Study/Reference	**Effect of Vitamin D and Omega-3 Fatty Acid Supplementation on Kidney Function in Patients with Type 2 Diabetes: A Randomized Clinical Trial (VITAL-DKD)**	
Purpose/Background	• Chronic kidney disease (CKD) is a common complication of type 2 diabetes that can lead to end-stage kidney disease and is associated with high cardiovascular risk. • Vitamin D and omega-3 fatty acid supplements may have the potential to prevent the development and progression of CKD in type 2 diabetes. • Previous clinical trials evaluating the kidney effects of vitamin D and omega-3 fatty acid supplements have been of short duration, evaluated only urine albumin excretion as an outcome, or examined kidney outcomes as secondary post hoc analyses.	

Study Design	The parent trial (VITAL) was a randomized, double-blind, placebo-controlled trial. A single site, Brigham and Women's Hospital Department of Preventative Medicine in Boston, Massachusetts, was in charge of enrolling and distributing medication.
	• The study included participants from all 50 states.
	• Using data from the VITAL trial, baseline blood samples were collected for around 2/3 of participants.
	  o Follow-up blood and urine samples were only collected from a subset of healthy participants living in Boston.
	• Enrollment was handled via mail and telephone contacts.
	  o Medications were distributed by mail
	  o Outcomes were evaluated remotely
	
	For this study (VITAL-DKD):
	• Enrolled a subset of parent trial participants with type 2 diabetes at baseline
	• Vitamin D from all sources needed to be limited to 800 IU per day.
	• Fish oil supplements that were not provided by the study needed to be discontinued.
	• Treatment assignments were concealed to both participants and investigators.
	• Drugs studied:
	  o Vitamin D_3 (2000 IU cholecalciferol)
	  o Omega-3 fatty acids (1g capsules containing 465mg eicosapentaenoic acid (EPA) + 375mg of docosahexaenoic acid (DHA))
	• Patients received questionnaires about anti-diabetic and BP lowering medications at baseline and throughout trial.
	
	Patients were randomly assigned in a 2 x 2 factorial design and assignments were computer generated in blocks stratified by age, sex, and race.
	• **Group 1 (n=370):**
	  o Vitamin D + omega-3 fatty acids
	• **Group 2 (n=333):**
	  o Vitamin D + placebo
	• **Group 3 (n=289):**
	  o Placebo + omega-3 fatty acids
	• **Group 4 (n=320):**
	  o Placebo + Placebo	

Inclusion/Exclusion Criteria	Inclusion: • Men > 50 yrs and women > 55 yrs • No known cardiovascular event or cancer	Exclusion: • Renal failure or dialysis • Cirrhosis • History of hypercalcemia • Diabetes diagnosis only during pregnancy • Diagnosis of diabetes before age 30 and treated with insulin over 20 years • CKD caused by something other than diabetes
Outcomes	<u>Primary:</u> • Change in estimated GFR (eGFR) from baseline to study year 5. <u>Secondary:</u> • Time to the composite outcome of at least a 40% decrease in eGFR from baseline, kidney failure, or death • Time to 40% decrease in eGFR from baseline • Change in urine albumin-creatinine ratio (ACR) from baseline to study year 5	
Stats	• A sample of 1320 patients was for 80% power to detect a 2.3 ml/min/1.73m^2 difference in change in eGFR from baseline to end of study. • Time was modeled as 3 non-ordered variables: baseline, year-2, and year-5 • The P value for interaction of treatment with time (year 5) was used to test treatment effects. • A 2-tailed $P<0.05$ was considered significant for each intervention. o Due to the potential for type 1 error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory. • Intent-to-treat protocol was used for primary analysis • A secondary analysis was conducted using a per protocol approach.	

- Only counted those participants who returned samples at baseline and year 5, had high-adherence rates, and did not show any signs of a urinary tract infection when urine was collected.
- Multiple imputation (M=20) was used for missing data to minimize potential bias due to loss to follow-up

Baseline Characteristics

	Vitamin D + Omega-3 N=370, n(%)	Vitamin D + Placebo N=333, n(%)	Omega-3 + Placebo N=289, n(%)	Placebo + Placebo N=320, n(%)
Diabetes Duration, y				
< 1	13 (4)	15 (5)	5 (2)	9 (3)
1-2	52 (14)	43 (13)	45 (16)	37 (12)
3-5	78 (21)	72 (22)	62 (22)	78 (24)
6-10	107 (29)	83 (25)	74 (26)	96 (30)
10-20	90 (24)	82 (25)	69 (24)	74 (23)
>20	29 (8)	37 (11)	3 3(11)	25 (8)
Diabetes Meds				
Biguanides	247 (67)	222 (67)	199 (69)	221 (69)
Sulfonylureas	109 (29)	100 (30)	85 (29)	99 (31)
Insulin	67 (18)	68 (20)	57 (20)	66 (21)
Thiazolidibediones	32 (9)	32 (10)	24 (8)	36 (11)
DPP4 inhibitors	33 (9)	26 (8)	22 (8)	34 (11)
GLP1 agonists	9 (2)	14 (4)	16 (6)	9 (3)
BP Lowering Meds				
ACE or ARB	223 (60)	205 (62)	177 (61)	198 (62)
ACE	163 (44)	148 (44)	121 (42)	133 (42)
Diuretics	111 (30)	87 (26)	82 (28)	84 (26)
B-Blockers	91 (25)	74 (22)	62 (21)	68 (21)
CCBs	75 (20)	76 (23)	58 (20)	66 (21)
ARB	67 (18)	64 (19)	60 (21)	69 (22)
MRAs	2 (1)	3 (1)	0	4 (1)
Prior Vit D supplement use	146 (39)	138 (41)	124 (43)	128 (40)
25-hydroxyvitamin D				
< 20	62 (17)	48 (15)	41 (15)	44 (14)
20 – 30	109 (31)	121 (38)	87 (32)	116 (37)
≥ 30	184 (52)	148 (47)	146 (53)	151 (49)

Results

- 1312 participants were enrolled but only 934 (71%) completed the study
  - The average eGFR at baseline was 85.8 (SD, 22.1) mL/min/1.73m^2

Primary Outcome: Change in estimated GFR (eGFR) from baseline to study year 5.

- For the Vitamin D group:
  - The average change in eGFR from baseline to year 5 was −12.3 (95%CI; −13.4 to −11.2) mL/min/1.73m^2
  - Placebo results showed an average change in eGFR from baseline to year 5 to be −13.1 (95%CI, −14.2 to −11.9) mL/min/1.73m^2
  - The difference between eGFR in these 2 groups was (difference, 0.9 [95%CI, −0.7 to 2.5] mL/min/1.73m^2) (p = 0.25)
- For the Omega-3 fatty acid group:
  - The average change in eGFR from baseline to year 5 was −12.2 (95%CI, −13.3 to −11.1) mL/min/1.73m^2
  - Placebo results showed an average change in eGFR from baseline to year 5 to be −13.1 (95%CI, −14.2 to −12.0) mL/min/1.73m^2
  - The difference between these 2 groups was (difference, 0.9 [95%CI, −0.7 to 2.6] mL/min/1.73m^2) (p = 0.27)

Secondary Outcomes:

- Composite outcome of at least a 40% decrease in eGFR from baseline, kidney failure, or death
  - Vitamin D Group:
    - Occurred in 85 patients in the treatment group – incidence rate = 2.5 (2.0-3.0)
    - Occurred in 79 patients in the placebo group – incidence rate = 2.7 (2.1-3.3)
    - P-value for these results is 0.61
  - Omega-3 Group:
    - Occurred in 86 patients in the treatment group – incidence rate = 2.7 (2.2-3.3)
    - Occurred in 78 patients in the placebo group – incidence rate = 2.5 (1.9-3.0)
  - Vitamin D vs Placebo hazard ratio, 0.92 (95% CI; 0.68-1.25) (p = 0.61)
  - Omega-3 vs Placebo hazard ratio, 1.11 (95% CI; 0.81-1.50) (p= 0.52)

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40% decrease in eGFR from baseline

Vitamin D Group:

Occurred in 42 patients in the treatment group – incidence rate = 1.6 (1.1-2.1)
Occurred in 38 patients in the placebo group – incidence rate = 1.7 (1.2-2.1)

Omega-3 Group:

Occurred in 40 patients in the treatment group – incidence rate = 1.6 (1.1-2.1)
Occurred in 40 patients in the placebo group – incidence rate = 1.6 (1.2-2.1)

Vitamin D vs Placebo hazard ratio, 0.97 (95% CI; 0.63-1.51) (p = 0.90)
Omega-3 vs Placebo hazard ratio, 0.99 (95% CI; 0.64-1.54) (p = 0.97)

Change (doubling and $\geq$ 30 mg/g) in urine ACR from baseline to study year 5

Vitamin D Group:

Occurred in 111 patients in the treatment group – incidence rate = 4.4 (3.6-5.2)
Occurred in 74 patients in the placebo group – incidence rate = 3.3 (2.5-4.0)

Omega-3 Group:

Occurred in 96 patients in the treatment group – incidence rate = 4.0 (3.2-4.8)
Occurred in 89 patients in the placebo group – incidence rate = 3.7 (3.0-4.5)

Vitamin D vs Placebo hazard ratio, 1.34 (95% CI; 1.00-1.80) (p = 0.05)
Omega-3 vs Placebo hazard ratio, 1.08 (95% CI; 0.81-1.44) (p = 0.60)

<u>Adherence</u>

Self-reported by patients
It was considered “high-adherence” if the patients reported that they took the supplements at least 2/3 of the time.

High-adherence rates - 92% at year 2 and 88% at year 5

<u>Adverse Events</u>

Kidney stones

32 patients in Vitamin D Group
26 in patients in placebo group

Blood in urine

57 patients in omega-3 group
59 patients in placebo group

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<tr><td>Conclusions</td><td colspan="2">
<u>Author Conclusions:</u>

There was no significant change in eGFR at 5 years with either Vitamin D or omega-3 fatty acids when compared with placebo in adults with type 2 diabetes.
The results of this trial do not support vitamin D_3 or omega-3 fatty acid supplementation in the prevention of CKD in adults with type 2 diabetes.

<u>My Conclusions:</u>

Vitamin D_3 and/or omega-3 fatty acid supplements should not be recommended at this time for the preservation of kidney function in adults with type 2 diabetes.
Further studies should be done to assess the effects of concomitant use of Vitamin D and Omega-3 on the same endpoints.
Another study focused on patients with vitamin D deficiencies and/or CKD would be beneficial to assess results on those populations because most patients were not vitamin D deficient or did not have CKD in this study.

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<tr><td>Strengths/Weaknesses</td><td>
Strengths:

The length was adequate to address long term effects
Unblinding was unlikely
Ancillary study to VITAL trial

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Weaknesses:

Only 71% of patients returned a serum sample at year 5 for eGFR calculation while 83% returned a serum sample after randomization.
Not many eGFR and ACR measurements collected per patient which limited slope evaluation and time-to-event analyses.
Results for the group taking vitamin D plus omega-3 fatty acids were not reported.
Patients that were vitamin D deficient or already had CKD were excluded from the study, but they could have potentially benefitted the most from the supplements.
Baseline vitamin D concentrations ranged from normal (20-30ng/mL) to high (>30ng/mL) which could have affected treatment outcomes.
Adherence was only evaluated by patients self-reporting.
Blood glucose and blood pressures were not evaluated throughout this study, so diabetes or hypertension control could not be assessed

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References:

De Boer IH, Zelnick LR, Ruzinski J, et al. Effect of vitamin D and omega-3 fatty acid supplementation on kidney function in patients with type 2 diabetes; a randomized clinical trial. JAMA. 2019;322(19):1899-1909.

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