethnicity were self-reported. Height, weight, and BP were measured using standardized procedures. All medications and dietary supplements being taken by the participant were brought in at the screening visit and recorded and reviewed at each follow-up encounter.

Statistical Methods

The sample size for the parent study was determined on the basis of a target of 508 diabetes events and a total sample size of 2382 participants randomized equally to the vitamin D and placebo groups. The rationale has been previously published (14). The analysis population for this study included all participants, regardless of follow-up status, who had available eGFR and UACR data at the baseline visit. All participants were analyzed according to their randomized treatment group, regardless of adherence to the assigned intervention (intention-to-treat population). Follow-up time was calculated as time from randomization until the occurrence of the kidney end point (*e.g.*, KDIGO worsening), death, withdrawal, or last follow-up encounter.

We imputed missing values for eGFR and UACR at follow-up visits using Markov chain Monte Carlo simulations assuming the data were from a multivariable normal distribution (25,26). We generated five fully imputed datasets and combined estimated results using Rubin's rules (27). Missing values were imputed for scheduled visits until the end-of-study date for each participant, which varied from participant to participant given that the parent trial was designed as event-driven (in relation to the diabetes outcome) (17). We imputed 8.9% of the data.

Between-group differences for the change in continuous variables compared with baseline were determined using a linear mixed-effects model approach to account for within-participant correlation across the time points. The outcome of the linear mixed model is change compared with baseline with randomization assignment as the single independent fixed effect. All postbaseline observations are weighted equally. Average change within each group and mean differences between groups along with 95% CIs are presented. Time-to-event end points were evaluated with the use of Kaplan–Meier estimates and Cox proportional hazards models. All models included group assignment, as the main predictor variable, and the stratification variables (trial site, BMI, and race).

Variability of response to vitamin D supplementation for confirmed KDIGO worsening was assessed in subgroups defined by key baseline variables: age, race, BMI, 25(OH)D concentration, and, given their known renoprotection, use of angiotensin-converting enzyme inhibitor (ACEi) /angiotensin II receptor blockers (ARB). We also evaluated change in eGFR and UACR in those without imputed values and in two select subsets: (*1*) those not taking vitamin D supplements at baseline and (*2*) those not on any ACEi/ARB during the study. No adjustments were made for multiple comparisons; therefore, only point estimates and 95% CIs are presented without *P* values.

This analysis was not prespecified, and, therefore, considered *post hoc*, exploratory. However, the statistical analysis plan (including the definition of kidney outcomes) was reviewed and approved by all coauthors and the study's publications and presentations committee before outcomes data were analyzed and presented by group. Statistical analyses were performed by an independent statistician using SAS version 9.4 (SAS Institute Inc.).

Results

Of 2423 participants randomized to vitamin D or placebo, 247 did not consent to the biorepository, and ten did not have baseline eGFR or UACR. After excluding these participants, a total of 2166 participants were included in the present analysis (see Supplemental Figure 2). Baseline characteristics of participants did not differ from the entire D2d cohort (Table 1 and Supplemental Table 3). The mean (±SD) age of the kidney cohort was 60 (±10) years and BMI was 32 (±5) kg/m^2. Over half (52%) reported use of antihypertensive medications; 33% were using ACEi/ARB (31% in the vitamin D versus 34% in the placebo). Forty-three percent reported some use of vitamin D supplementation at baseline; mean serum 25(OH)D was 28 ng/ml. Adherence to trial pills was high, with 83% of prescribed pills taken (83% in vitamin D versus 83% in placebo).

Kidney Function at Baseline in the D2d Kidney Cohort

Mean (±SD) eGFR was 87 (±16) ml/min per 1.73 m^2. eGFR was <60 ml/min per 1.73 m^2 in 4% of participants (3% in the vitamin D versus 5% in the placebo), and UACR≥30 mg/g was seen in 6%. Using the KDIGO classification, 10% of participants scored at or above moderate risk (yellow, orange, or red) (8% in the vitamin D versus 11% in the placebo).

Kidney Outcomes

Over a median follow-up of 2.9 years (interquartile range 2.0–3.5 years), there were 28 cases of confirmed worsening in KDIGO risk score (increase in KDIGO risk category on two consecutive visits) in the vitamin D group and 30 in the placebo group (hazard ratio for vitamin D, 0.89; 95% CI, 0.52 to 1.52) (Table 2). Reanalysis without imputed numbers showed similar results (data not shown). In sensitivity analysis in which the outcome included individuals who had worsening in KDIGO risk category at the last visit (and thus unconfirmed), there were a greater number of events in both groups but no differences between groups (hazard ratio, 1.04; 95% CI, 0.73 to 1.48). Table 2 also shows the incidence of eGFR<60 ml/min per 1.73 m^2 and UACR≥30mg/g, which also did not differ by group.

Mean change (95% CI) in eGFR and UACR at each study visit are shown in Table 3. Overall, there was a statistically significant greater decline in mean eGFR in the vitamin D

Table 1. Baseline characteristics of the Vitamin D and Type 2 Diabetes kidney cohort[a]

Variables	Overall (*n*=2166)	Vitamin D (*n*=1083)	Placebo (*n*=1083)
Characteristic			
Age, years	60±10	60±10	61±10
Women, no. (%)	958 (44)	475 (44)	483 (45)
Race, no. (%)[b]			
Asian	116 (5)	59 (5)	57 (5)
Black or African American	517 (24)	248 (23)	269 (25)
White	1477 (68)	746 (69)	731 (68)
Other	56 (3)	30 (3)	26 (2)
Hispanic or Latino ethnicity, no. (%)[a,b]	199 (9)	109 (10)	90 (8)
Family history of diabetes (first degree relative), no. (%)	1363 (63)	683 (63)	680 (63)
Smoking, no. (%)			
Never	1245 (58)	622 (57)	623 (58)
Former	764 (35)	385 (36)	379 (35)
Current	139 (6)	67 (6)	72 (7)
Unknown or not reported	18 (1)	9 (1)	9 (1)
Dietary supplement use[c]			
Vitamin D			
Participants taking vitamin D supplements, no. (%)	934 (43)	454 (42)	480 (44)
Vitamin D intake among all participants, IU/d[d]	315±399	313±404	318±394
Vitamin D intake among participants using supplements, IU/d	732±255	746±257	718±252
Calcium			
Participants taking calcium supplements, no. (%)	726 (34)	340 (31)	386 (36)
Calcium intake among all participants, mg/d[d]	105±177	102±178	109±177
Calcium intake among participants using supplements, mg/d	315±168	324±170	307±166
Physical activity, total MET hour/week			
Mean ±SD	112±161	110±158	113±165
Median (IQR)	56 (26–128)	60 (26–129)	55 (27–125)
Body mass index, kg/m^2	32±5	32±5	32±4
Body mass index category, kg/m^2, no. (%)			
30 kg/m^2	781 (36)	393 (36)	388 (36)
30–34.9 kg/m^2	808 (37)	410 (38)	398 (37)
≥35 kg/m^2	577 (27)	280 (26)	297 (27)
Systolic BP, mm Hg	128±14	128±13	129±14
Diastolic BP, mm Hg	77±9	77±9	77±10
Hypertension, no. (%)[e]	1703 (79)	850 (79)	853 (79)
Antihypertensive medication use, no. (%)	1133 (52)	555 (51)	578 (53)
Angiotensin II receptor blockers or ACE inhibitors	706 (33)	337 (31)	369 (34)
Other	427 (20)	218 (20)	209 (19)
Prediabetes category, no. (%)[f]			
Met all 3 glycemic criteria (IGT + iA1c + IFG)	775 (36)	384 (36)	391 (36)
Met two glycemic criteria only			
IGT + IFG	136 (6)	69 (6)	67 (6)
IGT + *i*A1c	205 (10)	92 (9)	113 (10)
IFG + *i*A1c	1050 (49)	538 (50)	512 (47)
Laboratory			
Fasting plasma glucose, mg/dl	108±7	108±7	108±8
2-hour post load plasma glucose, mg/dl	138±34	137±34	138±34
Hemoglobin A1c, %	5.9±0.2	5.9±0.2	5.9±0.2
Serum creatinine, mg/dl	0.9±0.2	0.9±0.2	0.9±0.2
eGFR, ml/min per 1.73 m^2			
Mean±SD	87±16	87±15	86±16
Median (IQR)	88 (76–97)	88. (76–98)	87 (75–97)
eGFR category, no. (%)			
≥60 ml/min per 1.73 m^2	2079 (96)	1046 (97)	1033 (95)
<60 ml/min per 1.73 m^2	87 (4)	37 (3)	50 (5)
Urine albumin-to-creatinine ratio, mg/g			
Mean±SD	11±48	11±52	12±4
Median (IQR)	3 (2–7)	3 (2–6)	3 (2–7)
Urine albumin-to-creatinine ratio category, no. (%)			
<30 mg/g	2040 (94)	1028 (95)	1012 (93)
30–300 mg/g	118 (5)	52 (5)	66 (6)
>300 mg/g	8 (0.4)	3 (0.3)	5 (1)
KDIGO classification, no. (%)			
Normal/low risk	1961 (91)	997 (92)	964 (89)
Moderate risk	191 (9)	79 (7)	112 (10)
High risk	12 (1)	5 (1)	7 (1)
Very high risk	2 (0.1)	2 (0.2)	0
Serum 25-hydroxyvitamin D, ng/ml	28.1±10.1	27.8±10.2	28.4±10.1

Table 1. (Continued)

Variables	Overall (n=2166)	Vitamin D (n=1083)	Placebo (n=1083)
Serum 25-hydroxyvitamin D category, no. (%)[g]			
<12 ng/ml	89 (4)	52 (5)	37 (3)
12–19 ng/ml	366 (17)	192 (18)	174 (16)
20–29 ng/ml	779 (36)	401 (37)	378 (35)
≥30 ng/ml	931 (43)	438 (40)	493 (46)

MET, metabolic equivalent of task ; IQR, interquartile range; ACE, angiotensin-converting enzyme; IGT, impaired glucose tolerance; *i*A1c, impaired hemoglobin A1c; IFG, impaired fasting glucose; KDIGO, Kidney Disease: Improving Global Outcomes.
[a]Plus-minus values are mean±SD. Percentages may not add up to 100 because of rounding.
[b]Race and ethnicity were reported by the participant. The category "other" includes American Indian or Alaska Native; Native Hawaiian or other Pacific Islander; or other race. Ethnicity includes any race.
[c]Data on vitamin D and calcium intake are derived from a specific question about use of dietary supplements, including multivitamins.
[d]Value shown is among all participants regardless of whether they reported use of supplements or not.
[e]Hypertension is defined as one of the following: (*1*) self-reported or (2) use of antihypertensive medication or (3) systolic BP ≥130 mm Hg or diastolic BP ≥80 mm Hg.
[f]IFG defined as fasting plasma glucose 100–125 mg/dl (5.6–6.9 mmol/L); IGT defined as 2-hour post load plasma glucose after a 75-g glucose load 140–199 mg/dl (7.8–11.0 mmol/L); or *i*A1c defined as hemoglobin A1c 5.7%–6.4% (39–47 mmol/mol).
[g]Categories of serum 25-hydroxyvitamin D are on the basis of the 2010 Dietary Reference Intakes for calcium and vitamin D recommended by the Food and Nutrition Board of the National Academy of Medicine (31).

group relative to the placebo group (mean difference −1.0 ml/min per 1.73 m^2; 95% CI, −1.4 to −0.6, for vitamin D versus placebo). This decrease in eGFR represented the average change over the full period of follow-up with all postbaseline observations weighted equally. The mean difference in change in UACR between groups was not statistically significant (0.7 mg/g; 95% CI, −1.5 to 2.9). Restricting the analyses to those without imputed numbers showed similar results (Supplemental Table 4).

Subgroup Analyses

Among participants who did not use ACEi/ARB at baseline, the hazard ratio for confirmed KDIGO worsening was 0.76 (95% CI, 0.35 to 1.64) for vitamin D compared with placebo (Supplemental Figure 3). Among those on ACEi/ARB, the hazard ratio for vitamin D versus placebo was 1.05 (95% CI, 0.49 to 2.28). Among participants with baseline serum 25(OH)D level <20 ng/ml, the hazard ratio for confirmed KDIGO worsening was 0.37 (95% CI, 0.10 to 1.30) for vitamin D versus placebo. The *P* value for interaction was not significant for any of the subgroup analyses.

As 43% of the D2d population was taking some form of vitamin D supplementation at baseline, we evaluated mean changes in eGFR and UACR in the subset not taking vitamin D. There was no significant difference in eGFR change from baseline between groups (mean difference −0.3 ml/min per 1.73 m^2; 95% CI, −1.0 to 0.5) (Supplemental Table 5). Mean change from baseline in UACR was 0.4 mg/g (95% CI, −2.0 to 2.9) in the vitamin D group and 4.0 mg/g (95% CI, 1.3 to 6.6) in the placebo group. The between-group difference at the end of 48 months was −3.5 mg/g (95% CI, −7.1 to 0.1).

Throughout the trial, there was a trend for less use of ACEi/ARB in participants on vitamin D compared with placebo (odds ratio, 0.88; 95% CI, 0.75 to 1.03; Supplemental Table 6). After excluding participants who were on ACEi/ARB at baseline and throughout the study, there was no statistically significant difference in eGFR change from baseline between groups (mean difference −0.5; 95% CI, −1.0 to 0.0) (Supplemental Table 7). There also was no statistically significant difference in UACR change from baseline between groups (mean difference −2.1 mg/g; 95% CI, −4.6 to 0.3; Supplemental Table 7).

There were no significant differences in adverse events, including hypercalcemia and nephrolithiasis, during the trial (14).

Table 2. Kidney outcomes in the vitamin D and placebo groups

Kidney Outcomes	Vitamin D No. of events/total No.	Placebo No. of events/total No.	Vitamin D versus Placebo Hazard Ratio (95% CI)
Higher KDIGO risk (confirmed)[a]	28/1083	30/1083	0.89 (0.52 to 1.52)
Higher KDIGO risk (confirmed and unconfirmed)[a,b]	73/1083	70/1083	1.04 (0.73 to 1.48)
eGFR<60 ml/min per 1.73 m^2	74/1046	60/1033	1.22 (0.86 to 1.72)
UACR≥30 mg/g	63/1028	75/1012	0.82 (0.58 to 1.17)

95% CI, 95% confidence interval; KDIGO, Kidney Disease: Improving Global Outcomes; UACR, urine albumin-to-creatinine ratio.
[a]Confirmed higher KDIGO risk was defined as increase by at least one KDIGO risk category from baseline on two consecutive visits.
[b]Unconfirmed higher KDIGO risk was defined as individuals who had worsening in KDIGO risk category at their last study visit only.

Table 3. Changes over time in eGFR and UACR in the vitamin D and placebo groups

Kidney Outcomes	Baseline	Month 3	Month 12	Month 24	Month 36	Month 48	Mean Difference Compared with Baseline (95% CI)[a]
eGFR ml/min per 1.73 m^2 [b]							
Vitamin D group	87±15	85±15	87±16	87±16	88±16	89±16	
No. analyzed	1083	1075	1047	952	589	229	
Difference compared with baseline		−2.2 (−2.7 to −1.6)	−1.0 (−1.5 to −0.4)	−0.52 (−1.1 to 0.1)	−0.3 (−1.1 to 0.4)	−0.2 (−1.6 to 1.3)	−1.0 (−1.3 to −0.7)
Placebo group	86±16	85±16	87±16	87±16	87±16	88±16	
No. analyzed	1083	1072	1049	948	593	228	
Difference compared with baseline		−1.8 (−2.4 to −1.3)	0.2 (−0.3 to 0.8)	0.4 (−0.2 to 1.0)	1.1 (0.4 to 1.9)	1.3 (0.0 to 2.6)	−0.1 (−0.4 to 0.2)
Between-group difference		−0.4 (−1.1 to 0.4)	−1.2 (−2.0 to −0.4)	−1.0 (−1.8 to −0.1)	−1.5 (−2.52 to −0.4)	−1.5 (−3.5 to 0.5)	−1.0 (−1.4 to −0.6)
P value[c]							< 0.01
UACR, mg/g[d]							
Vitamin D group	11±52	NA	12±63	12±44	13±46	14±45	
No. analyzed	1083		1047	952	589	229	
Difference compared with baseline			2.6 (0.1 to 5.2)	2.1 (−0.6 to 4.7)	3.6 (0.3 to 7.0)	3.6 (−1.8 to 9.1)	2.7 (1.2 to 4.3)
Placebo group	12±42	NA	13±65	13±47	15±67	12±35	
No. analyzed	1083		1049	948	593	228	
Difference compared with baseline			0.8 (−1.8 to 3.3)	1.7 (−1.01 to 4.3)	3.8 (0.4 to 7.2)	4.6 (−1.1 to 10.3)	2.0 (0.5 to 3.6)
Between-group difference			1.9 (−1.7 to 5.5)	0.4 (−3.4 to 4.2)	−0.2 (−5.0 to 4.6)	−1.0 (−8.8 to 6.9)	0.7 (−1.5 to 2.9)
P value[c]							0.52

95% CI, 95% confidence interval; UACR, urine albumin-to-creatinine ratio.

[a]Within-group differences over time and *P* values comparing between-group difference were calculated with a mixed model for repeated measures. Between-group difference reflect average change (compared with baseline) over the full period of follow-up.

[b]GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation. Serum creatinine was measured at the local laboratory in real time.

[c]*P* value for the comparison between the unadjusted means for vitamin D versus placebo groups at each follow-up visit is on the basis of the Wilcoxon rank-sums test (because the distributions are skewed).

[d]All time points for UACR for a given participant were analyzed in the same analytic run. UACR was not measured at Month 3.

Discussion

In people with prediabetes, vitamin D_3 supplementation had no significant effect on several kidney outcomes including a composite kidney outcome on the basis of KDIGO risk category, which includes eGFR and UACR measurements. Vitamin D supplementation also appeared to have no benefit when examining eGFR and UACR as separate variables using a continuous scale. There was a statistically significant, albeit clinically less meaningful, decline in eGFR of about 1 ml/min per 1.73 m^2 in the vitamin D group relative to the placebo group. This decrease in eGFR represents the average change over the full period of follow-up with all postbaseline observations weighted equally. Some prior studies have reported a decrease in eGFR with $1,25(OH)_2D$ analogs, such as paricalcitol (28,29), which was speculated to be due to a change in creatinine metabolism rather than a true decline in GFR. Cholecalciferol, however, has not been reported to affect creatinine metabolism. Future studies with vitamin D may want to assess GFR using a non–creatinine-based method.

Although observational studies have reported associations between low circulating 25(OH)D concentration and kidney disease (3–6), few trials have tested for an effect of vitamin D supplementation on kidney outcomes. Recently, the Vitamin D and Omega-3 Trial to Prevent and Treat Diabetic Kidney Disease (VITAL -DKD) study reported that supplementation with 2000 IU/d of vitamin D_3 compared with placebo had no significant effect on eGFR or UACR at 5 years in older persons with established diabetes (30). Similar to our study, the majority of participants had normal kidney function (mean eGFR of 86 ml/min per 1.73 m^2) and sufficient circulating 25(OH)D concentration at baseline by current guidelines (31). Interestingly, in both the VITAL-DKD study and ours, subgroup analyses in those with lower 25(OH)D seem to favor vitamin D intervention. In addition, in the subgroup not taking vitamin D at baseline, there was a trend to lower UACR in those randomized to vitamin D versus placebo. However, in both studies, confidence intervals were wide, and tests for interaction by 25(OH)D level were not significant. Thus, on the basis of both studies, vitamin D_3 supplementation is unlikely to appreciably affect kidney indices in a population with normal kidney function and adequate vitamin D status.

With the caveat that a clinical trial population may not represent the general population, our analysis informs on the prevalence and incidence of kidney dysfunction in a population with high risk for type 2 diabetes, using the modern ADA glucose criteria. In this cohort with over half on antihypertensive medications and about one third on ACEi/ARB, only 4% had kidney disease to begin with, defined as eGFR<60 ml/min per 1.73 m^2, and 6% had UACR 30 mg/g or greater. These proportions are somewhat lower than persons with prediabetes in NHANES diagnosed on the basis of either an elevated fasting glucose or hemoglobin A1c (32). In NHANES (survey periods 2011–2014), 5% had eGFR<60 ml/min per 1.73 m^2, and 8% had UACR 30 mg/g or greater. The prevalence of microalbuminuria is similar to the Diabetes Prevention Program (DPP) cohort who were selected on the basis of high 2-hour glucose during an oral glucose tolerance test. In DPP, a similar proportion (6%) to the D2d study had UACR≥30 mg/g, with less than 10% of the DPP cohort using ACEi or ARBs (33). Trial results, however, may not be generalizable to real-word settings.

Few studies have reported on incident kidney disease in the prediabetes population, and most have used fasting glucose to define prediabetes (34,35). In the current trial, 6% of individuals developed eGFR<60 ml/min per 1.73 m^2 and 7% developed UACR>30 mg/g after a median follow up of 2.9 years. Comparable populations reporting both eGFR and UACR were not found in the literature; thus, our analysis provides important information on the natural progression of kidney function in prediabetes.

The present analysis retains the strengths of the parent trial, including use of the gold standard assay for 25(OH)D, use of the latest ADA glycemic criteria to define prediabetes, and ascertainment of kidney function at yearly intervals. One study limitation is that although kidney outcomes were prespecified in the analytic plan, the trial was not designed for kidney outcomes and participants were not selected to be at particularly high risk for kidney disease. In addition, trial duration was relatively short and neither vitamin D nor placebo groups displayed clinically meaningful progression in kidney parameters. Although the vitamin D and placebo groups were well balanced, there also were some baseline differences in kidney indices and use of renin-angiotensin system inhibitors, which may have shifted the comparison between vitamin D and placebo toward null. Finally, participants were not selected on the basis of vitamin D status and, as a result, the cohort would be considered as having sufficient vitamin D status by current recommendations (31). Of interest, among participants not taking vitamin D at baseline, vitamin D supplementation lowered UACR compared with placebo.

In conclusion, the D2d study—the largest vitamin D diabetes prevention trial—showed no significant benefit of vitamin D_3 supplementation on kidney disease progression in individuals with high-risk prediabetes but low baseline risk for adverse kidney outcomes. As participants were not selected on the basis of baseline 25(OH)D concentrations, we cannot exclude a kidney benefit for those individuals with vitamin D deficiency.

Disclosures

R. Chatterjee has received research funding from Bristol Myers Squibb, Epigenomics, and Verily. S. Kashyap has served as a consultant for Fractyl Inc. and GI Dynamics, and has additionally received honoraria from GI Dynamics. S. Kim is an advisor for GI Dynamics and has received funding from Bayer. R. Pratley reports employment with AdventHealth Translational Research Institute. R. Pratley has served as a consultant for AstraZeneca, Glytec LLC, Janssen, Merck, Mundipharma, Novo Nordisk, Pfizer, Sanofi, Scohia Pharma Inc., and Sun Pharmaceutical Industries; except for services for Sanofi US Services Inc. on 2/12/2018 and 6/25/2018 (which were paid to R. Pratley personally), all payments are made directly to his employer (AdventHealth). R. Pratley has received research grants from Hanmi Pharmaceutical Co., Janssen, Metavention, Novo Nordisk, Poxel SA, and Sanofi; all payments are made directly to his employer (AdventHealth). He has also acted as a speaker for Merck and Novo Nordisk; all payments are made directly to his employer (AdventHealth). N. Rasouli has received research grants from Lilly and Novo Nordisk and has served as a consultant for Novo Nordisk. All payments are made directly to her employer (University of Colorado). M. Sarnak has acted as a consultant for Cardurian and as a steering committee

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Research idea and study design: Dr. Sun H. Kim and Dr. Anastassios G. Pittas. Data acquisition: Dr. Sun H. Kim, Dr. Irwin G. Brodsky, Dr. Ranee Chatterjee, Dr. Sangeeta R. Kashyap, Dr. Emilia Liao, Dr. Richard Pratley, Dr. Neda Rasouli, Dr. Anastassios G. Pittas, and Ms. Ellen M. Vickery. Data analysis/interpretation: Dr. Sun H. Kim, Dr. Irwin G. Brodsky, Dr. Ranee Chatterjee, Dr. Sangeeta R. Kashyap, Dr. William C. Knowler, Dr. Emilia Liao, Dr. Richard Pratley, Dr. Neda Rasouli, and Dr. Anastassios G. Pittas. Statistical analysis: Mr. Jason Nelson. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

Data Sharing Statement

Datasets generated and/or analyzed during this study and the associated data dictionary are not publicly available but are available from the D2d Coordinating Center at Tufts Medical Center on reasonable request after acceptance for publication through December of 2025. Protocol synopsis, contact details, publications, and the process for collaboration and data requests can be found on the website (d2dstudy.org).

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.00420121/-/DCSupplemental.

Supplemental Table 1: Inclusion and exclusion criteria.

Supplemental Table 2: Methods of creatinine measurement by site.

Supplemental Table 3: Baseline characteristics of the D2d cohort and kidney cohort.

Supplemental Table 4: Changes over time in eGFR and UACR in the vitamin D and placebo groups using available data without imputation.

Supplemental Table 5: Changes over time in eGFR and UACR in the vitamin D and placebo groups among participants not taking vitamin D supplements at baseline.

Supplemental Table 6: Changes over time in antihypertensive medication use.

Supplemental Table 7: Changes over time in eGFR and UACR in vitamin D and placebo groups not taking ACEi/ARB at any time during the trial.

Supplemental Figure 1: KDIGO risk classification.

Supplemental Figure 2: Participant flow.

Supplemental Figure 3: Subgroup analyses for the primary outcome of confirmed KDIGO worsening.

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* The D2d Research Group collaborators are Anastassios G. Pittas, Irwin Brodsky, Lisa Ceglia, Chhavi Chadha, Ranee Chatterjee, Bess Dawson-Hughes, Cyrus Desouza, Rowena Dolor, John Foreyt, Adline Ghazi, Daniel S. Hsia, Karen C. Johnson, Sangeeta R. Kashyap, Sun Kim, MD, Erin S. LeBlanc, Michael R. Lewis, Emilia Liao, Saul Malozowski, Lisa M. Neff, Patrick O'Neil, PhD, Jean Park, Anne Peters, Lawrence S. Phillips, Richard Pratley, Philip Raskin, Neda Rasouli, David Robbins, MD, Clifford Rosen, Vanita R. Aroda, Patricia Sheehan, Myrlene A. Staten, and William C. Knowler.

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AFFILIATIONS

[1]Division of Endocrinology, Gerontology and Metabolism, Department of Medicine, Stanford University School of Medicine, Stanford, California
[2]Endocrinology and Diabetes Center, Maine Medical Center, and Maine Medical Center Research Institute, Scarborough, Maine
[3]Department of Medicine, Duke University, Durham, North Carolina
[4]Department of Endocrinology, Diabetes, and Metabolism, Cleveland Clinic, Cleveland, Ohio
[5]Diabetes Epidemiology and Clinical Research Section, National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, Arizona
[6]Division of Endocrinology and Metabolism, Northwell Health Lenox Hill Hospital, New York, New York
[7]Tufts Clinical and Translational Science Institute, Biostatistics, Epidemiology, and Research Design Center, Tufts Medical Center, Boston, Massachusetts
[8]AdventHealth Translational Research Institute, Orlando, Florida
[9]Division of Endocrinology, Metabolism and Diabetes, University of Colorado, School of Medicine and Veterans Affairs Eastern Colorado Health Care System, Aurora, Colorado
[10]Division of Endocrinology, Diabetes and Metabolism, Tufts Medical Center, Boston, Massachusetts
[11]Division of Nephrology, Tufts Medical Center, Boston, Massachusetts

Vitamin D and type 2 diabetes

Effect of Vitamin D Supplementation on Kidney Function in Adults with Prediabetes: A Secondary Analysis of a Randomized Trial

SUPPLEMENT

Supplemental Table 1: Inclusion and exclusion criteria

Inclusion Criteria

1. Pre-diabetes ("at increased risk for diabetes") defined by meeting 2-out-of-3 of the following glycemic criteria, established by the ADA in the 2010 clinical practice guidelines, at the baseline visit:
    a. FPG 100-125 mg/dL, inclusive
    b. 2hPG 140-199 mg/dL, inclusive
    c. HbA1c 5.7-6.4%, inclusive
2. Age ≥ 30 years (≥25 years for people of the following races: American-Indian, Alaska Native, Native Hawaiian or Other Pacific Islander).
3. BMI ≥ 24.0 (22.5 for Asians) and ≤ 42.0 kg/m^2
4. Provision of signed and dated written informed consent prior to any study procedures.

Exclusion Criteria

Exclusion Criteria were selected to: (1) ensure participants' safety; (2) avoid conditions that would affect the outcomes (i.e. minimize competing risk); (3) make recruitment targets realistic; (4) amplify generalizability of study results; (5) maximize participants' adherence with study procedures.

5. Diabetes based on either of the following criteria:
    a. History (past 1 year) of hypoglycemic pharmacotherapy (oral or injectable medication approved by the FDA for type 2 diabetes) used for any condition (e.g. pre-diabetes, diabetes, polycystic ovarian syndrome).
    b. Meeting a glycemic criterion for diabetes, as defined by the ADA guidelines (FPG ≥ 126 mg/dL, 2hPG ≥ 200 mg/dL or HbA1c ≥ 6.5%) at the baseline visit.
6. History (past 3 years) of hyperparathyroidism, symptomatic or asymptomatic (i.e., radiographic) nephrolithiasis or hypercalcemia. [Safety]
7. Any medical condition (past 3 years) that in the opinion of the site investigator may increase risk for nephrolithiasis or hypercalcemia during the trial (e.g. sarcoidosis). [Safety]
8. Use of tanning devices within 12 weeks of the baseline visit and unwilling to stop using tanning devices for the duration of the study [interference with intervention]

Medications and Supplements

9. Use of supplements containing vitamin D at total doses higher than 1000 IU/day within 8-12 weeks (depending on dose, as described in Manual of Operations) of the baseline visit initiating the protocol and unwillingness to limit vitamin D supplementation dosage to no higher than 1000 IU/day for the duration of the study. [Safety]
10. Use of supplements containing calcium at total doses higher than 600 mg/day within 1 week of the baseline visit initiating the protocol and unwillingness to limit calcium supplementation dosage to no more than 600 mg/day for the duration of the study. [Safety]
11. Current use of medications or conditions (e.g. untreated celiac disease) that would interfere with absorption or metabolism of vitamin D.
12. Current use of medications approved by the FDA for weight management.
13. Use of thiazide diuretics at a total dose greater than 37.5 mg/day.
14. Use of anticonvulsant drug started within 6 months of screening. Stable regimen of anticonvulsants is allowed.
15. History of intolerance to vitamin D supplements. [Safety]

Other Medical History

16. Severe symptomatic cardiovascular disease based on history and physical examination (unstable angina, dyspnea on exertion, paroxysmal nocturnal dyspnea, arrhythmia, congestive heart failure NYHA class II or higher, claudication).
17. History (past 1 year) of myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft. [Safety]
18. History (past 1 year) of cerebrovascular disease (stroke, transient ischemic attack). [Safety]
19. Any type of cancer (past 5 years) except for basal cell skin cancer. [Safety] Participants with prostate cancer (for men over age 55) or well-differentiated thyroid cancer that are not expected to require treatment (except for suppression with thyroid hormone) over the next 4 years are not excluded. Volunteers with history of squamous cell cancer of the skin, which was completely excised and with no evidence of metastases, are eligible.
20. History (past 6 months) of treatment with oral (for > 7 days) or intravenous glucocorticoids or disease likely to require oral or intravenous glucocorticoid therapy during the study). [Interference with outcome assessment] Inhaled glucocorticoid use in not an exclusion. Epidural or intraarticular glucocorticoid injections are not exclusions but study visits need to be conducted at least a week after the injection. Persons with adrenal insufficiency treated with physiologic doses of glucocorticoids who are otherwise stable are not excluded.
21. History (past 1 year) of substance abuse or unstable psychiatric disorder that in the opinion of the site investigator would impede competence or adherence with study procedures or hinder completion of the study or increase risk. [Safety, adherence] Use of marijuana with a medical prescription is permitted.
22. History of bariatric surgery (e.g., Roux-en-Y gastric bypass, gastric sleeve) or planned bariatric surgery in the next 4 years. Participants with gastric banding more than 2 years ago with self-reported weight stability (defined as weight change no greater than 3 kg during the prior 6 months) are not excluded. [Interfere with vitamin D absorption]
23. A life-threatening event within 30 days of screening or currently planned major surgery.
24. Any other unstable active medical condition (including but not limited to liver disease, wasting illness, AIDS, tuberculosis, oxygen-dependent chronic obstructive pulmonary disease, organ transplant, Cushing's syndrome) that in the opinion of the site investigators would impede competence or adherence with study procedures or increase risk. [Safety, adherence, plasma 25OHD may decrease as an acute-phase response] Such conditions will be assessed based on self-report and/or review of medical records (if available).
25. Uncontrolled hypertension (systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg). [Safety]
26. Poor venous access. [Safety]

Laboratory Evaluation

27. Serum liver transaminase (ALT or AST) higher than 3 times the normal range for the clinical site's laboratory [Safety]
28. Anemia (hematocrit < 32 for women, < 36 for men), whole blood transfusion (within 6 months of screening) or chronic requirement, whole blood donation (within 3 months of screening) or other condition (hemolysis, hemoglobinopathy) rendering HbA1c results unreliable as indicator of chronic glycemia. [Interference with outcome assessment] Participants who donate platelets are not excluded. Whole blood transfusion or donation does not exclude participant, but screening and study visits need to be timed appropriately.

29. Low platelet count (< 50,000). [Safety for blood draws]
30. Chronic kidney disease, defined as estimated glomerular filtration rate [GFR] < 50 mL/min, from creatinine measured at the clinical site's laboratory and GFR calculated centrally. [Vitamin D homeostasis changes as GFR declines. These changes start when GFR falls around 40-60 mL/min per 1.73 m2. The planning committee selected 50 mL/min as the exclusion cutoff to ensure that participants maintain GFR > 40 mL/min during the study] Please note: to prevent potential confusion, GFR units will be denoted as mL/min throughout the protocol and associated documents.
31. Hypercalcemia, defined as serum calcium concentration greater than or equal to the upper limit of normal, measured at the clinical site's laboratory. [Safety]
32. Hypercalciuria, defined as spot urine (morning void) calcium-creatinine ratio > 0.275.258 [Safety]

Other

33. Participation (within 30 days of screening) in another interventional research study. [Conflict, "contamination"]
34. Previous randomization in the D2d study. Participants who did not qualify after screening may be screened again if the prior reason for exclusion has been addressed (e.g. high blood pressure is treated).
35. Any other reason that in the opinion of the site investigator would impede adherence with study procedures or hinder completion of the study or increase risk (e.g. use of non-approved or experimental drugs, inability to follow instructions or understand the informed consent, dementia, unable to remain in the program for the duration of the study, inability to comply with the study protocol for any reason). [Safety, adherence]

Women only

36. Pregnancy (past 1 year by report or positive pregnancy test at screening), intent to become pregnant in the next 4 years or unprotected intercourse. [Safety] History of gestational diabetes is not an exclusion criterion.
37. Currently breastfeeding. [Safety]
38. Use of oral contraceptives or menopausal hormone therapy started within 3 months of baseline. Stable regimen of oral contraceptives or any other hormonal method of contraception (e.g. implantable) is allowed. [Safety, interference with intervention]

Supplemental Table 2: Methods of creatinine measurement by site

Site	Site Name	Method	Method traceable to isotope dilution mass spectrometry? If not, please indicate other standardization method
1	Maine Medical Center Research Institute	Enzymatic	Yes, traceable to IDMS
2	Tufts Medical Center	Kinetic alkaline picrate (Jaffe Reaction)	Yes, traceable to IDMS
3	MedStar Health Research Institute	Enzymatic	Yes, traceable to IDMS
4	Duke University Medical Center	Kinetic alkaline picrate (Jaffe Reaction)	Yes, traceable to IDMS
5	Medical University of South Carolina	Kinetic alkaline picrate (Jaffe Reaction)	Yes, traceable to IDMS
6	Florida Hospital Translational Research	Enzymatic	Yes, traceable to IDMS
7	Atlanta VA Medical Center	Enzymatic	Yes, traceable to IDMS
8	Beth Israel Medical Center	Kinetic alkaline picrate (Jaffe Reaction)	Yes, traceable to IDMS
9	Northwestern University	Kinetic alkaline picrate (Jaffe Reaction)	Yes, traceable to IDMS
10	University of Tennessee Health Science Center	Enzymatic	Yes, traceable to IDMS
12	Pennington Biomedical Research Center	Kinetic alkaline picrate (Jaffe Reaction)	Yes, traceable to IDMS
13	HealthPartners Research Foundation	Enzymatic	Yes, the ARCHITECT Enzymatic Creatinine assay is calibrated with IDMS standardized calibrator, NIST SRM 967.
14	University of Kansas Medical Center	Kinetic alkaline picrate (Jaffe Reaction)	Yes, this method has been standardized against IDMS. For the USA, this method has been standardized against a primary reference material (SRM 914 and SRM 967 (ID/MS)
15	Baylor College of Medicine	Kinetic alkaline picrate (Jaffe Reaction)	Yes, traceable to IDMS
16	University of Nebraska Medical Center	Kinetic alkaline picrate (Jaffe Reaction)	Yes, traceable to IDMS
17	University of Texas Southwestern Medical Center	Enzymatic	Yes, traceable to IDMS
19	University of Southern California	Kinetic alkaline picrate (Jaffe Reaction)	Yes, traceable to IDMS
20	Stanford University Medical Center	Enzymatic	Yes, traceable to IDMS

21	Omaha VA Medical Center	Enzymatic	Yes, traceable to IDMS
22	MedStar Good Samaritan Hospital	Enzymatic	Yes, traceable to IDMS
23	Kaiser Permanente Center for Health Research	Enzymatic	Yes, traceable to IDMS
24	Cleveland Clinic	Enzymatic	Yes, traceable to IDMS
25	University of Colorado School of Medicine	Kinetic alkaline picrate (Jaffe Reaction)	Yes, traceable to IDMS
29	Lenox Hill Hospital	Rate-blanked colorimetric assay based on the Jaffe method	Yes, traceable to IDMS

Supplemental Table 3: Baseline characteristics of the D2d cohort and kidney cohort

Characteristic	Overall D2d (n=2,423)	Kidney cohort (n=2,166)
Age, years	60 ± 10	60 ± 10
Women, no. (%)	1086 (45)	958 (44)
Race, no. (%) [2]		
Asian	130 (5)	116 (5)
Black or African American	616 (25)	517 (24)
White	1616 (67)	1477 (68)
Other	61 (3)	56 (3)
Hispanic or Latino Ethnicity, no. (%) [2]	225 (9)	199 (9)
Family history of diabetes (first degree relative), no. (%)	1514 (63)	1363 (63)
Smoking, no. (%)		
Never	1410 (58)	1245 (58)
Former	838 (35)	764 (35)
Current	155 (6)	139 (6)
Unknown or Not reported	20 (1)	18 (1)
Dietary supplement use [3]		
Vitamin D		
Participants taking vitamin D supplements, no. (%)	1037 (43)	934 (43)
Vitamin D intake among all participants, IU/day [4]	313 ± 398	315 ± 399
Vitamin D intake among participants using supplements, IU/day	732 ± 254	732 ± 255
Calcium		
Participants taking calcium supplements, no. (%)	804 (33)	726 (34)
Calcium intake among all participants, mg/day [4]	103 ± 176	105 ± 177
Calcium intake among participants using supplements, mg/day	312 ± 167	315 ± 168
Physical activity, total MET hour/week		
Mean ± SD	110 ± 159	112 ± 161
Median (IQR)	56 (26-126)	56 (26-128)
Body-mass index, kg/m^2	32 ± 5	32 ± 5
Body-mass index category, kg/m^2, no. (%)		
<30 kg/m^2	864 (36)	781 (36)
30 to 34.9 kg/m^2	912 (38)	808 (37)
≥ 35 kg/m^2	647 (27)	577 (27)
Systolic blood pressure, mmHg	128 ± 13	128 ± 14
Diastolic blood pressure, mmHg	77 ± 9	77 ± 9
Hypertension, no. (%) [5]	1883 (78)	1689 (78.)
Anti-hypertensive medication use, no. (%)	1263 (52)	1133 (52)
Angiotensin II receptor blockers or ACE inhibitors	787 (33)	706 (33)
Other	476 (20)	427 (20)
Pre-diabetes category, no. (%)		
Met all 3 glycemic criteria (IGT + *i*A1c + IFG) [6]	856 (35)	775 (36)
Met two glycemic criteria only		

IGT + IFG	152 (6)	136 (6)
IGT + *i*A1c	231 (10)	205 (10)
IFG + *i*A1c	1184 (49)	1050 (49)
Laboratory		
Fasting plasma glucose (FPG), mg/dL	108 ± 7	108 ± 7
2-hour post-load plasma glucose (2hPG), mg/dL	137 ± 34	138 ± 34
Hemoglobin A1c, %	5.9 ± 0.2	5.9 ± 0.2
Serum creatinine, mg/dL	0.9 ± 0.2	0.9 ± 0.2
Estimated glomerular filtration rate (eGFR), mL/min/1.73m^2		
Mean ± SD	87 ± 16	87 ± 16
Median (IQR)	88 (76-98)	88 (76-97)
Estimated glomerular filtration rate (eGFR) category, no. (%)		
≥60 mL/min/1.73m^2	2328 (96)	2079 (96)
<60 mL/min/1.73m^2	95 (4)	87 (4)
Urine albumin creatinine ratio, mg/g	*Not available*	
Mean ± SD		11 ± 48
Median (IQR)		3 (2-7)
Urine albumin creatinine ratio category, no. (%)	*Not available*	
<30 mg/g		2040 (94)
30 to 300 mg/g		118 (5)
>300 mg/g		8 (0.4)
KDIGO classification, no. (%)	*Not available*	
Normal or low risk		1961 (91)
Moderate risk		191 (9)
High risk		12 (0.6)
Very high risk		2 (0.1)
Serum 25-hydroxyvitamin D, ng/mL	28.0 ± 10.2	28.1 ± 10.1
Serum 25-hydroxyvitamin D category, no. (%) [7]		
< 12 ng/mL	103 (4)	89 (4)
12 to 19 ng/mL	422 (17)	366 (17)
20 to 29 ng/mL	876 (36)	779 (36)
≥ 30 ng/mL	1021 (42)	931 (43)

[1] Plus-minus values are means±SD. Percentages may not add up to 100 because of rounding.

[2] Race and ethnicity were reported by the participant. The category "other" includes American Indian or Alaska Native; Native Hawaiian or other Pacific Islander; or other race. Ethnicity includes any race.

[3] Data on vitamin D and calcium intake are derived from a specific question about use of dietary supplements, including multivitamins.

[4] Value shown is among all participants regardless of whether they reported use of supplements or not.

[5] Hypertension is defined as one of the following: (1) self-reported or (2) use of anti-hypertensive medication or (3) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg.

[6] IFG, impaired fasting glucose defined as fasting plasma glucose 100–125 mg per deciliter (5.6–6.9 mmol/L); IGT, impaired glucose tolerance defined as 2-hour post-load plasma glucose after a 75-gram glucose load 140–199 mg/dL (7.8–11.0 mmol/L) or; *i*A1c, impaired A1c defined as HbA1c 5.7–6.4% (39–47 mmol/mol)

[7] Categories of serum 25-hydroxyvitamin D are based on the 2010 Dietary Reference Intakes for calcium and vitamin D recommended by the Food and Nutrition Board of the National Academy of Medicine.[32]

Supplemental Table 4: Changes over time in eGFR and UACR in the vitamin D and placebo groups using available data without imputation

	Baseline	Month 3	Month 12	Month 24	Month 36	Month 48	Mean difference compared to baseline (95% CI) [1]
eGFR [2]							
Vitamin D group	87 ± 15	85 ± 15	86 ± 16	87 ± 16	88 ± 16	89 ± 17	
No. analyzed	1083	1048	997	865	519	193	
difference compared to baseline (95% CI)		-2.2 (-2.7, -1.6)	-0.9 (-1.4, -0.3)	-0.5 (-1.1, 0.1)	-0.3 (-1.1, 0.5)	-0.1 (-1.4, 1.2)	-1.0 (-1.3, -0.7)
Placebo group	87 ± 16	85 ± 16	86 ± 16	86 ± 16	87 ± 16	88 ± 16	
No. analyzed	1083	1045	1000	869	523	198	
difference compared to baseline (95% CI)		-1.8 (-2.4, -1.3)	0.2 (-0.4, 0.7)	0.4 (-0.2, 1)	1.1 (0.3, 1.9)	1.3 (0.1, 2.6)	-0.2 (-0.5, 0.2)
Between group difference		-0.4 (-1.1, 0.4)	-1.0 (-1.8, -0.2)	-0.9 (-1.8, -0.0)	-1.4 (-2.6, -0.3)	-1.4 (-3.2, 0.4)	-0.9 (-1.3, -0.5)
P value [3]							<0.01
UACR [4]							
Vitamin D group	11 ± 52	NA	13 ± 64	12 ± 45	13 ± 48	14 ± 47	
No. analyzed	1083		1005	885	536	209	
difference compared to baseline (95% CI)			2.8 (0.2, 5.5)	2.1 (-0.7, 4.9)	3.6 (0.0, 7.2)	3.7 (-2.1, 9.5)	2.8 (1.2, 4.4)
Placebo group	12 ± 42	NA	12.6 ± 65.8	13 ± 48	15 ± 70	12 ± 35	
No. analyzed	1083		1010	891	537	207	
difference compared to baseline (95% CI)			1.0 (-1.6, 3.6)	1.8 (-1.0, 4.6)	3.8 (0.2, 7.5)	4.6 (-1.2, 10.4)	2.1 (0.5, 3.8)
Between group difference			1.8 (-1.9, 5.5)	0.3 (-3.7, 4.3)	-0.2 (-5.3, 4.9)	-0.9 (-9.1, 7.3)	0.7 (-1.6, 3.0)
P value [3]							0.56

Plus-minus values are means±SD.

[1] Within-group differences over time and P values comparing between-group difference were calculated with a mixed model for repeated measures. Between group difference reflect average change (compared to baseline) over the full period of follow-up.

[2] Glomerular Filtration Rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Serum creatinine was measured at the local laboratory in real-time.

[3] P-value for the comparison between the unadjusted means for vitamin D vs. placebo groups at each follow-up visit is based on the Wilcoxon rank-sums test (because the distributions are skewed).

[4] All timepoints for UACR for a given participant were analyzed in the same analytical run. UACR was not measured at Month 3.

Supplemental Table 5: Changes over time in eGFR and UACR in the vitamin D and placebo groups among participant not taking vitamin D supplements at baseline

	Baseline	Month 3	Month 12	Month 24	Month 36	Month 48	Mean difference compared to baseline (95% CI) [1]
eGFR [2]							
Vitamin D group	89 ± 16	87 ± 16	89 ± 16	90 ± 16	90 ± 16	92 ± 16	
No. analyzed	629	446	417	369	231	103	
difference compared to baseline (95% CI)		-2.5 (-3.4, -1.6)	-1.3 (-2.3, -0.4)	-0.1 (-1.1, 1.0)	-0.2 (-1.6, 1.1)	0.6 (-1.4, 2.6)	-1.1 (-1.6, -0.6)
Placebo group	88 ± 16	87 ± 16	89 ± 16	88 ± 16	90 ± 17	89 ± 17	
No. analyzed	603	404	379	313	188	76	
difference compared to baseline (95% CI)		-2.3 (-3.3, -1.4)	-0.5 (-1.5, 0.5)	-0.3 (-1.4, 0.8)	0.6 (-0.8, 2.0)	-0.3 (-2.5, 1.9)	-0.8 (-1.4, -0.3)
Between group difference		-0.2 (-1.5, 1.1)	-0.8 (-2.2, 0.5)	0.2 (-1.3, 1.7)	-0.8 (-2.7, 1.1)	0.9 (-2.1, 4.0)	-0.3 (-1.0, 0.5)
P value [3]							0.48
UACR [4]							
Vitamin D group	12 ± 64	NA	9 ± 27	8 ± 19	8 ± 18	10 ± 19	
No. analyzed	629		417	369	231	103	
difference compared to baseline (95% CI)			1.2 (-2.8, 5.1)	-0.2 (-4.4, 4.0)	-0.7 (-6.1, 4.7)	2.1 (-6.0, 10.2)	0.4 (-2.0, 2.9)
Placebo group	13 ± 48	NA	15 ± 98	16 ± 67	15 ± 80	7 ± 9	
No. analyzed	603		379	313	188	76	
difference compared to baseline (95% CI)			4.1 (-0.0, 8.3)	4.4 (-0.3, 9.0)	3.9 (-2.1, 9.8)	1.5 (-7.8, 10.8)	4.0 (1.3, 6.6)
Between group difference			-3.0 (-8.8, 2.8)	-4.6 (-10.9, 1.7)	-4.6 (-12.6, 3.5)	0.7 (-11.7, 13.0)	-3.5 (-7.1, 0.1)
P value [3]							0.05

Plus-minus values are means±SD.

[1] Within-group differences over time and P values comparing between-group difference were calculated with a mixed model for repeated measures. Between group difference reflect average change (compared to baseline) over the full period of follow-up.

[2] Glomerular Filtration Rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Serum creatinine was measured at the local laboratory in real-time.

[3] P-value for the comparison between the unadjusted means for vitamin D vs. placebo groups at each follow-up visit is based on the Wilcoxon rank-sums test (because the distributions are skewed).

[4] All timepoints for UACR for a given participant were analyzed in the same analytical run. UACR was not measured at Month 3.

Supplemental Table 6: Changes over time in anti-hypertensive medication use

	Baseline	Month 3	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48	No. (%) of participants using *Odds ratio (95% CI)*
Any anti-hypertensive medication, n (%)											*0.9 (0.8 to 1.0)*
Vitamin D group	555 (51)	556 (52)	558 (53)	557 (54)	559 (55)	527 (57)	430 (57)	328 (57)	211 (52)	122 (53)	629 (58)
Placebo group	578 (53)	580 (55)	585 (56)	589 (57)	593 (58)	560 (60)	459 (61)	360 (62)	237 (63)	133 (59)	671 (62)
P value for proportions	0.32	0.25	0.19	0.14	0.13	0.10	0.15	0.10	< 0.01	0.19	0.07
Angiotensin II receptor blockers or ACE inhibitors, n (%)											*0.9 (0.8 to 1.0)*
Vitamin D group	337 (31)	341 (32)	341 (32)	348 (34)	361 (36)	329 (35)	275 (36)	202 (35)	126 (31)	68 (29)	412 (38)
Placebo group	369 (34)	371 (35)	377 (36)	375 (36)	383 (38)	361 (39)	300 (40)	239 (41)	151 (40)	85 (38)	450 (42)
P value for proportions	0.14	0.15	0.08	0.20	0.31	0.11	0.20	0.04	0.01	0.06	0.10
Any diabetes medication, n (%)											*1.1 (0.8 to 1.6)*
Vitamin D group	3 (0.3)	2 (0.2)	8 (1)	26 (3)	41 (4)	47 (5)	48 (6)	47 (8)	30 (7)	25 (11)	75 (7)
Placebo group	0 (0)	1 (0.1)	1 (0.1)	12 (1)	28 (3)	41 (4)	52 (7)	48 (8)	30 (8)	12 (5)	83 (8)
P value for proportions	-	0.57	0.02	0.02	0.11	0.53	0.69	0.97	0.80	0.03	0.51

Supplemental Table 7: Changes over time in eGFR and UACR in vitamin D and placebo groups not taking ACEi/ARB at any time during the trial

	Baseline	Month 3	Month 12	Month 24	Month 36	Month 48	Mean difference compared to baseline (95% CI) [1]
eGFR [2]							
Vitamin D group	89 ± 15	87 ± 15	88 ± 16	89 ± 16	89 ± 16	90 ± 15	-0.9 (-1.3 to -0.5)
No. analyzed	667	660	644	580	359	149	
difference compared to baseline		-2.1 (-2.8, -1.4)	-0.9 (-1.6, -0.2)	-0.2 (-1.0, 0.6)	-0.4 (-1.5, 0.6)	0.5 (-1.1, 2.0)	
Placebo group	88 ± 16	86 ± 16	88 ± 16	87 ± 16	88 ± 16	89 ± 16	-0.4 (-0.8 to 0.0)
No. analyzed	627	619	603	536	329	132	
difference compared to baseline		-2.1 (-2.8, -1.4)	-0.2 (-1.0, 0.5)	0.2 (-0.6, 1.0)	1.1 (0.0, 2.2)	0.3 (-1.3, 2)	
Between group difference		0.0 (-1.0, 1.0)	-0.7 (-1., 0.4)	-0.4 (-1.5, 0.7)	-1.54 (-2.9, -0.2)	0.12 (-2.2, 2.5)	-0.5 (-1.0 to 0.0)
P value [3]							0.07
UACR [4]							
Vitamin D group	10 ± 58	NA	8 ± 19	8 ± 19	9 ± 24	10 ± 17	0.5 (-1.1 to 2.2)
No. analyzed	667		644	580	359	149	
difference compared to baseline			0.27 (-2.5, 3)	0.16 (-2.7, 3.0)	0.9 (-2.8, 4.6)	2.26 (-3.5, 8)	
Placebo group	10 ± 43	NA	12 ± 79	13 ± 55	19 ± 87	6 ± 8	2.7 (0.9 to 4.4)
No. analyzed	627		603	536	329	132	
difference compared to baseline			1.91 (-0.9, 4.8)	2.34 (-0.7, 5.4)	5.25 (1.4, 9.1)	1.01 (-5.0, 7.0)	
Between group difference			-1.6 (-5.6, 2.3)	-2.2 (-6.4, 2)	-4.4 (-9.7, 1.0)	1.3 (-7.1, 9.6)	-2.1 (-4.6 to 0.3)
P value [3]							0.08

Plus-minus values are means±SD.

[1] Within-group differences over time and P values comparing between-group difference were calculated with a mixed model for repeated measures. Between group difference reflect average change (compared to baseline) over the full period of follow-up.

[2] Glomerular Filtration Rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Serum creatinine was measured at the local laboratory in real-time.

[3] P-value for the comparison between the unadjusted means for vitamin D vs. placebo groups at each follow-up visit is based on the Wilcoxon rank-sums test (because the distributions are skewed).

[4] All timepoints for UACR for a given participant were analyzed in the same analytical run. UACR was not measured at Month 3.

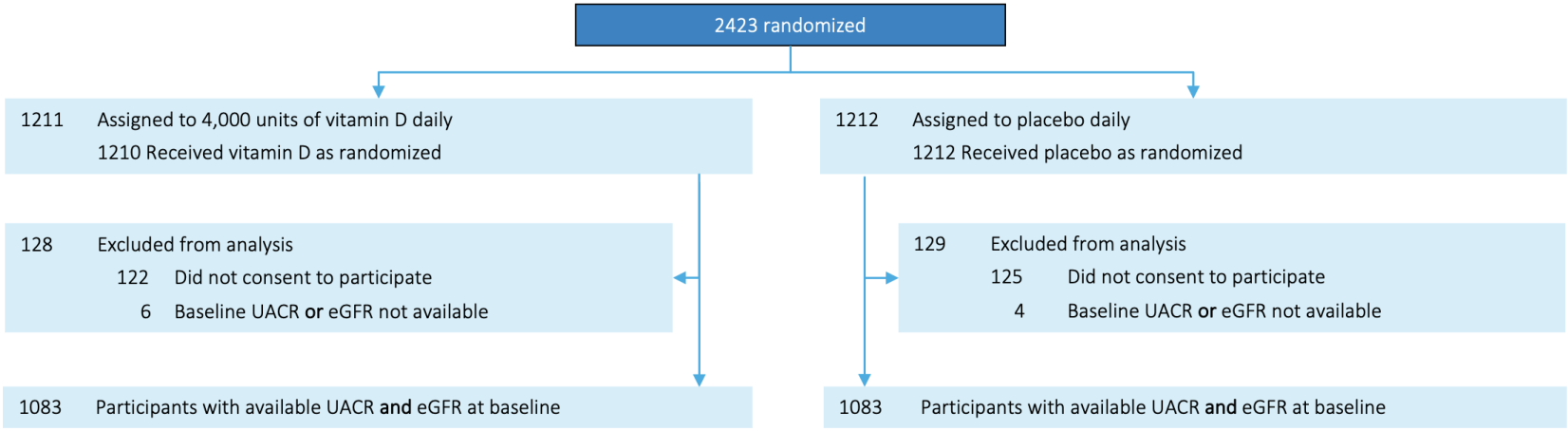
Supplemental Figure 1: KDIGO risk classification

Adapted from the Executive Summary and Glossary from a Kidney Disease: Improving global Outcomes (KDIGO) Consensus Conference.[19]

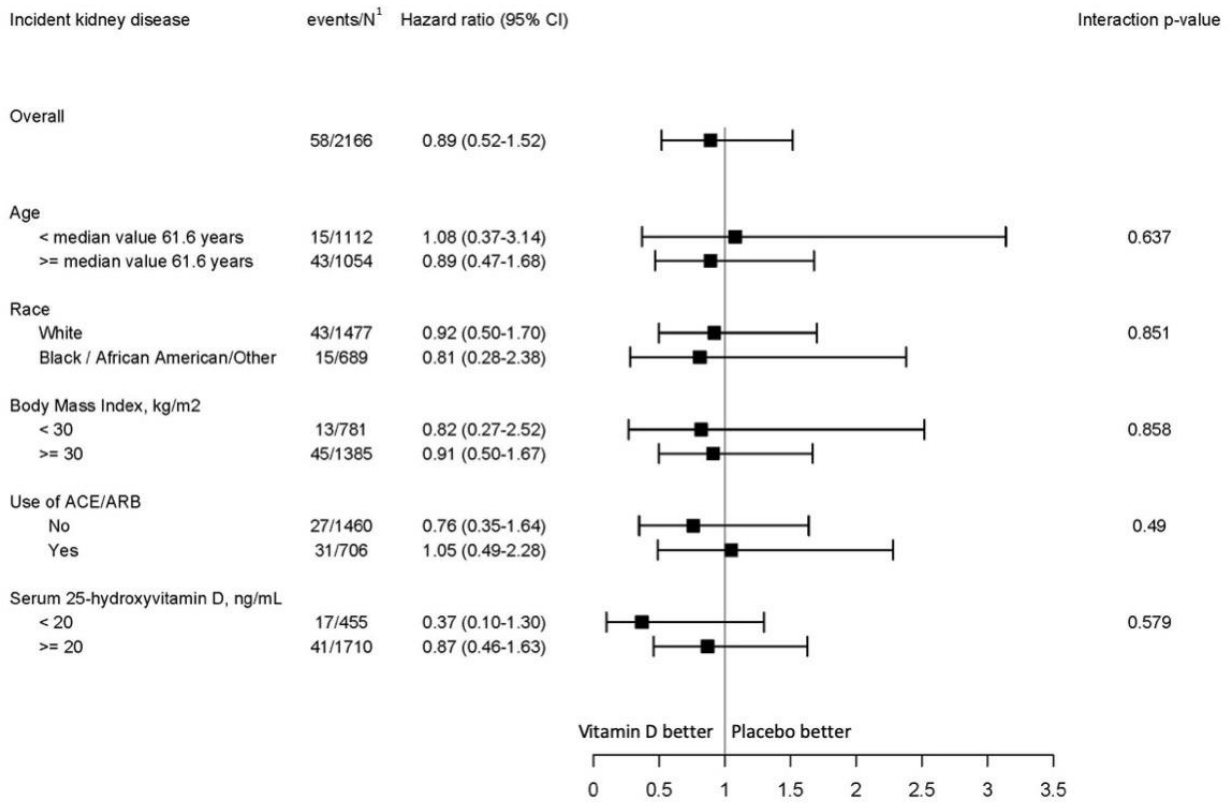
		Albuminuria Categories (mg/g)		
		<30	30-300	>300
GFR categories (ml/min/1.73m^2)	≥ 90			
	60-89			
	45-59			
	30-44			
	15-29			
	<15			

Green: low risk, Yellow: moderate risk, Orange: high risk, Red: very high risk

Supplemental Figure 2: Participant flow



Supplemental Figure 3: Sub-group analyses for the primary outcome of confirmed KDIGO worsening



[1] Number of events are pooled and rounded across imputed data sets.
ACE: Angiotensin converting enzyme inhibitors
ARB: Angiotensin receptor blockers