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ORIGINAL ARTICLE

Efficacy of high versus conventional dose of ergocalciferol supplementation on serum 25-hydroxyvitamin D and interleukin-6 levels among hemodialysis patients with vitamin D deficiency: A multicenter, randomized, controlled study

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Abstract

Long-term dialysis involves a chronic inflammatory state and produces a high prevalence of vitamin D deficiency. A clinical trial was conducted in hemodialysis with serum 25-hydroxyvitamin D (25[OH]D) level <30 ng/ml. The conventional-group ($N = 35$) and the high-dose group ($N = 35$) were treated with ergocalciferol according to the K/DOQI guidelines and double dosage of ergocalciferol from the recommendation for 8 weeks, respectively. The main outcomes were measured by serum 25[OH]D and interleukin-6 (IL-6). At the end of 8 weeks, a statistically significant greater increase was observed of mean serum 25[OH]D levels and a decrease of mean parathyroid hormone levels in the high-dose group compared with the conventional-dose group. The high dose group had the higher achievement of vitamin D sufficiency than the conventional-dose group (97.4% vs. 76.4%, $p = 0.012$). No significant difference was found in mean changes of serum IL-6 level in both groups, except subgroup patients with vitamin D deficiency or serum 25[OH]D <20 ng/ml, high dose treatment suppressed serum IL-6 level (−2.67 pg/ml [IQR −6.56 to −0.17], $p = 0.039$). No differences were observed between the two groups in adverse events. Oral high-dose ergocalciferol supplementation has achieved higher vitamin D sufficiency than standard dose in end stage renal disease patients on dialysis.

KEYWORDS

end stage renal disease, ergocalciferol, hemodialysis, inflammation, vitamin D deficiency

INTRODUCTION

Higher levels of circulating proinflammatory cytokines are associated with mortality among patients with end stage renal disease (ESRD) treated with hemodialysis (1). Proinflammatory cytokines especially interleukin (IL)-6 play important roles in the development of T cell dysregulation, atherosclerosis, chronic inflammation, and

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malnutrition in ESRD (2–6). Studies to improve high inflammatory cytokines in ESRD are limited.

Vitamin D has a wide range of biological actions, including inhibiting cellular proliferation and regulating both the innate and adaptive immune system (7, 8). Vitamin D deficiency and/or vitamin D insufficiency is also highly prevalent among patients with advanced chronic kidney disease (CKD) and ESRD (9, 10) and vitamin D deficiency related to developed inflammation, dysfunction of the immune systems, and increased cardiovascular disease (8, 11, 12). Major reasons for vitamin D deficiency in CKD are a significant lack of 25[OH]D, the precursor of the active vitamin D, and declined availability of renal 1α-hydroxylase, a key enzyme involved in the production of active vitamin D (12, 13). Vitamin D supplement could benefit the chronic inflammatory states in ESRD.

However, limited evidence is available for appropriate dosage and efficacy treatment of ergocalciferol supplements in ESRD on dialysis. Related studies have indicated that a conventional dose of ergocalciferol was inadequate for correcting vitamin D deficiency among patients with CKD (14) whereas a conventional dose of ergocalciferol supplement might increase serum 25[OH]D levels in hemodialysis patients without side effect (15). Moreover, vitamin D treatment with cholecalciferol has shown benefit concerning serum levels of inflammatory cytokines among patients on hemodialysis after 8–12 weeks of supplementation (16, 17). Lower serum 25[OH]D levels were associated with higher IL-6 and high sensitive CRP concentrations in metabolic health (18). Whether correcting vitamin D deficiency with high dose ergocalciferol could offer anti-inflammatory effects. Our study was to determine the efficacy of high dose compared with conventional dose ergocalciferol supplementation as recommended in the general population on serum 25[OH]D and inflammatory markers (IL-6) among patients with ESRD on hemodialysis who presented a serum level of 25[OH]D less than 30 ng/ml.

MATERIAL AND METHODS STUDY DESIGN

The present study comprised an 8-week multicentered, prospective randomized, controlled clinical trial comparing high dose and conventional dose ergocalciferol supplementation to treat vitamin D deficiency and/or vitamin D insufficiency in ESRD on hemodialysis. This study was conducted from April 1 through November 30, 2017, and was approved by the institutional review committee, Royal Thai Army Medical Department. All subjects gave written informed consent.

Inclusion criteria included all patients with ESRD undergoing hemodialysis from five dialysis units in Bangkok and Nonthaburi Province, Thailand, aged more than 18 years with a dialysis vintage of at least 3 months, serum 25[OH]D levels less than 30 ng/ml, corrected serum calcium less than 10.5 mg/dl, serum phosphate less than 4.5 mg/dl and serum albumin more than 3 g/dl. Vitamin D deficiency and insufficiency were defined as having serum 25[OH]D levels less than 20 ng/ml and levels in the range of 20–29.9 ng/ml, respectively (19, 20). Exclusion criteria comprised acute medical illness or active infection within the previous month, malignancy, history of chronic inflammatory disease, for example, autoimmune disease, inflammatory bowel disease, liver cirrhosis, pregnancy, breast feeding, previous renal transplantation, use of any vitamin D compound, glucocorticoids or immunosuppressants within 3 months before randomization, history of allergy to ergocalciferol or serum intact parathyroid hormone (intact-PTH) levels more than 500 pg/ml.

Patients on hemodialysis with a diagnosis of ESRD were screened and referred to the investigators for subject eligibility assessment. Demographic and clinical data were collected including age, cause of CKD, dialysis vintage, hemodialysis sessions, comorbidities, and medications. Body weight and height were measured, and body mass index (BMI) was calculated. Average pre-dialysis systolic and diastolic blood pressure were measured from the last three hemodialysis sessions. Adequacy of hemodialysis (KT/V), urea reduction ratio (URR), and normalized protein catabolic rate (normalized PCR) were also included in the analysis.

Eligible participants were randomly assigned by computer-generated randomization procedure in blocks of four. Patients were randomized with a concealed allocation to treatment in parallel groups with high dose or conventional dose ergocalciferol. After the randomization,

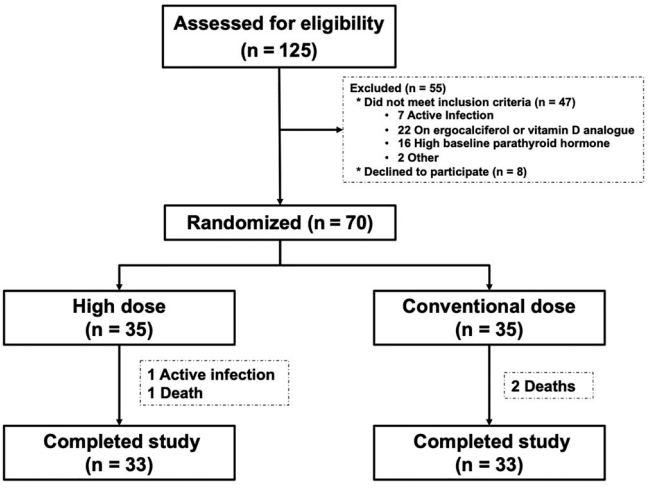


FIGURE 1 Flow chart study

every participant entered an 8-week repletion phase and received ergocalciferol (20 000 IU per capsule; Calciferol BD, the British Dispensary, Thailand). Oral ergocalciferol was prescribed in each group based on serum 25[OH]D levels. In the conventional group, patients with serum 25 [OH]D levels from 20 to 29.9 ng/ml, were given ergocalciferol orally at 50000 units monthly for 2 months and patients with serum 25(OH)D levels less than 20 ng/ml, were given ergocalciferol at 50000 units weekly for 2 months. However, in the high dose group, patients

TABLE 1 Baseline characteristics

Characteristics	High dose ($n = 35$)	Conventional dose ($n = 35$)	p value
Age (years)	58.1 ± 14.6	62.9 ± 13.5	0.164
Male (%)	18 (51.4)	15 (42.9)	0.473
Etiology of CKD			
Diabetes mellitus	19 (54.3)	20 (57.1)	0.213
Hypertension	5 (14.2)	9 (25.7)	
Polycystic kidney disease	2 (5.7)	1 (2.9)	
Chronic glomerulonephritis	8 (22.9)	2 (5.7)	
Others	1 (2.9)	3 (8.6)	
Dialysis vintage (months)	25 (3, 216)	36 (3, 156)	0.288
Hemodialysis session/week (%)			
2	5 (14.3)	10 (28.6)	0.145
3	30 (85.7)	25 (71.4)	
Vascular access (%)			
Arterial venous fistula	23 (65.7)	20 (57.1)	0.744
Arterial venous graft	2 (5.7)	3 (8.6)	
Catheter	10 (28.6)	12 (34.3)	
Comorbidity (%)			
Diabetes mellitus	21 (60)	20 (57.1)	0.808
Hypertension	35 (100)	35 (100)	1.000
Dyslipidemia	30 (85.7)	30 (85.7)	1.000
Ischemic heart disease	11 (31.4)	11 (31.4)	1.000
Medications (%)			
ACE-inhibitor	2 (5.7)	1 (2.9)	0.555
ARB	10 (28.6)	7 (20)	0.403
Beta-blocker	20 (57.1)	15 (42.9)	0.232
Calcium channel blocker	25 (71.4)	23 (65.7)	0.607
Diuretic	19 (54.3)	23 (65.7)	0.329
Other anti-hypertensive drugs	13 (37.1)	15 (42.9)	0.626
Calcium carbonate	32 (91.4)	21 (60)	0.002
Aluminum hydroxide	2 (5.7)	1 (2.9)	0.555
Sevelamer	0 (0)	1 (2.9)	0.314
Statin	29 (82.9)	28 (80)	0.473
Erythropoiesis-stimulating agents	30 (85.7)	29 (82.9)	0.457
Body mass index (kg/m^2)	25.4 ± 5.3	23.1 ± 5.0	0.068
Systolic blood pressure (mmHg)	145 ± 18	141 ± 16	0.301
Diastolic blood pressure (mmHg)	78 ± 10	73 ± 11	0.067

Note: Values expressed as mean ± SD, median (min, max) or *n* (%). *p*-value corresponds to Chi-square test, Independent *t* test or Mann–Whitney *U* test.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease.

TABLE 2 Baseline laboratory data

	High dose ($n = 35$)	Conventional dose ($n = 35$)	p value
Hemoglobin (g/dl)	10.4 ± 1.6	10.8 ± 1.4	0.232
White blood cell count (cells/μl)	6112 ± 1836.9	6289.4 ± 1996.2	0.145
Absolute lymphocyte count (cells/μl)	1456.3 ± 724.7	1710.6 ± 596.1	0.124
Platelet count ($\times 10^3$/μl)	254.7 ± 297.4	277.9 ± 262.5	0.774
Transferrin saturation (%)	33.6 ± 16.9	32.7 ± 14.7	0.808
Serum ferritin (ng/ml)	448.7 ± 386.6	326.1 ± 250.7	0.121
Hemoglobin A1c (%)	5.9 ± 1.2	5.9 ± 1.3	0.975
Serum albumin (g/dl)	3.8 ± 0.5	3.7 ± 0.5	0.227
Vitamin D status: serum 25[OH]D (%)			
<20 ng/ml	15 (42.9)	12 (34.3)	0.461
20–29.9 ng/ml	20 (57.1)	23 (65.7)	
Intact parathyroid hormone (pg/ml)	302.6 ± 186	227 ± 156.6	0.070
Calcium (mg/dl)	8.9 ± 0.7	8.8 ± 0.8	0.445
Phosphorus (mg/dl)	3.5 ± 0.8	3.3 ± 0.8	0.403
Alkaline phosphatase (U/L)	105.1 ± 45.1	121.2 ± 114.3	0.439
Urea reduction ratio (%)	71.1 ± 6.9	72.5 ± 6.9	0.414
KT/V	1.5 ± 0.4	1.6 ± 0.3	0.424
Normalized PCR (g/kg/day)	1.0 ± 0.2	0.9 ± 0.2	0.424

Note: Values expressed as mean ± SD, median (min, max) or n (%). p value corresponds to Chi-square test, independent t test or Mann–Whitney U test.
Abbreviations: 25[OH]D, 25-hydroxyvitamin D; normalized PCR, normalized protein catabolic rate.

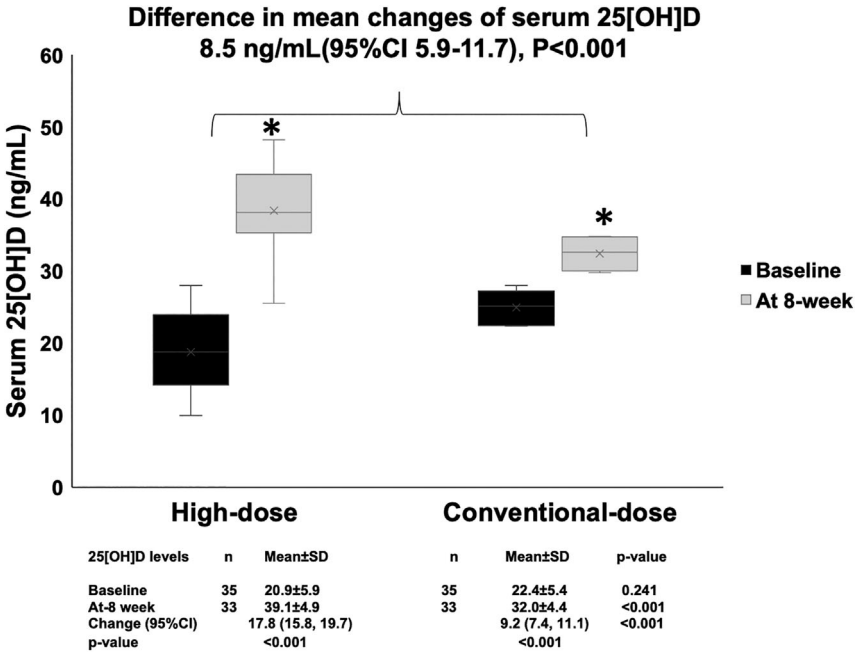


FIGURE 2 Changes in serum 25[OH]D level from baseline during 8 weeks of treatment intergroup differences reached statistical significance (mean change difference of serum 25[OH]D 8.5 ng/ml, 95% CI 5.9–11.7). Values expressed as mean ± SD and mean change (95% CI). 25(OH)D, 25-hydroxyvitamin D

with serum 25[OH]D levels from 20 to 29.9 ng/ml, were given ergocalciferol orally at 100000 units monthly for 2 months and patients with serum 25[OH]D levels less than 20 ng/ml, were given ergocalciferol at 100 000 units weekly for 2 months). Achieved target of treatment or vitamin D sufficiency was defined as serum 25[OH]D level more than 30 ng/ml (21, 22). All patients were advised to take their medicine in the morning and adherence was monitored based on pill counts by a hemodialysis nurse at the hemodialysis unit. Treatment with active

vitamin D compounds, for example, calcitriol, paricalcitol, or doxercalciferol, was prohibited throughout the study. All patients typically continued their normal daily activities during both treatments and were instructed to adhere to a disease and weight-oriented diet and exercise regimen throughout the study.

All blood samples were collected at baseline and at 8 weeks after ergocalciferol administration. Laboratory testing included serum 25[OH]D, urea, creatinine, calcium, phosphorus, albumin, alkaline phosphatase, intact-PTH, hemoglobin, complete blood counts, ferritin, and IL-6 concentrations. Serum 25[OH]D and IL-6 were measured using electrochemiluminescence binding assay (COBAS E 411 analyzer for immunoassay analysis, Roche, Switzerland). The efficacy of a given dose of ergocalciferol was the achievement of vitamin D sufficiency and mean change of serum IL-6 concentrations at the end of treatment. Adverse events and cause-specific hospitalization were monitored during the study.

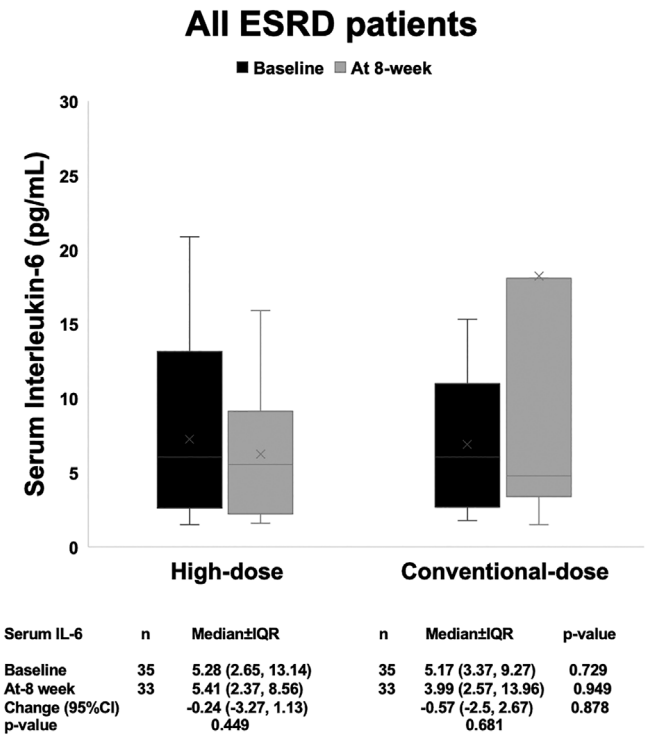
Statistical analysis

Efficacy analyses were prespecified and conducted in the intention-to-treat population. Categorical variables were described as frequencies and continuous variables were described as mean ± SD with normal distribution and as median and interquartile range (IQR) for skewed distribution. Student's *t* test was performed to evaluate differences between continuous variables in cases and controls. Categorical data were compared using the Chi-square test and Fisher's exact test. Results are reported as change of mean or median from baseline to week 8 with 95% confidence intervals (95% CI). *p* values <0.05 were considered statistically significant. All statistical analyses were conducted using the Statistical Package for Social Sciences for Windows, Version 22.

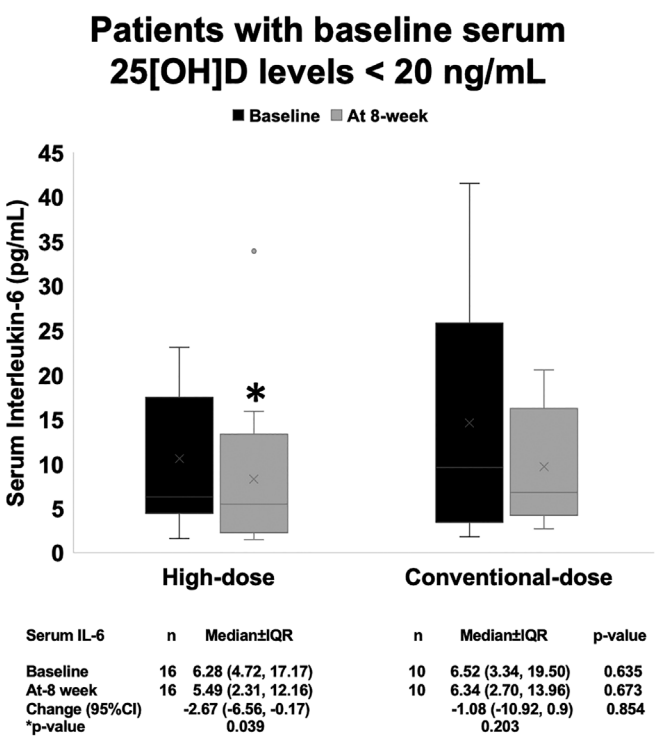
RESULTS

Patients characteristics

Patients were recruited from five dialysis units between April and August 2017. One hundred twenty-five participants were assessed for study eligibility, and 70 patients were randomized (Figure 1). Mean age of the study population was 60.5 ± 14.1 years with median dialysis vintage of 20 (3, 216) months. Major causes of ESRD included diabetes (55.7%) and hypertension (20%). All subjects had vitamin D deficiency ($n = 27$, 38.6%) and vitamin D insufficiency ($n = 43$, 61.4%). Both groups were similar



Serum IL-6	n	Median±IQR	n	Median±IQR	p-value
Baseline	35	5.28 (2.65, 13.14)	35	5.17 (3.37, 9.27)	0.729
At-8 week	33	5.41 (2.37, 8.56)	33	3.99 (2.57, 13.96)	0.949
Change (95%CI)		-0.24 (-3.27, 1.13)		-0.57 (-2.5, 2.67)	0.878
p-value		0.449		0.681	



Serum IL-6	n	Median±IQR	n	Median±IQR	p-value
Baseline	16	6.28 (4.72, 17.17)	10	6.52 (3.34, 19.50)	0.635
At-8 week	16	5.49 (2.31, 12.16)	10	6.34 (2.70, 13.96)	0.673
Change (95%CI)		-2.67 (-6.56, -0.17)		-1.08 (-10.92, 0.9)	0.854
*p-value		0.039		0.203	

FIGURE 3 Changes in serum IL-6 level in all patients with ESRD (a) and patients with ESRD with baseline serum 25[OH]D <20 ng/ml (b) no difference in median changes of serum IL-6 was fund between groups. Serum IL-6 levels decreased significantly among high dose treated patients with baseline serum 25[OH]D <20 ng/ml ($p = 0.039$). Values were expressed as mean ± SD, median ± IQR, and mean or median change (95% CI). 25(OH)D, 25-hydroxyvitamin D; IL-6, interleukin-6

TABLE 3 Changes in other biochemical measurements

Mean changes	High dose ($n = 35$)	Conventional dose ($n = 35$)	p-value between groups
Hemoglobin (g/dl)	0.4 (0.09, 0.79)*	−0.1 (−0.4, 0.3)	0.054
White blood cell count (cells/μl)	232.7 (−459.6, 925)	11.2 (−489.3, 511.7)	0.599
Absolute lymphocyte count (cells/μl)	275.6 (67.3, 483.9)*	138.1 (−78.2, 354.4)	0.355
Serum albumin (g/dl)	−0.03 (−0.2, 0.1)	0.03 (−0.09, 0.14)	0.171
Serum ferritin (ng/ml)	−44.3 (−126.2, 37.7)	44.2 (3.36, 85.0)*	0.055
Intact-parathyroid hormone (pg/ml)	−57.8 (−93.5, −22.2)*	24 (−5.7, 53.6)	0.001
Calcium (mg/dl)	0.4 (0.15, 0.65)*	0.3 (0.1, 0.5)*	0.604
Phosphorus (mg/dl)	0.4 (0.2, 0.7)*	0.4 (0.2, 0.7)*	0.983
Alkaline phosphatase (U/L)	−0.4 (0–13.5, 12.8)	11.2 (−20.1, −2.2)*	0.171

Note: Data mean with 95% CI and * represent statistically significant $p < 0.05$ within group by Pair t test analysis.

TABLE 4 Adverse events during study

Adverse events (N, %)	High dose ($n = 35$)	Conventional dose ($n = 35$)	p-value
All hospitalization	6 (17.1)	5 (14.3)	0.743
Hospitalization from infection	4 (11.4)	3 (8.6)	0.690
Hospitalization from vascular access	1 (2.9)	1 (2.9)	1.000
Hospitalization from cardiovascular disease	1 (2.9)	1 (2.9)	1.000
Hospitalization from fall/fracture	1 (2.9)	1 (2.9)	1.000
Serum calcium >10.5 mg/dl	0 (0)	0 (0)	NA
Serum phosphorus >4.5 mg/dl	6 (18.2)	3 (9.1)	0.282
Serum intact parathyroid <150 pg/ml	0 (0)	0 (0)	NA
Constipation	16 (45.7)	16 (45.7)	0.643
Nausea and vomiting	0 (0)	2 (5.7)	0.124

Note: Values presented as n (%). p-value corresponds to Chi-square test.

with respect to age, sex, comorbid diseases, baseline laboratory values, and adequacy of dialysis parameters (Tables 1 and 2). All of them were 100% adherent to the high dose or conventional dose ergocalciferol. Prescription based on pill counts.

Overall, the mean serum 25[OH]D level was 21.6 ± 4.9 ng/ml at baseline. After 8 weeks of treatment, more patients in the high dose group achieved vitamin D sufficiency than patients in the conventional dose group (97.4% vs. 76.4%, $p = 0.012$). Serum 25[OH]D level significantly increased from 20.9 ± 5.9 to 39.1 ± 4.9 ng/ml in the high dose ergocalciferol group ($p < 0.001$) and increased from 22.4 ± 5.4 to 32 ± 4.4 ng/ml in the conventional dose ergocalciferol group ($p < 0.001$). Moreover, a statistically significantly greater increase of serum 25[OH]D levels was found in the high dose group (17.8, 95% CI 15.8–19.7 ng/ml) compared with the conventional dose group (9.2, 95% CI 7.4–11.1 ng/ml) at 8 weeks ($p < 0.001$) (Figure 2). No significant difference was found in mean changes of serum IL-6 level in both groups, except the patients with baseline serum 25[OH]D levels less than 20 ng/ml had a statistically significant decline in median serum IL-6 (−2.67 with interquartile range −6.56 to −0.17 pg/ml, ($p = 0.039$) in the high dose group (Figure 3).

During the treatment period, no differences were found in mean changes of hemoglobin, white blood cell counts, absolute lymphocyte counts, serum albumin, ferritin, calcium, phosphorus, and alkaline phosphate between both groups except serum intact-PTH significantly decreased after 8 weeks of treatment in the high dose group compared with the conventional dose group (−57.8, 95% CI −93.5 to −22.2 vs. 24.0, 95% CI −5.7 to 53.6 pg/ml, $p = 0.001$) (Table 3).

Adverse events including hospitalization were similar in both treatment groups. The major adverse event was constipation (45.7%). No significant difference was found in hyperphosphatemia (serum phosphorus >4.5 mg/dl)

between both groups. No patients developed low intact PTH (intact-PTH <150 pg/ml) and hypercalcemia (serum calcium >10.5 mg/dl) during study (Table 4).

DISCUSSION

KDIGO guidelines suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population among patients with CKD (21). However, guidelines do not recommend specific dose, frequency, or duration of therapy among patients with ESRD undergoing hemodialysis (21, 23). Although serum 25[OH]D concentration typically increases with both cholecalciferol and ergocalciferol, several studies have reported that the complete restoration of vitamin D status is often not achieved for vitamin D sufficiency. Higher doses of vitamin D supplement may be necessary to effectively correct vitamin D deficiency among patients with CKD (14, 24, 25). In the present study, we found that a high dose of ergocalciferol supplementation for 8 weeks was effective in restoring the vitamin D status of patients with vitamin D insufficiency/deficiency on maintenance dialysis (vitamin D sufficiency was achieved in 97% in the high dose group and 76% in the conventional dose group). Moreover, a statistically significantly greater increase of 25[OH]D levels was found in the high dose group compared with the conventional dose group at 8 weeks. Inconsistent with the results of the Dialysis Infection and Vitamin D study in New England (DIVINE), the vitamin D sufficiency achieved in the long-term hemodialysis group was higher in the high dose ergocalciferol supplementation (91%) group than in the conventional dose ergocalciferol supplementation (65%) group after 12 weeks of therapy (15).

Improved vitamin D status results in decreased inflammatory cytokines in the general population. Multiple studies have suggested that elevations in C-reactive protein (CRP), and inflammatory cytokines are central factors in the network of uremia and strong predictive value for cardiovascular mortality among patients with ESRD (2, 5, 8, 13). Renal CYP27B1 activity decreases in ESRD patients, resulting in the impaired formation of 1,25(OH)2D3. Most therapeutic approached to treat vitamin D deficiency in ESRD patients favor the use of active calcitriol instead of the use of nutritional vitamin D forms. The initial study demonstrated that cholecalciferol supplementation attenuated inflammatory biomarkers among patients undergoing dialysis (16, 17, 26). Our study found no significant impact of ergocalciferol supplementation on serum IL-6 levels. However, lower serum IL-6 levels in high-dose ergocalciferol treatment were observed among patients whose baseline serum 25[OH]D levels were <20 ng/ml. This finding supports our hypothesis that correcting low serum 25[OH]D levels using ergocalciferol supplementation might improve the inflammatory cytokines of the patients with ESRD undergoing hemodialysis especially in the subgroup of patients with vitamin D deficiency. Anti-inflammatory effect might relate to extrarenal production of calcitriol in the setting of minimal renal CYP27B1 activity in ESRD patients.

Low nutritional vitamin D status leads to secondary hyperparathyroidism (9). Cholecalciferol supplement improves hyperparathyroidism among patients with ESRD on dialysis (25, 27). However, no any potential effects were observed of ergocalciferol supplementation on PTH suppression among patients undergoing dialysis (15, 25, 28, 29). We found that high dose of ergocalciferol over the short term of the study was more effective in suppressing PTH because the higher achievement of vitamin D sufficiency resulted in an increase in 1,25[OH]D production and lowering of PTH. Negative findings to decreasing serum PTH level in prior trials may have resulted from lower dose ergocalciferol supplementation. Moreover, no significant treatment effect was found on serum calcium and phosphorus levels between high and convention ergocalciferol supplementation, but a higher percentage of calcium carbonate treatment was found in high-dose group. Thus, it required a larger population and longer follow-up study. Our study showed that adverse event of constipation (45.7%) was similar in the high-dose and conventional-dose group among ESRD patients. It is consistent with systematic review, constipation was reported highly prevalent in subjects on dialysis (14%–90%) (30).

Strengths of the study included the study design, intention-to treat-analysis, and exclusion of participants who concomitantly used active vitamin D or vitamin D analog to directly evaluate the ergocalciferol efficacy. The limitations of the present study included short term follow-up period and lack of biomarker measurements in serum $1,25[OH]_2D$ levels, FGF-23 levels, and other inflammatory cytokines in response to ergocalciferol supplementation. Future studies should also identify the appropriate dose of vitamin D in the long term, frequency, route of administration, and its safety among patients undergoing dialysis.

CONCLUSION

Oral high-dose ergocalciferol administration to 25[OH]D deficient patients on hemodialysis achieved higher vitamin D sufficiency and suppression PTH than the

standard recommended dose after 8 weeks of treatment. It did not show significant benefit on inflammatory cytokine especially IL-6 levels among patients with ESRD, but it might benefit patients with vitamin D deficiency.

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DATA AVAILABILITY STATEMENT

All relevant data are within the paper.

FUNDING

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CONFLICT OF INTERESTS

The authors have declared that no conflicts of interests exist.

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