Pulse Dose versus Continuous Dose of Calciferol on Vascular Stiffness in Diabetic Kidney Disease: A Randomized Trial

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Abstract

Objective: Vitamin D deficiency is a common condition among chronic kidney disease (CKD) patients. It is associated with cardiovascular mortality. Giving calciferol to CKD patients could help reduce vascular stiffness and decrease the risks of coronary artery disease and mortality. The current recommendation for treating vitamin D deficiency in CKD patients is using the same treatment strategies for the general population. However, there is no recommendation on the exact dose and duration. The purpose of this trial is to compare the effects of pulse dose versus continuous dose of calciferol on vascular stiffness in diabetic kidney patients.

Methods: 31 patients with type 2 diabetes mellitus (T2DM), eGFR 15-59 mL/min/1.73 m2, and 25(OH) D level < 30 ng/mL, were enrolled in this randomized, open-label trial to receive either pulse dose (200,000 IU at the 0th and 8th weeks) or continuous dose (40,000 IU weekly for 8 weeks then 20,000 IU weekly for 2 weeks) of calciferol. The primary outcome was the vascular stiffness measured by the changes in carotid-femoral pulse wave velocity (cfPWV) at 10th week.

Results: The mean 25(OH)D level at the baseline was 18.7 ng/mL in the pulse dose versus 19.9 ng/mL in the continuous dose. In the pulse dose, 10 patients (66.7%) achieved optimal vitamin D level while 6 patients (40%) did in the continuous dose. The mean change of cfPWV between the two groups, which was -0.5 (95%CI -3.15 to 2.15) (p=0.703), was not statistically significant. No adverse effect was reported.

Conclusion: 10 weeks of calciferol given to CKD patients with T2DM and 25(OH)D < 30 ng/mL could achieve a higher reduction of Cardio-ankle vascular index in the pulse dose group than in the continuous dose group. Despite the lack of statistically significant change in Carotid-femoral pulse wave velocity (cfPWV), there seemed to be a higher cfPWV reduction in the pulse dose, with the achievement of 25(OH)D level.

Keywords: calciferol, chronic kidney disease, pulse wave velocity

การให้แคลซิเฟอรอลขนาดสูงเปรียบเทียบกับการให้ทุกสัปดาห์ต่อการเปลี่ยนแปลงความยืดหยุ่นของหลอดเลือดในผู้ป่วยไตเรื้อรังจากเบาหวาน

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บทคัดย่อ

บทนำ: ภาวะขาดวิตามินดีพบบ่อยในผู้ป่วยโรคไตเรื้อรัง ซึ่งสัมพันธ์กับความเสี่ยงในการเกิดโรคหลอดเลือดหัวใจตีบและการเสียชีวิต การให้แคลซิเฟอรอลในผู้ป่วยไตเรื้อรังจะช่วยลดการแข็งตัวของหลอดเลือด ซึ่งอาจช่วยลดความเสี่ยงในการเกิดโรคหลอดเลือดหัวใจตีบและการเสียชีวิต ปัจจุบันภาวะขาดวิตามินดีในผู้ป่วยไตเรื้อรัง ให้รักษาเช่นเดียวกันกับประชากรทั่วไป โดยยังไม่มีข้อแนะนำขนาดและระยะเวลาในการรักษาที่ชัดเจน จุดประสงค์ของการวิจัยนี้คือการเปรียบเทียบการให้แคลซิเฟอรอลสองวิธีที่แตกต่างกัน เพื่อศึกษาการเปลี่ยนแปลงความยืดหยุ่นของหลอดเลือดในผู้ป่วยไตเรื้อรังจากเบาหวาน

วิธีดำเนินการวิจัย: จำนวนประชากรในการศึกษาทั้งหมด 31 คน เป็นโรคเบาหวานชนิดที่สอง มีระดับการกรองของไต 15-59 มิลลิลิตรต่อนาทีต่อ 1.73 ตารางเมตร และมีระดับ 25(OH)D น้อยกว่า 30 นาโนกรัมต่อมิลลิลิตร นำมาคัดเลือกแบบสุ่มได้กลุ่มละ 15 คน กลุ่มที่หนึ่งรับประทานแคลซิเฟอรัลขนาดสูง (200,000 IU ที่ 0 และ 8 สัปดาห์) กลุ่มที่สองรับประทานแคลซิเฟอรัลทุกสัปดาห์ (40,000 IU ทุกสัปดาห์เป็นเวลา 8 สัปดาห์ หลังจากนั้นรับประทาน 20,000 IU ทุกสัปดาห์) วัดการเปลี่ยนแปลงความยืดหยุ่นของหลอดเลือดด้วย carotid-femoral pulse wave velocity ที่ 10 สัปดาห์ ซึ่งเป็นผลลัพธ์หลักของการศึกษา

ผลการวิจัย: ระดับวิตามินดีเฉลี่ยก่อนรักษาในกลุ่มที่ให้แคลซิเฟอรัลสองครั้งเท่ากับ 18.7 นาโนกรัมต่อมิลลิลิตร และกลุ่มที่ให้แคลซิเฟอรัลทุกสัปดาห์เท่ากับ 19.9 นาโนกรัมต่อมิลลิลิตร หลังการรักษาพบว่า 10 คน (ร้อยละ 66.7) ในกลุ่มที่ให้แคลซิเฟอรัลสองครั้งมีระดับวิตามินดีเพิ่มขึ้นจนถึงระดับปกติ ได้มากกว่ากลุ่มที่ให้ทุกสัปดาห์ซึ่งมีเพียง 6 คน (ร้อยละ 40) การเปลี่ยนแปลงเฉลี่ยของ carotid-femoral pulse wave velocity ทั้งสองกลุ่มที่ 10 สัปดาห์ไม่มีความแตกต่างกัน [-0.5 (95%CI -3.15 to 2.15) (p=0.703)] แต่พบว่าในกลุ่มที่ได้รับแคลซิเฟอรัลขนาดสูง cardio-ankle vascular index ลดลงมากกว่าในกลุ่มที่ได้รับแคลซิเฟอรัลทุกสัปดาห์อย่างมีนัยสำคัญทางสถิติ โดยทั้งสองกลุ่มไม่มีการรายงานถึงผลข้างเคียง และไม่พบการเปลี่ยนแปลงระดับแคลเซียมและฟอสฟอรัสในเลือด

สรุป: ในผู้ป่วยโรคไตเรื้อรังจากเบาหวาน และมีระดับวิตามินดีน้อยกว่า 30 นาโนกรัมต่อมิลลิลิตร หลังให้การรักษาด้วยแคลซิเฟอรัลสองครั้ง พบว่าสามารถลด cardio-ankle vascular index ที่ 10 สัปดาห์ได้ดีกว่า การรักษาด้วยแคซิเฟอรัลทุกสัปดาห์ แต่พบว่าทั้งสองกลุ่มลด carotid-femoral pulse wave velocity ได้ไม่แตกต่างกัน อย่างไรก็ตาม กลุ่มที่ให้แคลซิเฟอรัลสองครั้งพบว่าเพิ่มระดับวิตามินดีได้เร็วกว่า และไม่พบผลข้างเคียงแต่อย่างใด

คำสำคัญ : แคลซิเฟอรอล, โรคไตเรื้อรัง, ความเร็วคลื่นชีพจรที่ผ่านหลอดเลือด

Introduction

Vitamin D has pleiotropic effects due to its anti-inflammatory, anti-apoptotic, and anti-fibrotic properties. It is also beneficial to the cardiovascular system. The cross-sectional cohort study of LaClair RE. *et al.* found a high prevalence of calcidiol deficiency and insufficiency in patients with moderate and severe chronic kidney disease (CKD)[1]. The high burden of cardiovascular mortality and all-cause mortality was found in CKD patients. The major cause of cardiovascular mortality in CKD was vascular calcification. The more vascular calcification, the more vascular stiffness affects the blood pressure by increasing the systolic blood pressure, decreasing the diastolic blood pressure, and increasing the pulse pressure and the afterload. Later, it causes endothelial dysfunction followed by cardiovascular disease and death. Vitamin D was believed to be the modifying factor in reducing vascular calcification.

We frequently use Flow-mediated dilatation (FMD)[2] and pulse wave velocity (PWV) as a clinical measurement of vascular stiffness[3]. Carotid-femoral PWV (cfPWV) is the non-invasive gold standard tool to measure vascular stiffness according to ESH/ESC guideline 2013[4]. The study of Vlachopoulos, *et. al.* found that an increase in aortic PWV by 1 m/s was associated with the cardiovascular event (14%) and cardiovascular mortality (15%)[5]. Another parameter used to measure vascular stiffness is the cardio-ankle vascular index (CAVI), which is independent of the blood pressure level at the time of measurement[6].

Chitalia N. *et al.* found that there was an association between vitamin D deficiency (25-OH vitamin D < 37.5 ng/mL) and vascular stiffness in CKD patients[7]. Giving calciferol supplementation to CKD patients with vitamin D deficiency helped improve vascular stiffness. A randomized, double-blind, placebo-controlled trial of Kumar V. *et al.* found that 16 weeks of cholecalciferol supplementation in non-diabetic, stage 3-4 CKD patients significantly increased endothelium-dependent brachial artery flow-mediated dilation[8].

The intervention also led to a significant favorable reduction in pulse wave velocity, parathyroid hormone (iPTH), alkaline phosphatase (ALP), and circulating interleukin-6 level (IL-6). In this trial, vitamin D supplementation may improve vascular function in non-diabetic patients with stage 3–4 CKD and vitamin D deficiency.

In 2017, the Kidney Disease Improving Global Outcomes (KDIGO) suggested that patients with stage 3-5 CKD and vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population[9]. The Endocrine Society suggests that all vitamin D deficient adults be treated with 50,000 IU of vitamin D2 or vitamin D3 once a week for 8 weeks to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 1500 –2000 IU per day[10]. However, there was a study that demonstrated the pulse dose of vitamin D, the study of Albert Shieh, *et al.* which found no hypercalcemia or vitamin D toxicity (100,000 IU weekly for 5 weeks)[11].

There is limited data for vitamin D supplementation in the diabetic patient with CKD. The purpose of this trial is to compare the effects of pulse dose versus continuous dose of calciferol on vascular stiffness in diabetic kidney patients.

Objectives

The primary objective of this study is to compare the effects of pulse dose versus continuous dose of calciferol on vascular stiffness in patients with stage 3-4 CKD, type 2 diabetes mellitus, and vitamin D deficiency. We hypothesized that calciferol supplement with pulse dose would result in a greater reduction in carotid-femoral pulse wave velocity.

Material and methods

The study was an open-label, randomized, block-design trial. Patient enrollment started in January of 2018 and completed in January of 2019, approved by the ethics committee (COA number: 112/2561) and Thai Clinical Trials Registry

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(TCTR20211004007). CKD patients of nephrology clinic with an eGFR between 15 and 60 ml/min per 1.73 m^2 (using the Chronic Kidney Disease Epidemiology Collaboration Formula) were eligible for screening. Inclusion criteria included age 18–75 years, vitamin D deficiency [serum 25(OH)D level ≤ 30 ng/ml], and diabetes mellitus type 2 (evidence of glycated hemoglobin level (HbA1C) ≥ 6.5% or 2 of fasting plasma glucose ≥ 126 mg/dL). Exclusion criteria were serum Calcium (Ca) > 10 mg/dL, serum Phosphorus (P) > 8 mg/dL, intact parathyroid hormone (iPTH) < 15 pg/mL, or alkaline phosphatase (ALP) > 3 times the upper normal limit, dialysis, kidney transplantation, peripheral arterial disease (radiologic findings or ankle-brachial index ≤ 0.9), active infection, pregnancy, and lactation, present or past malignancy, vitamin D (ergocalciferol or cholecalciferol) supplementation within the past 30 days, systolic blood pressure (BP) ≥ 160 mmHg or diastolic BP ≥ 100 mmHg, rheumatologic disease or loss to follow-up.

All patients submitted a written informed consent prior to enrollment. To establish a baseline, hemoglobin level (Hb), blood urea nitrogen (BUN), serum creatinine (sCr), Ca, P, iPTH, 25(OH)D, ALP, HbA1c, and glucose of fasting blood samples, urine analysis, urine albumin creatinine ratio (UACR), cardio-ankle vascular index (CAVI), ankle-brachial index (ABI) and carotid-femoral pulse wave velocity (cfPWV) were measured.

The patients were randomized using a block design technique, prescribed 2 oral doses of Ergocalciferol and assigned 1 of 2 interventions. The pulse dose group received 200,000 IU (10 capsules of Calciferol) at the 0th and 8th weeks while the continuous dose group received 40,000 IU (2 capsules) once a week for 8 weeks and 20,000 IU (1 capsule) once a week for 2 weeks. Both groups were under direct observation. Follow-up visits were done at the 8th and 10th weeks after the baseline visit. cfPWV, CAVI, 25(OH)D, iPTH, sCr, eGFR, Ca, P ALP, and UACR were measured at baseline and the week 10 visit.

Vitamin D supplementation at normal doses usually has no side effects. The toxicity may occur with excessive doses. Symptoms may include nausea, vomiting, loss of appetite, constipation, dehydration, fatigue, irritability, confusion, weakness, and/or weight loss. The patients who had these symptoms could directly consult in the follow-up visits or by phone.

The carotid-femoral pulse wave velocity definition

The patients requested to withhold caffeine and tobacco, arrived in the morning, and rested for 15 minutes. The cfPWV measurement was conducted in a quiet room with low ambient lighting by the same trained investigator who used a Philips IE33 with a linear transducer. The site of cfPWV measurement is between the right common carotid artery and the right femoral artery. We used the Doppler ultrasonographic method to obtain the transit time (Δt) by measuring the length between the right common carotid artery and the right femoral artery. We then transformed the algorithm of maximum upstroke into the intersecting tangent algorithm, with the equation of Millasseau et al.[12]. (equation 1)

$$\Delta t_{\text{intersecting tangent}} = \frac{\Delta t_{\text{maxmal upstroke}} - 14.96}{0.8486} (\text{ms})$$

(equation 1)

The pulse wave velocity was calculated by measuring the direct distance between the carotid and the femoral sites (X_{direct}), divided by $\Delta t_{\text{intersecting tangent}}$ (Δt). Then we used a scaling factor of 0.8 derived from Sugawara et al.[13] (equation 2)

$$\text{PWV} = 0.8 \frac{X_{\text{direct}}}{\Delta t} \left(\frac{m}{s}\right)$$

(equation 2)

cfPWV is a non-invasive, operator-dependent method. From the data of A Yamashina, et al., there is no interobserver or intraobserver variability affecting the validity and reproducibility of PWV

measurement[14]. In this study, the cfPWV measurement was performed by one cardiothoracic technologist and supervised by one cardiologist.

Statistical analysis

The mean (standard deviation [SD]) was used for normally distributed data and the median (interquartile range [IQR]) was used for skewed data. Unadjusted 10-week changes of primary and secondary outcomes were compared between two groups by *t* test and reported with 95% confidence interval (CI).

The sample size was calculated using the equation by Bernard, R., 2000 with the expected cfPWV difference of 1 m/s between groups providing 80% power to demonstrate the cfPWV difference of 1 m/s between groups, with 0.05 target α for a two-sided test. When using a 10% drop-off, the sample size would be at 80 participants (40 in each group). The analyses were performed using STATA software, version 15 (STATACorp LLC, Texas)

Results

Picture 1 depicts the flow of participants in this trial. Of 40 participants initially screened, 31 were randomized and assigned to the pulse dose group (n=16) or the continuous dose group (n=15). One of them in the pulse dose group was lost to follow-up. There were no statistically significant differences in the baseline characteristics, either statins or Renin-angiotensin system (RAS) blocker use (table 1). The mean age was 58 years old. The study participants were all Asian and predominantly female (70%). Only 3.3% had a history of coronary artery disease. The mean BP, eGFR, and 25(OH)D level were 139/75 mmHg, 32 ml/min/1.73 m^2, and 19.3 ng/ml.

Without a baseline adjustment, there was no statistically significant difference in the primary outcome, which was the cfPWV change during the 10-week study, between the pulse and continuous dose groups. The mean difference in the pulse dose group was -1.61 m/s (95% CI -2.85 to -0.36)

Table 1:

baseline characteristics

Variable		Calciferol			
		Pulse dose n = 15		Continuous dose n = 15	
Age	mean (SD), years	58.60	(8.30)	58.47	(8.43)
Body mass index	mean (SD), Kg/m^2	28.85	(6.46)	30.67	(5.23)
Sex	Female	11	(73.3%)	10	(66.7%)
SBP	mean (SD), mmHg	139.73	(12.2)	133.93	(11.3)
DBP	mean (SD), mmHg	76.6	(8.27)	73.33	(13.21)
eGFR	mean (SD), ml/min/1.73m^2	31	(9.12)	33.47	(11.19)
Coronary artery disease		2	(13.3%)	1	(6.7%)
Current smoking status		1	(6.7%)	0	(0.0%)
25(OH)D level	ng/ml	18.78	(5.00)	19.94	(7.56)
Statins		12	(80.0%)	14	(93.3%)
RAS blocker		12	(80%)	10	(66.7%)

(DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; RAS, Renin-angiotensin system; SBP, systolic blood pressure; 25(OH)D, 25-hydroxyvitamin D)

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while it was -1.11 m/s (95%CI -3.59 to 1.37) in the continuous dose group. The mean difference at 10 weeks between the pulse dose group and the continuous dose group was -0.5 (95%CI -3.15 to 2.15) (p=0.703). In the pulse dose group, there seemed to be a bigger cfPWV reduction than in the continuous dose group although without any statistical significance. The primary and secondary outcome data were summarized in Table 2.

The analysis of the secondary outcome, which was the change in the Cardio-ankle vascular index (CAVI) during week 10, demonstrated statistically significant differences. The mean differences at 10 weeks between the pulse dose group and the continuous dose group were -0.97 (95%CI -1.93 to -0.02) (p=0.046) in right CAVI and -1.28 (95%CI -2.4 to -0.16) (p=0.027). In the pulse dose group, the decrease in right CAVI was -0.77 (95%CI -1.57 to 0.04) and -0.92 (95%CI -1.82 to -0.02) in left CAVI, while in the continuous dose group, the decrease in right CAVI was 0.21 (95%CI -0.39 to 0.8) and 0.36 (95%CI -0.39 to 1.11) in left CAVI. The change in the urine albumin-creatinine ratio (UACR) during week 10, demonstrated statistically significant differences. In the pulse dose group, the decrease in UACR was 152.9 mg/g Cr (95%CI -657.1 to 0.9), while in the continuous dose group, the increase in UACR was 107.5 mg/g Cr (95%CI -7.7 to 375) (p=0.011). Apart from the UACR and CAVI changes, there was no statistically significant difference in blood pressure, intact parathyroid hormone, alkaline phosphatase, calcium, or phosphorus as illustrated in Table 2.

There was a statistically significant increase in 25(OH)D level in the pulse dose group (12.89 ng/mL) compared to the continuous dose group (7.72 ng/mL) (p = 0.031). Moreover, more participants in the pulse dose group (n = 10, 66.7%) could achieve the targeted vitamin D level (>30 ng/mL) than in the continuous dose group (n = 6, 40%). Correspondingly, there were more participants who forgot to take ergocalciferol during the study in the continuous dose group (n = 3, 20%) than in the pulse dose

group (n = 1, 6.7%). There were no serious adverse events reported during the vitamin D treatment.

Discussion

The pulse and continuous administration of calciferol supplementation in our study did not result in a statistically significant difference in cfPWV reduction. Both methods of administration demonstrated 1 m/s cfPWV decrease in stage 3-4 CKD patients with diabetes type 2 and 25(OH)D < 30 ng/mL. This is in keeping with possible mechanisms by which vitamin D deficiency affects the vascular tone: the supplementation of vitamin D reduces vascular stiffness. Furthermore, the secondary outcome resulted in a statistically significant difference in CAVI. According to the subgroup analysis of Adeera Levin, et al.[15], the 6-month treatment of vitamin D deficiency in CKD with either calcitriol or calcifediol could help reduce PWV and iPTH when the 25(OH)D level achieved normal range. From the study of Kumar V, et al.[8] and Adeera Levin, et al.[15], supplementation with either calciferol or calcifediol could reduce vascular stiffness in CKD patients. The reason why our study did not achieve the primary outcome might be from the short duration of the study.

Another limit of this study was the unequal dose of calciferol in each group. In the continuous dose group, we determined the dose based on the supplementation recommendation for treating vitamin D deficiency in the general population.

Apart from the intimal calcification caused by atherosclerosis, the specific site of vascular calcification in CKD patients originated from tunica media. Several pathophysiologies of the media calcification were the dedifferentiation of vascular smooth muscles, an increase in apoptotic bodies, a change in elastin and bone remodeling, and a reduction in the inhibitors of vascular calcification such as fetuin-A, matrix-gla protein, osteoprotegerin, and inorganic pyrophosphate. Vitamin D is believed to be one of the modifying factors that help reduce vascular calcification by increasing Klotho and fetuin-A and decreasing PTH and pro-inflammatory cytokines.

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Table 2:

Primary and secondary outcome

Variable		Calciferol			P-value
		Pulse dose n = 15	Continuous dose n = 15	Pulse vs Continuous	
Carotid-femoral pulse wave velocity (m/s)					
Baseline,	mean (SD)	11.71 (4.38)	12.43 (4.88)		
At 10 weeks,	mean (SD)	10.10 (3.30)	11.32 (6.06)		
Change at 10 weeks,	(95% CI)	-1.61 (-2.85 to -0.36)	-1.11 (-3.59 to 1.37)	-0.5 (-3.15 to 2.15)	0.703
25(OH)D level (ng/mL)					
Baseline,	mean (SD)	18.78 (5.00)	19.94 (7.56)		
At 10 weeks,	mean (SD)	31.71 (8.34)	27.61 (8.68)		
Change at 10 weeks,	(95% CI)	12.93 (9.33 to 16.53)	7.68 (4.51 to 10.84)	5.26 (0.68 to 9.83)	0.025
Right cardio-ankle vascular index					
Baseline,	mean (SD)	8.9 (0.95)	8.12 (1.2)		
At 10 weeks,	mean (SD)	8.13 (1.43)	8.33 (1.5)		
Change at 10 weeks,	(95% CI)	-0.77 (-1.57 to 0.04)	0.21 (-0.39 to 0.8)	-0.97 (-1.93 to -0.02)	0.046
Left cardio-ankle vascular index					
Baseline,	mean (SD)	9.07 (1.18)	7.95 (1.14)		
At 10 weeks,	mean (SD)	8.15 (1.52)	8.31 (1.28)		
Change at 10 weeks,	(95% CI)	-0.92 (-1.82 to -0.02)	0.36 (-0.39 to 1.11)	-1.28 (-2.4 to -0.16)	0.027
Intact parathyroid hormone (pg/mL)					
Baseline,	mean (SD)	72.74 (33.64)	81.75 (41.51)		
At 10 weeks,	mean (SD)	63.93 (32.48)	77.69 (40.30)		
Change at 10 weeks,	(95% CI)	-8.81 (-12.21 to -5.4)	-4.06 (-16.78 to 8.66)	-4.75 (-17.76 to 8.27)	0.450
Microalbumin					
Baseline,	median (IQR)	1362.2 (3224.7)	260.3 (737.2)		
At 10 weeks,	median (IQR)	670.4 (32.48)	531.1 (1081)		
Change at 10 weeks,	(95% CI)	-152.9 (-657.1 to -0.9)	107.5 (-7.7 to 375)		0.011
Alkaline phosphatase (U/L)					
Baseline,	mean (SD)	81.93 (21.33)	86.67 (22.45)		
At 10 weeks,	mean (SD)	78.33 (27.84)	86.64 (20.42)		
Change at 10 weeks,	(95% CI)	-3.6 (-15.27 to 8.07)	-0.2 (-8.09 to 7.69)	-3.4 (-12.21 to -5.4)	0.608
Calcium (mg/dL)					
Baseline,	mean (SD)	8.23 (3.21)	9.17 (0.41)		
At 10 weeks,	mean (SD)	8.59 (2.41)	9.09 (0.62)		
Change at 10 weeks,	(95% CI)	0.36 (-0.98 to 1.7)	-0.09 (-0.26 to 0.08)	0.45 (-0.9 to 1.79)	0.488

Table 2:

Primary and secondary outcome (continued)

Variable		Calciferol			P-value
		Pulse dose n = 15	Continuous dose n = 15	Pulse vs Continuous	
Phosphorus (mg/dL)					
Baseline,	mean (SD)	4.15 (0.44)	4.05 (0.46)		
At 10 weeks,	mean (SD)	4.1 (0.6)	4.01 (0.47)		
Change at 10 weeks,	(95% CI)	-0.05 (-0.41 to 0.32)	-0.04 (-0.2 to 0.12)	-0.01 (-0.4 to 0.38)	0.971
Systolic blood pressure (mmHg)					
Baseline,	mean (SD)	139.73 (12.2)	133.93 (11.31)		
At 10 weeks,	mean (SD)	136.6 (14.73)	136.53 (15.55)		
Change at 10 weeks,	(95% CI)	-3.13 (-12.22 to 5.95)	2.6 (-9.09 to 14.29)	-5.73 (-19.87 to 8.41)	0.413
Diastolic blood pressure (mmHg)					
Baseline,	mean (SD)	76.6 (8.27)	73.33 (13.21)		
At 10 weeks,	mean (SD)	75.13 (10.88)	74.67 (14.8)		
Change at 10 weeks,	(95% CI)	-1.47 (-9.66 to 6.73)	1.33 (-7.35 to 10.02)	-2.8 (-14.2 to 8.6)	0.618

However, a meta-analysis of MC Mann, et al.[16] showed that vitamin D supplementation was not beneficial to mortality and cardiovascular outcomes among CKD. Currently, it remains inconclusive that vitamin D supplementation reduces the risks of death or cardiovascular disease.

From this study, a pulse dose of calciferol can be given to patients to treat vitamin D deficiency, reduce vascular stiffness and rapidly restore a normal vitamin D level, with the added benefit of convenience.

Conclusion

10 weeks of calciferol given to CKD patients with T2DM and 25(OH)D < 30 ng/mL could achieve a more reduction of Cardio-ankle vascular index in the pulse dose than in the continuous dose groups. Although no statistically significant change in Carotid-femoral pulse wave velocity (cfPWV), there seemed to be a bigger cfPWV reduction in the pulse dose, with the achievement of 25(OH)D level. Furthermore, the pulse dose of vitamin D was

considered to be attractive to restore normal vitamin D status rapidly and conveniently without any side effects.

Conflict of interest

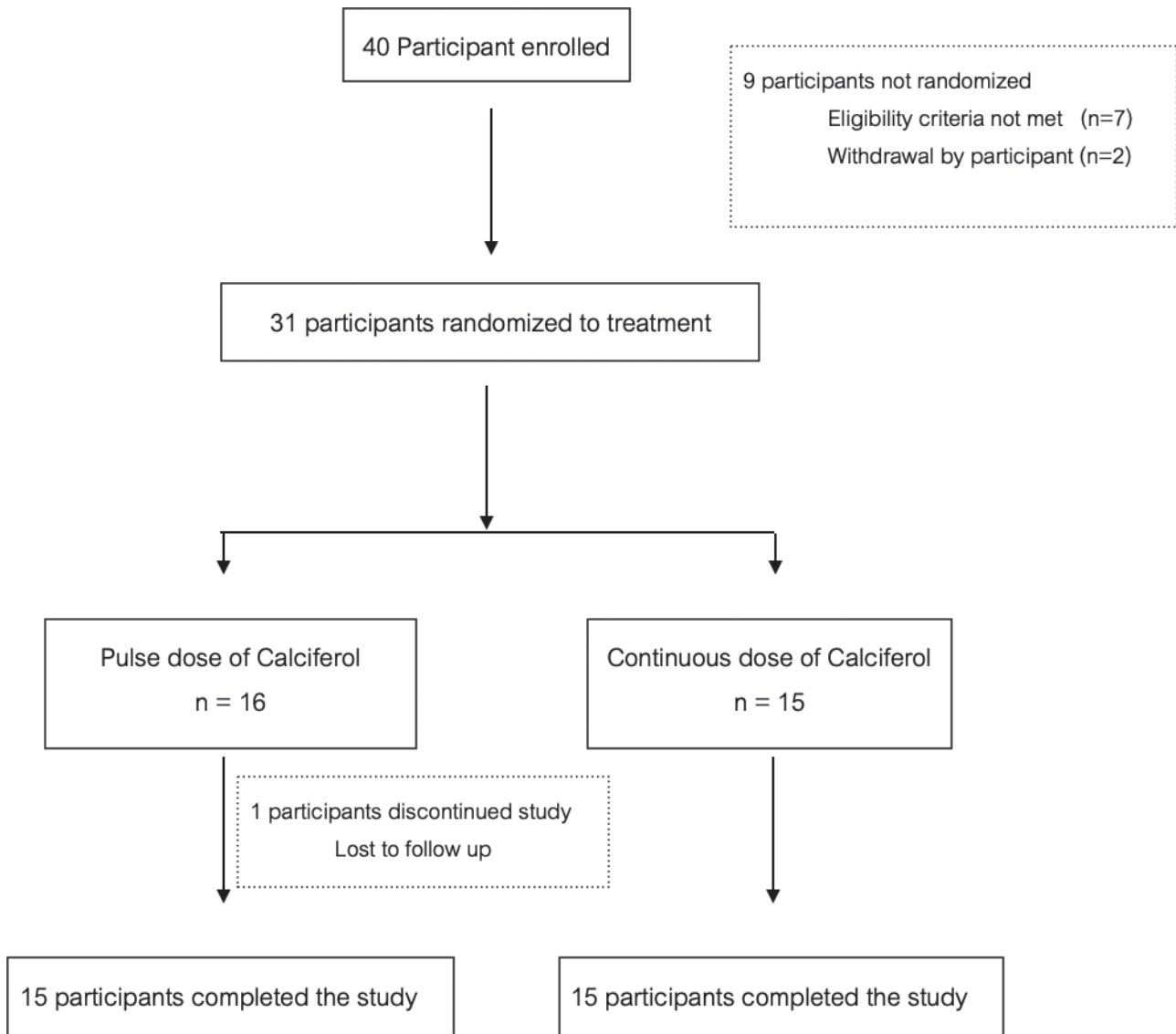There is no conflict of interest to declare.

Acknowledgements

Figure 1: Flow diagram of participants in the study.

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