

SUPPLEMENTARY DATA

Supplementary Table 1. Description of DCCT/EDIC study population at the time of biomarker measurement, except for CAC/IMT measures which occurred at year 6. N=1193 subjects underwent measurements of vitamin D metabolites.

Variable	All measured participants	24,25(OH) ₂ D ₃			
		≥ 12.7 nmol/L	9.4-12.7 nmol/L	6.2-9.4 nmol/L	<6.2 nmol/L
Number in group	1193	289	283	305	303
Age (years), mean (SD)*	32.4 (2.6)	31.5 (2.6)	32.5 (2.6)	32.2 (2.6)	33.4 (2.6)
Duration of diabetes (years), mean (SD)*	7.5 (2.1)	6.8 (2)	7.5 (2.1)	7.5 (2.1)	8.2 (2.1)
Female gender, N (%)*	564 (47)	103 (36)	133 (47)	149 (49)	170 (56)
Nonwhite race, N (%)*	42 (4)	3 (1)	1 (0)	9 (3)	23 (8)
DCCT intensive diabetes therapy, N (%)	598 (50)	160 (55)	139 (49)	157 (51)	135 (45)
Current smoking, N (%)	236 (20)	60 (21)	54 (19)	49 (16)	69 (23)
Body mass index (kg/m ²), mean (SD)*	25.7 (1.9)	25.1 (1.7)	25.6 (1.9)	25.6 (1.8)	26.3 (2)
Systolic blood pressure (mmHg), mean (SD)*	114.8 (3.4)	115.2 (3.4)	113.3 (3.4)	114.8 (3.4)	116.1 (3.5)
Diastolic blood pressure (mmHg), mean (SD)*	74 (2.9)	74 (2.9)	72.9 (3)	74 (2.8)	74.9 (2.9)
Hemoglobin A1c (%), mean (SD)	8.1 (1.3)	8.1 (1.2)	8.2 (1.3)	8.2 (1.3)	8.1 (1.2)
Iothalamate GFR (mL/min), mean (SD)	132.9 (4.8)	135.1 (4.3)	136.7 (5.1)	131.5 (5.1)	128.9 (4.8)
Serum creatinine (μmol/l), mean (SD)	65.3 (11.3)	74.6 (12.5)	65 (11.7)	67.9 (12.3)	54.7 (3.6)
Creatinine clearance (mL/min/1.73m ³), mean (SD)	122.3 (5)	124.9 (5.1)	122.7 (5)	122.5 (4.9)	119.3 (4.8)
Creatinine clearance (mL/min), mean (SD)*	133.6 (5.6)	138.6 (5.7)	133.8 (5.6)	132.9 (5.6)	129.5 (5.5)
HDL cholesterol (mmol/L), mean (SD)	1.3 (0.6)	1.3 (0.5)	1.3 (0.6)	1.3 (0.6)	1.3 (0.5)
LDL cholesterol (mmol/L), mean (SD)	2.8 (0.9)	2.8 (0.9)	2.8 (0.9)	2.8 (0.9)	2.8 (0.9)
Total 25-hydroxyvitamin D(nmol/L), mean (SD)*	63.3 (4.7)	88.5 (4.4)	68.1 (3.1)	57.9 (3.2)	42.1 (3.4)
24-25 dihydroxyvitamin D ₃ (nmol/L), mean (SD)*	9.9 (2.3)	17 (2)	11.1 (1)	7.9 (0.9)	4.4 (1.1)
Total 1-25	107.5 (5.5)	114.7 (5.6)	103.7 (5.1)	107.7 (5.4)	102.6 (5.6)

SUPPLEMENTARY DATA

dihydroxyvitamin D (pmol/L), mean (SD) *					
FGF-23 (pg/mL), mean (SD) *	31.4 (2.9)	34.8 (3.1)	30.1 (2.8)	30.1 (2.7)	31 (3)
PTH (ng/L), mean (SD) *	30.8 (3.7)	26.3 (3.1)	28.1 (3.4)	30.7 (3.3)	36.9 (4)
Non-zero CAC, N (%)	329 (30)	90 (34)	85 (33)	75 (27)	76 (28)
CAC score (Agatston units, among those with CAC >0), geometric mean (geometric SD)	51.2 (2.5)	60.9 (2.5)	49.2 (2.5)	55.9 (2.4)	41.3 (2.5)
Common carotid IMT thickness (μ m), mean (SD)	619.8 (10.8)	615.3 (10.6)	626.2 (11.2)	607.8 (10.1)	628.9 (11.3)
Internal carotid IMT thickness (μ m), mean (SD)	729.1 (18.7)	744.3 (19.5)	761 (19.5)	713.3 (18)	694.5 (17.2)

SD = standard deviation. * - indicates that $P < 0.05$ for a test comparing means, geometric means, or proportions, where appropriate, across 24,25(OH)D groups.

Supplementary Table 2. Description of DCCT/EDIC study population at the time of biomarker measurement, except for CAC/IMT measures which occurred at year 6. N=1193 subjects underwent measurements of vitamin D metabolites.

Variable	All measured participants	1,25(OH) ₂ D			
		≥ 122 pmol/L	101-122 pmol/L	88-101 pmol/L	<88 pmol/L
Number in group	1193	283	289	261	315
Age (years), mean (SD) *	32.4 (2.6)	31.4 (2.7)	32.8 (2.6)	32.4 (2.6)	33 (2.6)
Duration of diabetes (years), mean (SD)	7.5 (2.1)	7.2 (2.1)	7.3 (2.1)	7.4 (2)	8 (2.1)
Female gender, N (%) *	564 (47)	161 (57)	125 (43)	124 (48)	135 (43)
Nonwhite race, N (%)	42 (4)	13 (5)	12 (4)	9 (3)	6 (2)
DCCT intensive diabetes therapy, N (%)	598 (50)	150 (53)	135 (47)	138 (53)	152 (48)
Current smoking, N (%)	236 (20)	55 (19)	53 (18)	42 (16)	78 (25)
Body mass index (kg/m^2), mean (SD)	25.7 (1.9)	25.5 (1.9)	25.6 (1.9)	25.7 (1.9)	26 (1.9)
Systolic blood pressure (mmHg), mean (SD)	114.8 (3.4)	114.4 (3.4)	114.7 (3.4)	115.1 (3.4)	115.2 (3.5)
Diastolic blood pressure (mmHg), mean (SD)	74 (2.9)	73.9 (2.9)	74 (2.9)	73.9 (2.8)	73.9 (3)
Hemoglobin A1c (%), mean (SD)	8.1 (1.3)	8.2 (1.3)	8 (1.2)	8.2 (1.3)	8.2 (1.2)
Iothalamate GFR (mL/min), mean (SD)	132.9 (4.8)	131.7 (4.8)	133.7 (5)	131.7 (4.8)	133.2 (4.7)

SUPPLEMENTARY DATA

Serum creatinine ($\mu\text{mol/l}$), mean (SD)	65.3 (11.3)	61 (10.8)	61.3 (8.8)	70.7 (12.8)	62.3 (8.6)
Creatinine clearance ($\text{mL/min}/1.73\text{m}^3$), mean (SD)	122.3 (5)	123 (4.8)	121.8 (4.7)	122.1 (5.1)	121.4 (5)
Creatinine clearance (mL/min), mean (SD)*	133.6 (5.6)	131.3 (5.5)	134.4 (5.5)	133.8 (5.8)	134.2 (5.4)
HDL cholesterol (mmol/L), mean (SD)	1.3 (0.6)	1.3 (0.5)	1.3 (0.6)	1.3 (0.5)	1.3 (0.6)
LDL cholesterol (mmol/L), mean (SD)	2.8 (0.9)	2.9 (0.9)	2.9 (0.9)	2.8 (0.8)	2.8 (0.9)
Total 25-hydroxyvitamin D (nmol/L), mean (SD)*	63.3 (4.7)	70.5 (5.1)	65.3 (4.7)	60.4 (4.3)	57.2 (4.3)
24-25 dihydroxyvitamin D ₃ (nmol/L), mean (SD)*	9.9 (2.3)	10.8 (2.4)	10.6 (2.3)	9.2 (2.1)	8.9 (2.2)
Total 1-25 dihydroxyvitamin D (pmol/L), mean (SD)*	107.5 (5.5)	148.8 (5.1)	112.3 (2.4)	96.1 (1.9)	75.6 (3.2)
FGF-23 (pg/mL), mean (SD)*	31.4 (2.9)	29.2 (2.9)	31.6 (2.8)	35.4 (3.4)	31.9 (2.7)
PTH (ng/L), mean (SD)*	30.8 (3.7)	30.4 (3.7)	31.9 (3.8)	32.4 (3.5)	29.5 (3.4)
Non-zero CAC, N (%)	329 (30)	81 (33)	76 (29)	63 (26)	93 (33)
CAC score (Agatston units, among those with CAC >0), geometric mean (geometric SD)	51.2 (2.5)	64.3 (2.5)	35.4 (2.4)	44.6 (2.4)	62 (2.5)
Common carotid IMT thickness (μm), mean (SD)	619.8 (10.8)	607.9 (10.3)	617.9 (10.5)	614.1 (10.1)	635.1 (12)
Internal carotid IMT thickness (μm), mean (SD)*	729.1 (18.7)	699 (18.5)	732.1 (18.3)	694 (15.4)	773.3 (20.7)

SD = standard deviation. * - indicates that $P < 0.05$ for a test comparing means, geometric means, or proportions, where appropriate, across 1,25(OH)D groups.

SUPPLEMENTARY DATA

Supplementary Table 3. Associations of circulating vitamin D metabolites measured at the end of the DCCT with coronary artery calcium measured during the EDIC Study among 1081 DCCT/EDIC participants. Estimates are relative risks from a binomial regression model with robust inference.

Vitamin D metabolite	N	N with CAC (%)	Adjusted prevalence ratio (95% CI)	
			Model 1**	Model 2***
25-hydroxyvitamin D				
≥75 nmol/L	285	87(30.5)	1(Ref.)	1(Ref.)
50 - 75 nmol/L	503	159(31.6)	1.04(0.85 to 1.27)	1.01(0.83 to 1.23)
< 50 nmol/L	293	83(28.3)	0.94(0.74 to 1.2)	0.87(0.68 to 1.11)
P			0.667	0.378
Per 25 nmol/L lower*			0.94(0.85 to 1.05)	0.91(0.82 to 1.01)
P*			0.286	0.079
24,25-dihydroxyvitamin D				
≥12.7 nmol/L	264	90(34.1)	1(Ref.)	1(Ref.)
9.4 – 12.7 nmol/L	257	85(33.1)	0.97(0.77 to 1.21)	0.94(0.75 to 1.18)
6.2 – 9.4 nmol/L	283	75(26.5)	0.82(0.65 to 1.03)	0.8(0.64 to 1.01)
<6.2 nmol/L	267	76(28.5)	0.84(0.66 to 1.07)	0.78(0.61 to 0.99)
P			0.257	0.117
Per 2.5 nmol/L lower*			0.98(0.94 to 1.02)	0.97(0.93 to 1)
P*			0.241	0.084
1,25-dihydroxyvitamin D				
≥122 pmol/L	247	81(32.8)	1(Ref.)	1(Ref.)
101 - 122 pmol/L	259	76(29.3)	0.77(0.61 to 0.98)	0.78(0.62 to 0.99)
88 - 101 pmol/L	244	63(25.8)	0.72(0.56 to 0.94)	0.74(0.57 to 0.96)
< 88 pmol/L	286	93(32.5)	0.82(0.65 to 1.03)	0.8(0.63 to 1.01)
P			0.061	0.072
Per 25 pmol/L lower*			0.94(0.87 to 1.01)	0.93(0.86 to 1)
P*			0.088	0.052

* Evaluates each vitamin D metabolite as a continuous variable, scaled as indicated. P-value for trend created using this model.

** Adjusted for scanner type, age and duration of diabetes at the time of biomarker measurement as well as sex, race, and DCCT treatment assignment.

*** Additionally adjusted for body mass index, albumin excretion rate, and estimated glomerular filtration rate at the time of biomarker measurement as well as solar irradiation of DCCT clinic site.

SUPPLEMENTARY DATA

Supplementary Table 4. Associations of circulating vitamin D metabolites measured at the end of the DCCT with coronary artery calcium measured during the EDIC Study among 1081 DCCT/EDIC participants. Estimates are coefficients from tobit regression models on the natural log of CAC. Estimates are interpreted as the geometric mean ratio in the latent variable that is CAC had no zeros been observed associated with a unit difference in the exposure.

Vitamin D metabolite	N with CAC > 0	Mean Agatston score (among those with CAC>0) (SD)	Adjusted weighted geometric mean ratio (95% CI)	
			Model 1**	Model 2***
25-hydroxyvitamin D				
≥75 nmol/L	87	92.34(340.84)	1(Ref.)	1(Ref.)
50 - 75 nmol/L	159	63.81(253.64)	0.82(0.35 to 1.93)	0.74(0.32 to 1.72)
< 50 nmol/L	83	42.56(138.74)	0.57(0.21 to 1.55)	0.41(0.15 to 1.13)
P			0.529	0.216
Per 25 nmol/L lower*			0.72(0.47 to 1.11)	0.61(0.4 to 0.94)
P*			0.14	0.027
24,25-dihydroxyvitamin D				
≥12.7 nmol/L	90	86.67(331.34)	1(Ref.)	1(Ref.)
9.4 – 12.7 nmol/L	85	72.69(272.61)	0.79(0.29 to 2.12)	0.75(0.28 to 1.99)
6.2 – 9.4 nmol/L	75	57.39(229.81)	0.38(0.14 to 1.02)	0.35(0.13 to 0.94)
<6.2 nmol/L	76	48.6(175.74)	0.41(0.15 to 1.11)	0.3(0.11 to 0.81)
P			0.153	0.053
Per 2.5 nmol/L lower*			0.87(0.73 to 1.03)	0.83(0.69 to 0.98)
P*			0.114	0.031
1,25-dihydroxyvitamin D				
≥122 pmol/L	81	79.83(261.47)	1(Ref.)	1(Ref.)
101 - 122 pmol/L	76	46.01(225.62)	0.23(0.08 to 0.63)	0.24(0.09 to 0.64)
88 - 101 pmol/L	63	46.72(203.4)	0.21(0.07 to 0.62)	0.22(0.08 to 0.63)
< 88 pmol/L	93	79.71(280.2)	0.38(0.14 to 1.03)	0.33(0.12 to 0.91)
P			0.012	0.013
Per 25 pmol/L lower*			0.74(0.54 to 1.01)	0.71(0.52 to 0.97)
P*			0.054	0.03

* Evaluates each vitamin D metabolite as a continuous variable, scaled as indicated. P-value for trend created using this model.

** Adjusted for scanner type, age and duration of diabetes at the time of biomarker measurement as well as baseline internal IMT, sex, race, and DCCT treatment assignment.

*** Additionally adjusted for body mass index, albumin excretion rate, and estimated glomerular filtration rate at the time of biomarker measurement as well as solar irradiation of DCCT clinic site.

SUPPLEMENTARY DATA

Supplementary Table 5. Associations between Vitamin D metabolites and subclinical CVD in subgroups defined by treatment group and gender. Models are fully adjusted as in the above tables.

subgroup	CAC (odds ratios)	Common IMT (mean differences)	Internal IMT (geom. mean ratios)
25(OH)D	per 25 nmol/L lower	per 25 nmol/L lower	per 25 nmol/L lower
Overall	0.8(0.68 to 0.96)	2.36(-2.45 to 7.17)	0.99(0.98 to 1)
Intensive therapy	0.84(0.66 to 1.07)	-0.07(-6.84 to 6.7)	0.98(0.96 to 1)
Standard therapy	0.78(0.62 to 0.98)	4.63(-3.98 to 13.24)	1(0.97 to 1.03)
Male	0.81(0.65 to 1.01)	4.12(-2.53 to 10.76)	0.99(0.97 to 1.01)
Female	0.8(0.61 to 1.04)	0.6(-5.2 to 6.4)	0.99(0.97 to 1.01)
24, 25(OH)2D3	per 2.5 nmol/L lower	per 2.5 nmol/L lower	per 2.5 nmol/L lower
Overall	0.92(0.86 to 0.98)	-1.02(-2.97 to 0.92)	0.99(0.99 to 1)
Intensive therapy	0.92(0.84 to 1.01)	-2.2(-4.86 to 0.46)	0.99(0.98 to 1)
Standard therapy	0.92(0.83 to 1.01)	0.21(-3.04 to 3.47)	0.99(0.98 to 1)
Male	0.9(0.83 to 0.98)	-0.97(-3.63 to 1.69)	0.99(0.98 to 0.99)
Female	0.95(0.85 to 1.07)	-1.09(-3.59 to 1.42)	1(0.99 to 1)
1,25(OH)2D	per 25 nmol/L lower	per 25 nmol/L lower	per 25 nmol/L lower
Overall	0.88(0.77 to 1)	2.63(-0.96 to 6.22)	1(0.99 to 1.01)
Intensive therapy	0.91(0.75 to 1.1)	1.68(-3.59 to 6.95)	1.01(0.99 to 1.02)
Standard therapy	0.86(0.72 to 1.02)	3.43(-2.3 to 9.16)	1(0.98 to 1.01)
Male	0.85(0.72 to 1.02)	2.92(-2.71 to 8.54)	1(0.98 to 1.02)
Female	0.91(0.75 to 1.11)	2.44(-1.62 to 6.5)	1(0.99 to 1.01)