Vitamin D Deficiency is Associated with Depletion of Circulating Endothelial Progenitor Cells and Endothelial Dysfunction in Patients with Type II Diabetes

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Background

• Vitamin D deficiency is a common condition in patients with type II diabetes.

• On the other hand, vitamin D deficiency is associated with endothelial dysfunction.

• However, the relationship between vitamin D deficiency, circulating endothelial progenitor cells (EPCs) and endothelial dysfunction in patients with type II diabetes remains unclear.

Methods

• Baseline demographic data, CVD risk factors and cardiovascular medications were documented. Serum hydroxyvitamin D [25(OH)-D] and circulating CD133/KDR+ EPCs were measured by ELISA kit and flow cytometry respectively.

• Patients with a serum concentration of 25(OH)D 20 - 30ng/mL were defined as vitamin D insufficient, while those with a concentration < 20ng/mL as vitamin D deficient.

• Endothelial function was measured as flow-mediated dilatation of the brachial artery assessed by vascular ultrasound following a standard protocol.

Table 1. Clinical characteristics of study populations (n=282)

Age (years)	68.1 ± 10.0
Male [n (%)]	172 (61)
Ever smoker [n (%)]	106 (38)
Body weight (kg)	64.6 ± 11.8
BMI (kg/m2)	25.6 ± 3.8
Waist-to-hip ratio (%)	0.94 ± 0.07
History of cardiovascular disease [n (%)]	71 (25)
Hypertension [n (%)]	200 (71)
Systolic blood pressure (mmHg)	142 ± 21
Diastolic blood pressure (mmHg)	78 ± 9
Hyperlipidemia [n (%)]	187 (66)
Serum LDL-C (mmol/L)	2.56 ± 0.74
Serum HDL-C (mmol/L)	1.30 ± 0.36
Diabetes duration (year)	10.3 ± 7.9
HbA1c level (%)	7.75 ± 1.44
Medication	
Antihypertensive [n (%)]	238 (84)
Lipid lowering agents [n (%)]	159 (56)
Oral hypoglycemic agent [n (%)]	279 (99)
Insulin [n (%)]	57 (20)
Flow-mediated dilation (%)	3.63 ± 2.22
Serum 25(OH)D (ng/mL)	25.0 ± 9.2

Table 2. Characteristics of patients with type II diabetes according to 25(OH)D status

	Deficiency (< 20) (n=100)	Insufficiency (≥20-<30) (n=119)	Sufficiency (≥30) (n=73)	P value
Age (y)	65.2 ± 10.5	69.0 ± 10.0	70.5 ± 8.57	0.001
Male [n (%)]	45 (45.0)	74 (62.2)	53 (72.6)	0.001
History of MI or CAD [n (%)]	20 (20.0)	31 (26.1)	20 (27.4)	0.450
Ever smoker [n (%)]	22 (22.0)	49 (41.2)	35 (47.9)	0.001
Body weight (kg)	65.5 ± 12.6	64.1 ± 12.3	64.3 ± 10.0	0.690
BMI (kg/m2)	26.5 ± 4.1	25.3 ± 3.8	25.0 ± 3.2	0.023
Waist-to-hip ratio	0.92 ± 0.07	0.94 ± 0.07	0.95 ± 0.05	0.074
Hypertension [n (%)]	60 (60.0)	84 (70.6)	56 (76.7)	0.053
Sytolic BP (mmHg)	142 ± 23	142 ± 20	143 ± 19	0.950
Diastolic BP (mmHg)	79 ± 9	77 ± 9	79 ± 9	0.260
Hyperlipidemia [n (%)]	60 (60.0)	74 (62.2)	53 (72.6)	0.200
Serum LDL-C (mmol/L)	2.80 ± 0.72	2.53 ± 0.77	2.29 ± 0.59	<0.001
Serum HDL-C (mmol/L)	1.32 ± 0.38	1.26 ± 0.36	1.30 ± 0.35	0.410
Diabetes duration (y)	9.2 ± 7.0	12.0 ± 8.1	9.2 ± 8.4	0.017
HbA1c level (%)	7.83 ± 1.35	7.78 ± 1.42	7.59 ± 1.57	0.530
Total calories (Kcal)	1945 ± 991	1900 ± 807	2003 ± 879	0.770
Serum creatinine (mmol/L)	86.3 ± 45.5	86.3 ± 29.1	92.3 ± 23.1	0.440
Medications				
Antihypertensives [n (%)]	79 (79.0)	96 (80.7)	63 (86.3)	0.450
Lipid lowering agents [n (%)]	44 (44.0)	62 (52.1)	53 (72.6)	0.001
Oral hypoglycemic drugs [n (%)]	97 (97.0)	114 (95.8)	68 (93.2)	0.470
Insulin [n (%)]	21 (21.0)	27 (22.7)	7 (9.7)	0.210
Brachial FMD (%)	3.15 ± 1.81	3.58 ± 2.28	4.37 ± 2.46	0.002
CD34/KDR+ EPC (%)	0.746 ± 0.465	0.628 ± 0.354	0.747 ± 0.412	0.149
CD133/KDR+ EPC (%)	0.228 ± 0.198	0.282 ± 0.197	0.350 ± 0.172	0.003

Table 3. Effect of 25(OH)D status on FMD after adjustment by backward stepwise regression model

	Stepwise multivariate regression model	
	B (95% CI)	P value
Waist-to-hip ratio (%)	-4.302 (-8.249, -0.356)	0.052
Diabetes duration (y)	-0.014 (-0.046, 0.019)	0.461
Systolic blood pressure (mmHg)	-0.011 (-0.024, 0.001)	0.095
HbA1c level (%)	-0.323 (-0.536, -0.110)	0.007
Serum 25(OH)D		
Deficiency (<20 ng/mL)	-1.066 (-1.876, -0.255)	0.010
Insufficiency (>=20 and <30 ng/mL)	-0.644 (-1.430, 0.142)	0.197

Table 4. Effect of 25(OH)D status on CD133/KDR+ EPC counts after adjustment by backward stepwise regression model

|	Stepwise multivariate regression model	
	B (95% CI)	P value
Age (y)	0.002 (0.000, 0.005)	0.122
Ever smoker [n (%)]	0.035 (-0.019, 0.089)	0.253
BMI (kg/m2)	0.011 (0.005, 0.018)	0.003
History of MI or CAD [n (%)]	0.048 (0.014, 0.110)	0.169
Hypertension [n (%)]	0.025 (-0.030, 0.080)	0.416
Diastolic blood pressure (mmHg)	-0.004 (-0.007, 0.002)	0.006
Serum 25(OH)D		
Deficiency (<20 ng/mL)	-0.113 (-0.198, -0.029)	0.008
Insufficiency (>=20 and <30 ng/mL)	-0.080 (-0.160, 0.001)	0.080
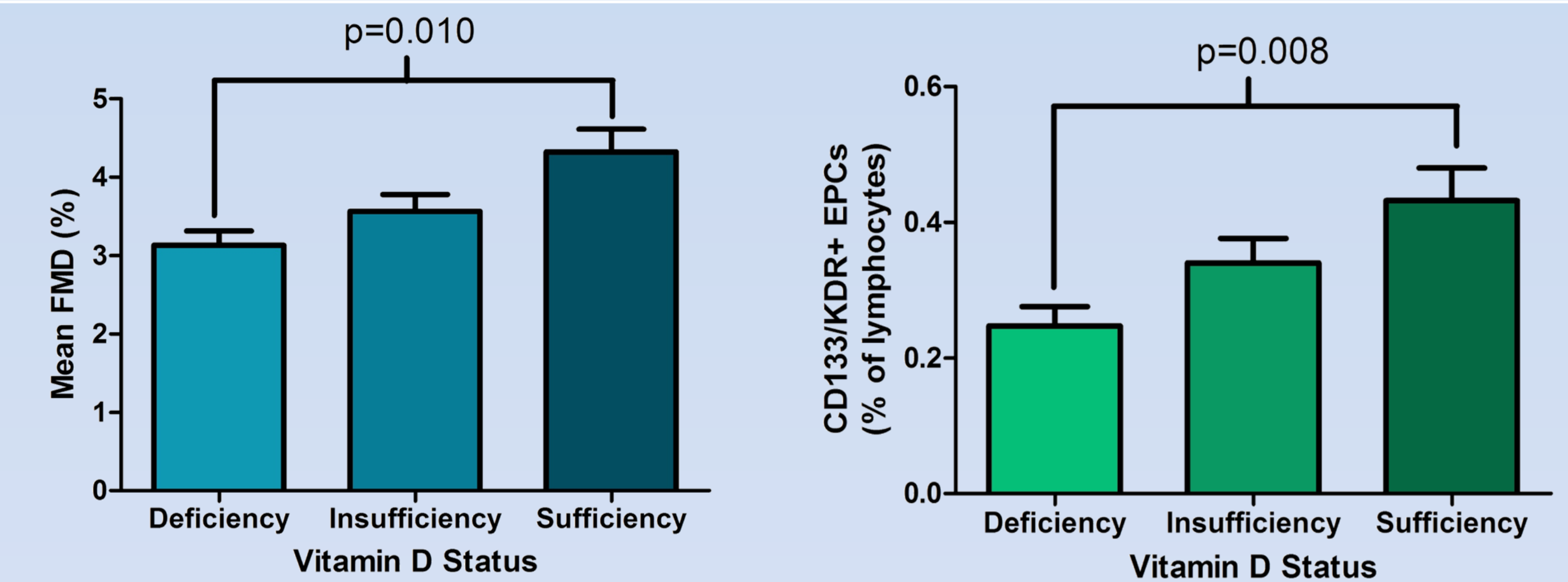
Figure. Mean (± SEM) values of FMD and CD133/KDR+ EPCs

Results

• The study population consisted of 282 pts. Their baseline characteristics are summarized in Table 1.

• Their mean age was 68±10 years; 61% of them were men. 42% of subjects were vitamin D insufficient [25(OH)-D 20-30 ng/ml] and 35% of subjects were vitamin D deficient [25(OH)-D < 20 ng/ml].

• As shown in Table 2, patients with 25(OH)D level > 30 ng/mL were more likely to be older, male sex, ever smoker, treated with lipid lowering agents, and had lower BMI and LDL-C level.

• Significantly, patients with the vitamin D deficiency had significantly lower brachial FMD and CD133/KDR+ EPCs compared with those with sufficient serum 25(OH)D concentration (Figure).

• After adjustment for age, sex and cardiovascular risk factors using a backward stepwise regression model, vitamin D deficiency was significantly associated with an absolute 1.07% (95% CI: 0.26 to 1.88, P=0.01) decrease in FMD and an absolute 0.11% (95% CI: 0.03 to 0.20, P=0.01) decrease in CD133/KDR+ EPC.

• On the other hand, there was no relationship between FMD and CD133/KDR+ EPCs, suggesting vitamin D level was associated with increased FMD and CD133/KDR+ EPCs independently.

Conclusion:

Our results demonstrated that serum 25 (OH)-D level was significantly associated with brachial artery FMD and circulating CD133/KDR+ EPCs, suggesting vitamin D deficiency might contribute to depletion of EPC and endothelial dysfunction in type II DM patients.