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NEPHROLOGY - REVIEW

Vitamin D supplementation for the improvement of vascular function in patients with chronic kidney disease: a meta-analysis of randomized controlled trials

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Abstract

Background The efficacy of vitamin D on vascular function remains controversial in chronic kidney disease (CKD) patients. The aim of the present work was to perform a meta-analysis of randomized controlled trials to evaluate the efficacy of vitamin D on vascular function in CKD patients.

Methods We searched Medline, the Cochrane Central Register of Controlled Trials, Embase, the Science Citation Index, and clinical trial registries for randomized controlled trials comparing vitamin D with a placebo in CKD patients.

Results We included seven trials. For flow-mediated dilation (FMD), there was no significant difference between the two groups (WMD 1.66%; 95% CI −0.2 to 3.51, $p=0.08$; with significant heterogeneity, $p<0.0001$, $I^2=89\%$). We conducted a subgroup analysis. In the cholecalciferol group, compared with the placebo group, cholecalciferol significantly increased FMD (WMD 5.49%; 95% CI 4.36–6.62, $p<0.0001$). In the 2 ug paricalcitol group, compared with the placebo group, paricalcitol significantly increased FMD (WMD 2.09%; 95% CI 1.28–2.9, $p<0.0001$; without significant heterogeneity, $p=0.47$, $I^2=0\%$). In the 1 ug paricalcitol group, there was no significant difference between the two groups. For pulse wave velocity (PWV), vitamin D significantly decreased PWV compared with the placebo (WMD −0.93 m/s; 95% CI −1.71 to −0.15, $p=0.02$; without significant heterogeneity, $p=0.14$, $I^2=45\%$). For calcium (Ca) and parathyroid hormone (PTH), there was a significant difference between the vitamin D group and the placebo group. For 25-hydroxyvitamin D [25(OH)D], there was a significant difference between the inactive vitamin D group and the placebo group. For phosphorus (P), systolic blood pressure (SBP), and diastolic blood pressure (DBP), there were no significant differences between the two groups.

Conclusions We speculate that vitamin D might be able to improve vascular function in CKD patients. The effect of vitamin D might be associated with its doses and earlier stages of the disease might respond better to vitamin D. Furthermore, trials with larger populations and longer durations are needed in order to provide more reliable evidence.

Keywords Vitamin D · Vascular function · Chronic kidney disease

Introduction

CKD has become an important public health problem. In China, the prevalence of adults with CKD is about 10% [1]. CKD is also an independent risk factor for cardiovascular events and all-cause mortality in these patients. Cardiovascular disease (CVD) is the major cause of morbidity and mortality in CKD patients [2]. Minor renal function reduction is associated with an increased risk of CVD [3]. Most CKD patients die from CVD before developing end-stage renal disease. Therefore, CVD risk reduction is regarded as being important for CKD patients. Vascular dysfunction is present in the early stages of CKD and is one of the main factors that lead to CVD in CKD patients. Vascular

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dysfunction has also been demonstrated to be an independent predictor of cardiovascular risk in these patients [4]. In addition, improvement in endothelial function reflects a reduced risk of CVD in CKD patients.

Active vitamin D insufficiency or deficiency is often observed in the progression of CKD. Low serum 25(OH) D has been demonstrated to be an independent predictor of vascular dysfunction in CKD patients [5]. Furthermore, 25(OH)D deficiency is associated with proteinuria, elevated cardiovascular morbidity and mortality, and lower glomerular filtration rates in CKD patients. Ravani [6] found that serum 25(OH)D is an independent inverse predictor of disease progression and death in CKD patients. In a non-randomized study, Nihil et al. [7] found that vitamin D improved endothelial vasomotor function in stage 3 CKD patients. Another study also demonstrated that vitamin D improves vascular function in experimental diabetes [8]. However, in a randomized study, the outcome showed that vitamin D did not improve endothelial function in women [9]. In another randomized, double-blind study, Witham et al. [10] found that vitamin D supplementation did not improve vascular function in patients with a history of cardiovascular events. It is well known that CKD patients often need supplementation with vitamin D. Therefore, we need to know whether supplementation with vitamin D improves vascular function in CKD patients.

To our knowledge, no published meta-analysis has evaluated the effect of vitamin D on vascular function in CKD patients. In order to find out whether vitamin D can improve vascular function in CKD patients, we included interventional, randomized, and placebo-controlled trials to evaluate its effects.

Methods

Inclusion and exclusion criteria

The systematic review was performed in accordance with preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines and checklists. The studies should meet the following inclusion criteria: (1) The patient should have chronic kidney disease; (2) The primary outcome should represent vascular functions such as FMD or PWV; (3) The study should report the primary outcome; (4) We included all randomized controlled trials that compared vitamin D with a placebo in the treatment of patients with CKD; and (5) CKD is defined as involving a glomerular filtration rate of < 60 mL/min/1.73 m^2 for at least 3 months. We excluded trials if the treatment combined vitamin D with calcium, and if they were reports, letters, comments, or reviews.

Data sources and searches

We searched Medline, Embase, the Science Citation Index, the Cochrane Central Register of Controlled Trials, and clinical trial registries with a search deadline of June 2018. MeSH (Medical Subject Headings) terms and surrogate words for CKD and vitamin D were used in all database searches. The following key words were used: "vitamin D," "vitamin D analog*," "vascular function," "endothelial function," "chronic kidney disease," "chronic kidney failure," "chronic renal insufficiency," "chronic renal disease," "random* controlled trial," and so on (Fig. 1). We only searched English language papers. We also scanned the citations of included studies to identify potentially pertinent trials.

Data extraction and quality assessment

Two independent reviewers extracted the relevant information pertaining to each trial (e.g., number of participants, study length, interventions, outcomes, etc.). Each trial was assessed using the Cochrane risk of bias tool. It contains the following criteria: random sequence generation and allocation sequence (selection bias), blinding (performance and

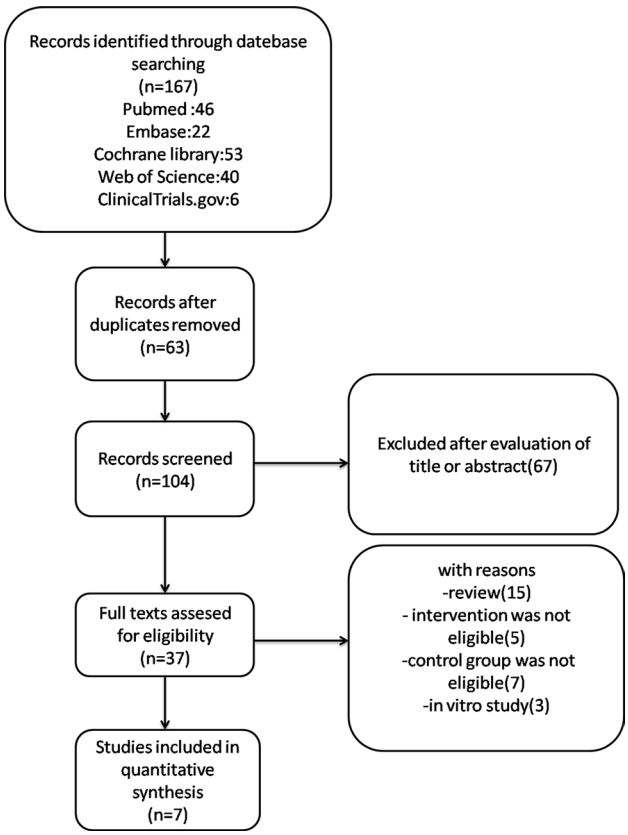

Fig. 1 Selection of studies

detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other possible sources of bias. If there are discrepancies in the data extraction, the third author will independently extract the data. We will then compare the data extracted by the different authors and discuss which data will be used in the review.

Outcome definition

The outcome was the change in FMD, PWV, Ca, P, 25(OH) D, PTH, SBP, and DBP from the baseline to the end of the treatment.

Data synthesis and analysis

The effect size was assessed by weighted mean differences (WMDs) for continuous outcomes and by risk ratio (RR) for dichotomous outcomes with 95% confidence intervals (CI). Heterogeneity was assessed with I^2 statistics. If there were no significant homogeneous results, a fixed-effect model was used. We used Begg's test and Egger's test to investigate publication bias. The heterogeneity was calculated with I^2 statistics. If I^2 was lower than 50%, it was considered as mild heterogeneity. If I^2 was between 50 and 75%, it was considered as moderate heterogeneity. If I^2 was higher than 75%, it was considered as significant heterogeneity. All data were analyzed using Review Manager, version 5.3 (Oxford, UK).

Results

Literature selection and study characteristics

We identified a total of 167 relevant publications in the initial search. Afterwards, 63 duplicates were excluded, and 67 trials were removed based on the title or abstract. The remaining 37 full-text articles were reviewed, and we subsequently excluded 30 trials. This resulted in seven trials [11–17], involving a total of 429 patients (Table 1). Six of the trials involved patients who were in CKD stage 3–4, and one trial involved patients who were in CKD stage 1–3 (Table 1). Four of the trials treated patients with paricalcitol in doses of 1 ug or 2 ug. One trial used ergocalciferol in doses of 5000 IU per week for 1 month followed by 5000 IU/month. One trial used calcitriol in doses of 0.5 ug thrice weekly or calcifediol in doses of 5000 IU thrice weekly. One trial used cholecalciferol in doses of 300,000 IU at baseline and 8 weeks (Table 1). The baseline means of trial outcomes are displayed in Table 2. The procedure for selecting clinical trials is shown in Fig. 1. The duration of treatment was from 1 month to 6 months.

Quality assessment and risk of bias

All trials [11–17] were randomized trials. Three trials [14–16] did not report concrete randomization methods. Two trials [14, 16] did not report selection bias. One trial [16] did not report performance bias. All trials did not report other biases (Fig. 2). There was no significant publication bias in the result of Begg's test ($z=0.368$, $p>0.05$) or Egger's test ($z=0.694$, $p>0.05$). We performed a sensitivity analysis by removing the trial, but the results and heterogeneity did not significantly change.

Effects on FMD (%) and PWV (m/s)

Five trials [11, 12, 14, 15, 17] reported the comparison of FMD between a vitamin D group and a placebo group. The result showed that there was no significant difference between the two groups (WMD 1.66%; 95% CI −0.2 to 3.51, $p=0.08$), Fig. 3; with significant heterogeneity ($p<0.0001$, $I^2=89\%$, Fig. 3). Therefore, we conducted a subgroup analysis. In the cholecalciferol group, compared with the placebo group, cholecalciferol significantly increased FMD

Table 1 Basic characteristics of subjects and treatments of trials

References	No. of patients (treatment/control)	Type of patient	Interventions		Duration (months)
			Treatment	Control	
Alborzi et al. [11]	24 (16/8)	CKD1-3	Paricalcitol (1ug or 2ug)	Placebo	1
Zoccali et al. [12]	88 (44/44)	CKD3-4	Paricalcitol 2ug daily	Placebo	3
Dreyer et al. [13]	29 (14/15)	CKD3-4	ergocalciferol (5000 IU per week for 1 month followed by 5000 IU per month)	Placebo	6
Lundwall et al. [14]	36 (24/12)	CKD3-4	Paricalcitol (1 ug or 2 ug per day)	Placebo	3
Thethi et al. [15]	46 (23/23)	CKD3-4	Paricalcitol (1 mcg per day)	Placebo	3
Levin et al. [16]	89 (55/34)	CKD3b-4	Calcitriol (0.5 ug thrice weekly) Calcifediol (5000 IU thrice weekly)	Placebo	6
Kumar et al. [17]	117 (58/59)	CKD3-4	Cholecalciferol (300,000 IU at baseline and 8 weeks)	Placebo	4

CKD chronic kidney disease

Table 2 Baseline mean of study outcomes

References	FMD% (treatment/control)	PWV m/s (treatment/control)	Ca mg/dL (treatment/control)	P mg/dL (treatment/control)	25(OH)D ng/mL (treatment/control)	PTH pg/mL (treatment/control)	SBP mmHg (treatment/control)	DBP mmHg (treatment/control)
Pooneh [11] paricalcitol 1ug	5.8/5.9	8.4/8.5	–	–	–	66.8/124.9	121/130	64/74
Pooneh [11] paricalcitol 2 ug	6.2/5.9	–	–	–	–	76/124.9	124/130	65/74
Carmine [12]	3.4/3.27	–	9.01/8.85	3.7/3.8	13.2/15.2	102/102	–	–
Gavin [13]	–	–	8.8/8.8	3.8/3.5	–	0.1/0.13	118/123	74/70
Kristina [14] paricalcitol 1ug	5.15/4.6	–	9.05/9.05	3.4/3.09	28.7/25.9	7.3/9.3	147/130	–
Kristina [14] paricalcitol 2ug	4.5/4.6	–	9.13/9.05	3.4/3.09	27.7/25.9	7/9.3	134/130	–
Tina [15]	3.4/2.4	–	–	–	–	–	–	–
Adeera [16] Calcitriol	–	12.2/10.6	9.3/9.3	3.5/3.5	26.6/29.4	–	135/140	70/74
Adeera [16] Calcifediol	–	12.4/10.6	9.2/9.3	3.5/3.5	25.2/29.4	–	140/140	72/74
Vivek [17] Cholecalciferol	7.65/7.85	7.98/7.98	9.01/9.09	3.65/4.03	13.4/13.21	139/146	128/127	83/82

FMD flow-mediated dilation, *PWV* pulse wave velocity, *Ca* calcium, *P* phosphorus, *25(OH)D* 25 hydroxyvitamin D, *PTH* parathyroid hormone, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

(WMD 5.49%; 95% CI 4.36–6.62, $p < 0.0001$, Fig. 3). In the 1 ug paricalcitol group, there was no significant difference between the two groups (WMD − 0.22%; 95% CI − 1.33 to 0.88, $p = 0.69$), Fig. 3; without significant heterogeneity ($p = 0.92$, $I^2 = 0\%$, Fig. 3). In the 2 ug paricalcitol group, compared with the placebo group, paricalcitol significantly increased FMD (WMD 2.09%; 95% CI 1.28–2.9, $p < 0.0001$), Fig. 3; without significant heterogeneity ($p = 0.47$, $I^2 = 0\%$, Fig. 3).

Pulse wave velocity was compared in three trials [13, 16, 17]. Compared with the placebo group, PWV was significantly decreased in the vitamin D group (WMD − 0.93 m/s; 95% CI − 1.71 to − 0.15, $p = 0.02$; without significant heterogeneity, $p = 0.14$, $I^2 = 45\%$, Fig. 4).

Effects on Ca (mg/dL), P (mg/dL), 25(OH)D (ng/mL), and PTH (pg/mL)

Ca was compared in five trials [12–14, 16, 17]. Compared with the placebo, vitamin D significantly increased serum Ca (WMD 0.3 mg/dL; 95% CI 0.14–0.45, $p = 0.0002$; without significant heterogeneity, $p = 0.19$, $I^2 = 31\%$).

P was compared in five trials [12–14, 16, 17]. There was no significant difference between the two groups (WMD 0.16 mg/dL; 95% CI 0–0.31, $p = 0.05$; without significant heterogeneity, $p = 0.50$, $I^2 = 0\%$).

25(OH)D was compared in four trials [12, 14, 16, 17]. We divided vitamin D into an inactive vitamin D group (cholecalciferol, calcifediol) and an active vitamin D group (paricalcitol, calcitriol). Compared with the placebo group, the inactive vitamin D group significantly increased serum 25(OH)D (WMD 46.41 ng/mL; 95% CI − 0.12 to 92.94, $p = 0.05$; with significant heterogeneity, $p < 0.0001$, $I^2 = 97\%$). We did not conduct subgroup analysis because of the lack of data. As for the active vitamin D group, there was no significant difference between the two groups.

Five trials reported the complete PTH data. Compared with the placebo group, vitamin D significantly decreased serum PTH (WMD −17.55 pg/mL; 95% CI − 29.4 to − 5.69, $p = 0.004$; with significant heterogeneity, $p < 0.0001$, $I^2 = 95\%$). We did not conduct subgroup analysis because of the lack of data.

Effects on SBP (mmHg) and DBP (mmHg)

SBP was compared in five trials [11, 13, 14, 16, 17]. There was no significant difference between the two groups (WMD 2.25 mmHg; 95% CI − 0.97 to 5.47, $p = 0.17$; without significant heterogeneity, $p = 0.60$, $I^2 = 0\%$).

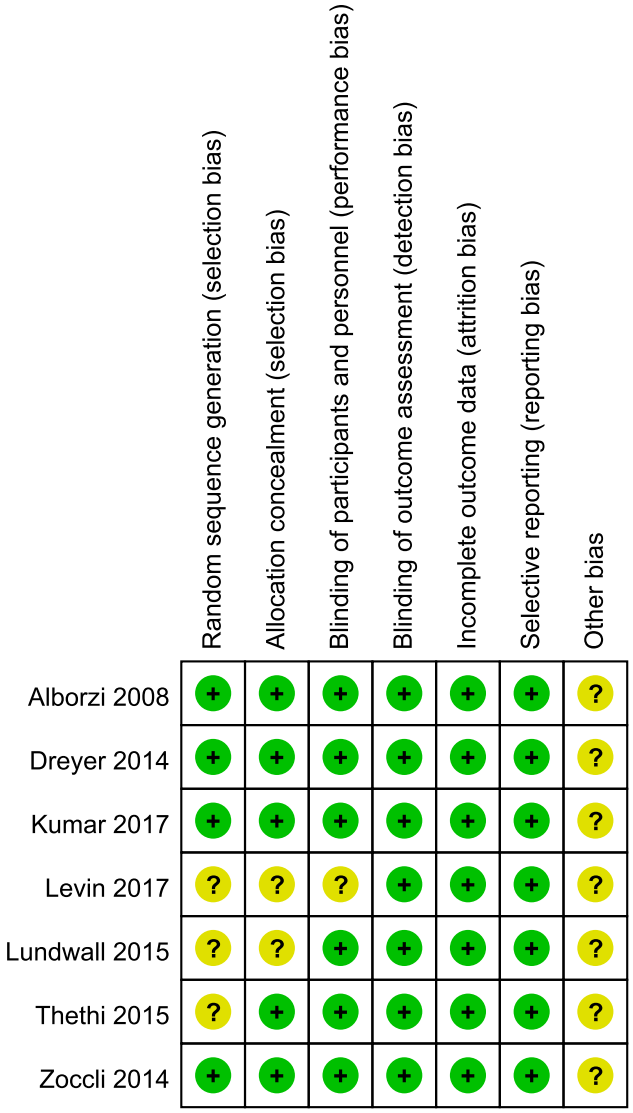

Fig. 2 Risk of bias graph according to recommendations from the Cochrane collaboration

DBP was compared in four trials [11, 13, 16, 17]. There was no significant difference between the two groups (WMD 1.84 mmHg; 95% CI −0.67 to 4.35, $p=0.15$; without significant heterogeneity, $p=0.41$, $I^2=2\%$).

Discussion

We conducted a comprehensive search of randomized controlled trials to evaluate the effect of vitamin D on vascular function in CKD patients. In this review, we included seven trials involving 429 patients. Our review found that vitamin D can improve vascular function in CKD patients.

The measurement of FMD was introduced as a noninvasive approach to assess vasodilator function in patients about 20 years ago. FMD can predict cardiovascular events and provide independent prognostic information in CKD patients [18]. In an observational study, Yilmaz [19] found that the use of FMD was better than intimamedia thickness measurements for monitoring the risk of cardiovascular events in CKD patients. We can observe the improvement of FMD after cardiovascular risk reduction. In summary, FMD can be used as a surrogate marker of vascular function. The association between vitamin D levels and vascular function has been demonstrated in observational and case control studies [5, 20]. Vitamin D improved endothelium-dependent vasodilatation in 5/6 nephrectomized rats and, more importantly, the effect of vitamin D was independent of blood pressure control and serum PTH levels [21]. In a clinical study, Tentori [8] found that CKD patients who received vitamin D had a lower mortality risk compared to those who did not receive vitamin D.

We chose random-model statistical analysis in our review because there was heterogeneity in FMD. We performed subgroup analysis and no heterogeneity was observed. We can infer that the heterogeneity might come from different types and doses of drugs. The largest trial [17], involving 117 patients, had the most significant effect. In this trial, the researcher used cholecalciferol as the treatment, and the other trials used paricalcitol. In these trials [11, 12, 14], 2 ug doses of paricalcitol improved FMD in CKD patients. However, we did not observe improved FMD with 1 ug doses of paricalcitol. Therefore, we speculate that the effect of vitamin D on vascular function might be associated with its doses. We observed that the most obvious effect occurred in the youngest patients [17], which might be because advanced vascular remodeling has not yet been established [22]. The improvement in vascular function might be related to the nitric oxide (NO) system. In vitro and vivo trials, vitamin D supplementation increased endothelial NO synthase gene expression and activity, and improved arterial stiffness [13]. In a vital study, the researchers found that vitamin D reduced albuminuria in patients with diabetic nephropathy [23]. Albuminuria is one of the risks for atherosclerotic complications in CKD patients, and the reduction of albuminuria might improve vascular function in CKD patients. An inflammatory state is associated with vascular dysfunction and cardiovascular mortality in CKD patients. The study found that vitamin D reduced the level of inflammatory biomarkers in CKD patients, such as C-reactive protein, tumor necrosis factor-α, and interlueukin-1 [24]. Therefore, the reduction in inflammatory state could delay the progression of arterial stiffness in CKD patients.

PWV is a marker of arterial stiffness and is associated with cardiovascular risks in CKD patients. Blacher et al. [25] demonstrated a PWV increase of 1 m/s in CKD patients. The all-cause mortality-adjusted odds ratio was 1.39 (95% CI 1.19–1.62). Furthermore, PWV is an independent predictor

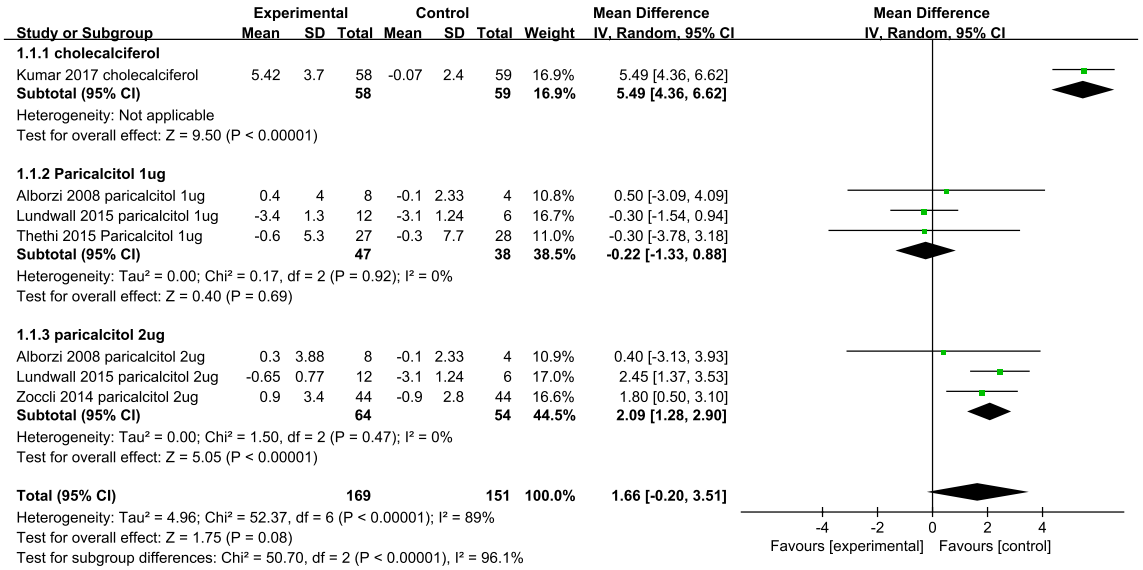

Fig. 3 Forest plots of FMD in CKD patients

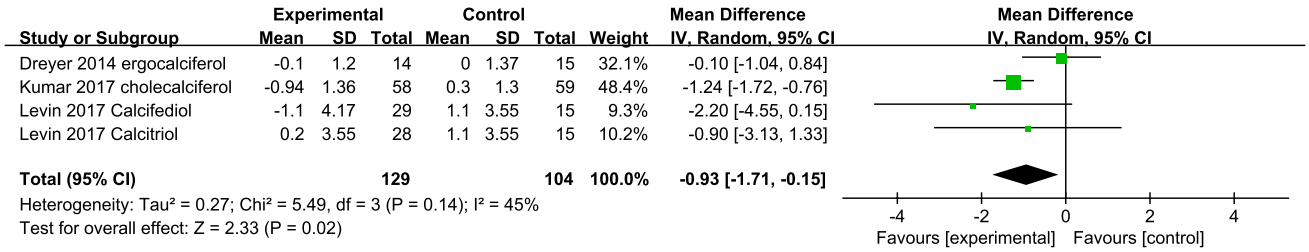

Fig. 4 Forest plots of PWV in CKD patients

of all-cause mortality. In a non-randomized trial, vitamin D supplementation improved PWV [10]. PWV can be used to measure arterial stiffening and calcification, and also reflects arterial remodeling [26]. In the present meta-analysis, all types of vitamin D supplementation improved PWV. The pooled result also showed that vitamin D had a positive effect on PWV. In one study, Levin [16] found that participants who achieved the highest 25(OH)D levels were associated with the greatest decrease in PWV. This further suggests that the effect of vitamin D on vascular function might be related to the dose of vitamin D.

Impaired renal function leads to mineral disorders. Depending on the stage of CKD, we observed a decreased level of serum Ca and an increased level of serum P and PTH in CKD patients. The consequences of these abnormal changes could lead to vascular calcification, renal osteodystrophy, and the development of secondary hyperparathyroidism. In a large, prospective, observational study [27], hypocalcemia was seen to be an independent predictor of all-cause mortality in CKD patients with heart failure. In addition, hypocalcemia is associated with ventricular diastolic dysfunction in CKD patients [28]. Several studies have demonstrated that hyperphosphatemia and increased levels of PTH are associated with increased mortality, cardiovascular events, and fractures in CKD patients [29, 30]. In the present meta-analysis, we found that vitamin D supplementation decreased serum PTH. Although there is heterogeneity in the result, all of the trials showed PTH improvements in the vitamin D group. The reason for the heterogeneity of PTH was that different trials showed different effects on PTH, but all showed positive effects. Therefore, we can conclude that vitamin D improves PTH in CKD patients. We also found that vitamin D supplementation increased serum Ca without increasing P. The effect of vitamin D supplementation on serum Ca, P, and PTH should have benefits for CKD patients.

The prevalence of 25(OH)D deficiency is about 25% in stage 2 CKD patients and 56% in stage 5 CKD patients [7]. In a large sample study, it was reported that 78% of new dialysis patients developed 25(OH)D deficiency [31]. Several factors could lead to 25(OH)D deficiency, such as reduced sun exposure, dietary intake, decreased production

of 25(OH)D precursor molecules, and the loss of renal function [32]. 25(OH)D deficiency has been demonstrated to be associated with vascular calcification and arterial stiffness in CKD patients [33]. Several clinical trials have shown that vitamin D can improve vascular function in CKD patients [34]. In our meta-analysis, we found that inactive vitamin D, including cholecalciferol and calcifediol, increased 25(OH)D in CKD patients, which should have cardiovascular benefits for patients.

There were several limitations in the present meta-analysis. First, we included a relatively small number of participants. Second, we found no significant publication bias in Begg's test and Egger's test. However, the validity of publication biases was limited.

In conclusion, we speculate that vitamin D might be able to improve vascular function in CKD patients. The effect of vitamin D might be associated with its doses and earlier stages of the disease might respond better to vitamin D. Furthermore, trials with larger populations and longer durations are needed in order to provide more reliable evidence.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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