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Vitamin D supplementation and recombinant human erythropoietin utilization in vitamin D–deficient hemodialysis patients

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Abstract

Introduction: **We sought to examine the impact of ergocalciferol (ERGO) on recombinant human erythropoietin (EPO) use in a cohort of 25-OH vitamin D (25-D)–deficient hemodialysis (HD) patients.**

Methods: **Baseline 25-D levels were obtained for all patients who received HD >6 months in our unit. Patients with levels between 10 and 30 ng/mL received ERGO 50,000 IU x 4 doses and patients with levels <10 ng/mL received 50,000 IU x 6 doses over a 4-month period. Monthly dose of EPO was recorded at baseline and after ERGO supplementation.**

Results: **Baseline 25-D levels were <30 ng/mL in 89% of tested patients. Eighty-one patients were included in this study. Mean baseline 25-D level was 15.3 ± 7.1 ng/mL and increased to 28.5 ± 8.6 ng/mL after ERGO (p<0.0001), and median baseline EPO dose was 21,933 U/month (interquartile range [IQR] 13,867-35,967) and decreased to 18,400 U/month (IQR 11,050-33,000) after ERGO (p=0.17). Forty-six patients (57%) required less EPO after ERGO compared with baseline: 15,450 U/month (IQR 10,056-23,575) vs. 26,242 U/month (IQR 15,717-40,167), respectively (p<0.0001). Thirty-five patients (43%) required a higher dose of EPO after ERGO, 26,350 U/month (IQR 15,875-46,075) vs. 17,667 U/month (IQR 12,021-23,392), respectively (p=0.016). Mean age, sex, vintage, diabetes status, race and 25-D levels did not differ in these 2 groups of patients, either at baseline or after ERGO. Monthly hemoglobin, iron saturation, albumin, intact parathyroid hormone, calcium and phosphorus were unchanged after ERGO in these 2 groups.**

Conclusions: **ERGO use in 25-D–deficient HD patients may lessen the need for EPO. We recommend more aggressive supplementation with ERGO in future studies to achieve levels >30 ng/mL.**

Key words: *Anemia, Calcidiol, Ergocalciferol, Erythropoietin, Hemodialysis, Vitamin D*

Introduction

Vitamin D deficiency is associated with a multitude of clinical consequences, including cardiovascular disease (1, 2), decreased bone mineralization (3-5) and early mortality (6). Treatment of 25-hydroxyvitamin D (25-D) deficiency has been associated with positive outcomes including a reduction in falls and improvements in muscle function in elderly individuals (7), reduced risk of hip and nonvertebral fractures (8) and decreased insulin resistance (9).

Prospective clinical trials of 25-D supplementation in patients with end-stage renal disease (ESRD) are currently lacking, and the impact of 25-D on clinical outcomes such as bone histomorphology is less clear. Several studies have demonstrated that most hemodialysis (10) and peritoneal dialysis patients are deficient in 25-D (11) and that levels frequently normalize with aggressive supplementation using either ergocalciferol (ERGO) or cholecalciferol (12, 13). The impact of 25-D supplementation on outcomes such as secondary hyperparathyroidism in hemodialysis patients appears to be nominal (14), theoretically because dialysis patients lack the capacity to convert 25-D to 1,25-OH_2 vitamin D (calcitriol), but possibly because the adequate dose for supplementation has yet to be established.

While correction of 25-D deficiency appears to have a limited impact on renal osteodystrophy in patients with ESRD, it may improve other clinical outcomes, such as anemia in renal disease. A recent safety and efficacy study of ergocalciferol in hemodialysis patients found a significant reduction in use of recombinant human erythropoietin (EPO) in treated patients (15), with 64% of patients experiencing a reduction in EPO dose after ergocalciferol supplementation.

Correction of anemia with EPO has dramatically improved anemia management in hemodialysis patients (16), but

higher doses are an independent predictor of mortality (17). While the specific mechanism responsible for this increase in mortality is not fully understood, efforts to maximize the benefits of EPO at the lowest possible doses should be investigated. We therefore sought to examine the impact of ERGO supplementation on markers of mineral metabolism, anemia and EPO dose in a cohort of 25-D–deficient hemodialysis patients who were followed prospectively in this pilot study.

Subjects and methods

Study subjects

Baseline D-25 levels were obtained in all patients who received hemodialysis for at least 6 months at Southern California Permanente Medical Group (SCPMG), Los Angeles Medical Center (LAMC) in September of 2008. Patients with any of the following active conditions during the 12-month study period were excluded from the analysis: gastrointestinal bleeding, nonrenal causes of anemia (including myelodysplastic syndrome, multiple myeloma, pure red cell aplasia, thalassemia and sickle cell anemia), active malignancy, major surgery/hospitalization resulting in significant blood loss, and transplantation. We also excluded those patients who refused EPO or ERGO and those who did not require EPO during the 2-month period prior to ERGO supplementation. The study was in adherence with the Declaration of Helsinki and was approved by our institutional review board.

25-D supplementation protocol

25-D deficiency was defined as a baseline 25-D level <30 ng/mL (nmol/L) for our study. Study patients with a baseline 25-D level ≤10 ng/mL received 50,000 IU of ERGO weekly for 1 month (4 doses) followed by 50,000 IU monthly for 3 months (3 doses), totaling 350,000 IU over a 4-month period. Those patients with a baseline 25-D level between 10 and 30 ng/mL received ERGO 50,000 IU monthly for 4 months, totaling 200,000 IU over a 4-month period. ERGO capsules were administered by the hemodialysis nursing staff to all study patients to ensure compliance.

Baseline demographics

Baseline demographics including age, sex, race, cause of ESRD, type of vascular access, first dialysis date and presence of diabetes mellitus were recorded for all study patients. Vintage was calculated using the difference between the date of first dialysis and the study start date (November 1, 2008). This number was then divided by 30 and reported in months.

Laboratory measurements

Baseline and monthly levels were recorded for serum hemoglobin (Hgb), iron saturation (iron sat), ferritin, calcium (Ca^{++}), phosphorus (Phos), intact parathyroid hormone (iPTH) and albumin starting 6 months prior to ERGO supplementation and ending 2 months after final ERGO dose was received by study subjects. Levels of Hgb, Ca and Phos were also measured midmonth for all patients. Monthly laboratory data were recorded between May 1, 2008 and April 31, 2009 (12 months). 25-D levels were measured at baseline and approximately 4 months after the first ERGO supplement was dispensed.

EPO and iron supplementation protocol

Adjustments in EPO (Epogen; Amgen, Thousand Oaks, CA, USA) and iron doses were performed by rounding nephrologists (including fellows in training) according to a protocol that was approved by the Nephrology Department at SCPMG LAMC. Our anemia protocol targeted a Hgb between 10.5 and 12 g/dL. The majority of our hemodialysis patients received EPO as a subcutaneous injection delivered between 1 and 3 times weekly.

Mean monthly dose of EPO (U/month) and mean monthly dose of iron dextran (Infed; Watson Pharmaceuticals Inc., Corona, CA, USA) or sodium ferric gluconate (Ferrlecit; Watson Nephrology, Morristown, NJ, USA) were recorded for all study patients (mg/month). The majority of patients received iron dextran (>90%).

We aimed for an iron saturation level between 20% and 50% and a ferritin level between 300 and 800 ng/mL, but we did not have a strict ceiling for ferritin levels when administering intravenous (i.v.) iron to patients with functional iron deficiency. Adjustments in EPO were generally only made on a monthly basis, but were performed midmonth for patients with a precipitous change in Hgb level or for those with an absolute Hgb level ≥14 g/dL. EPO was held if Hgb exceeded 13.9 g/dL and restarted when Hgb was ≤12.6 g/dL.

Responders vs. nonresponders

Patients were classified as responders if they achieved a final 25-D level ≥30 ng/mL and nonresponders if they did not achieve this level after 4 months of ERGO supplementation.

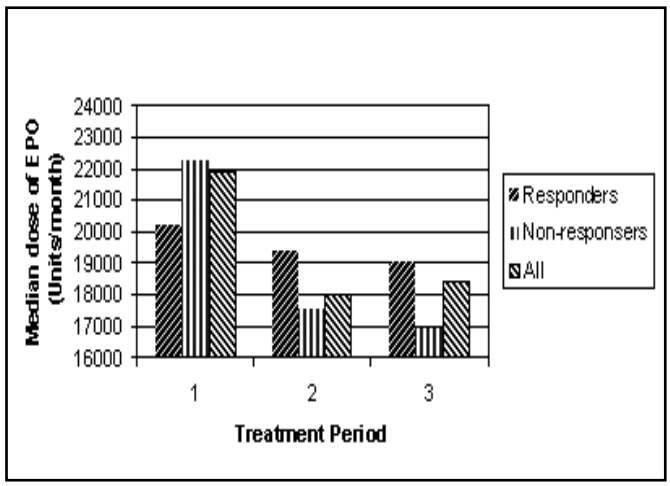

Fig. 1 - Median monthly doses of recombinant human erythropoietin (EPO) at baseline (columns 1), treatment (columns 2) and follow-up periods (columns 3).

Statistics

Normally distributed continuous variables were compared using Student's *t*-test and are presented as the mean ± standard deviation. Continuous variables that were not normally distributed are presented as the median with the interquartile range and compared using the Mann-Whitney *U*-test. Categorical variables were compared using the chi-square analysis, but when cell entries were smaller than 5, Fisher's exact probability test was used.

Results

Baseline 25-D levels were obtained for 126 patients in our hemodialysis unit (1 patient was missing at the time of blood draw). Eighty-nine percent of patients were found to have a level <30 ng/mL and 22% had a level ≤10 ng/mL. We excluded 11 patients who had received hemodialysis for less than 6 months and another 20 patients who met other exclusion criteria, leaving 81 study patients for the final analysis. The mean baseline 25-D level was 15.3 ± 7.1 ng/mL for study patients compared with a mean of 28.5 ± 8.6 ng/mL after 4 months of ERGO supplementation (p<0.0001). Median EPO dose was 21,933 U/month (interquartile range [IQR] 13,867-35,967) at baseline and decreased to 18,400 U/month (IQR 11,050-33,000) after ERGO (p=0.17). Mean baseline 25-D level was 18.6 ± 6.4 ng/mL for men and 12.6 ± 6.6 ng/mL for women (p=0.0002). Vascular access type differed between responders and nonresponders (p=0.043).

Baseline demographics for study patients are listed in Table I. Thirty-six patients (44%) achieved final 25-D levels ≥30 ng/mL. Table II compares laboratory and medication utilization data during the 6 months prior to 25-D supplementation (baseline) with data obtained during the 4 months of ERGO supplementation (treatment) and data obtained during the final 2 months after 25-D supplementation (follow-up) for both responders and nonresponders. Responders increased from a mean baseline 25-D level of 18.2 ± 6.6 to 36.2 ± 4.9 ng/mL (p<0.0001), and nonresponders increased from a baseline of 12.9 ± 6.6 to 22.5 ± 5.0 ng/mL (p<0.0001). Median EPO dose was 20,208 U/month (IQR 14,654-31,000) at baseline and 19,000 U/month (IQR 11,963-29,825) during follow-up in responders (p=0.34). Median EPO dose was 22,233 U/month (IQR 12,633-39,250) at baseline and 16,900 U/month (IQR 10,500-34,750) during follow-up in nonresponders (p=0.19). Median monthly dose of EPO is shown in Figure 1 during baseline, treatment and follow-up study months.

Mean monthly levels of serum calcium, phosphorus and albumin did not differ significantly for responders and nonresponders when compared during baseline, treatment and follow-up study periods (data not shown). Median monthly iPTH levels were 302 pg/mL (IQR 241-523) for nonresponders and 225 pg/mL (IQR 181-304) for responders when compared at baseline (p<0.01), but did not differ significantly during treatment and follow-up periods. Monthly levels (mean or median) for serum calcium, phosphorus, albumin and iPTH did not change significantly after ERGO supplementation for either responders or nonresponders.

Forty-six patients (57%) required a lower dose of EPO during the follow-up period than during the baseline period prior to ERGO supplementation (Tab. III). For this subgroup of patients, the median EPO dose was 26,242 U/month (IQR 15,717-40,167) prior to ERGO, 15,819 U/month (IQR 12,225-36,938) during treatment months (p<0.0001) and 15,450 U/month (IQR 10,056-23,575) during the follow-up period (p<0.001, vs. baseline). Thirty-five patients (43%) required a higher monthly dose of EPO during the follow-up period compared with baseline. This subgroup received a median dose of 17,667 U/month (IQR 12,021-23,392), 24,700 U/month (IQR 14,725-43,538) and 26,350 U/month (IQR 15,875-46,075) of EPO during baseline, treatment and follow-up months, respectively (p=0.066 for baseline compared with treatment months, and p=0.016 for baseline compared with follow-up months).

Monthly laboratory values and iron dosing are compared for patients who required less EPO after ERGO (EPO ↓) and patients who required more EPO after ERGO (EPO ↑) in Table IV. Monthly levels of serum Ca^{++}, Phos and iPTH did not differ significantly when compared during baseline, treat-

TABLE I
BASELINE PATIENT DEMOGRAPHICS FOR ALL PATIENTS AND BY RESPONSE TO ERGOCALCIFEROL mL

	All patients (n=81)	25-D ≥30 ng/mL (n=36)	25-D <30 ng/mL (n=45)	p Value
Mean age ± SD, years	62.1 ± 13.3	63.0 ± 13.7	61.4 ± 13.1	0.58
No. of males (%)	38 (47)	23 (64)	15 (33)	0.0119
Median vintage (IQR), months	35.1 (17.5-54.7)	35.4 (17.5-50.9)	35.1 (20.6-64.8)	0.339
Race, no. (%)				0.1598
Hispanics	39 (48)	16 (44)	23 (51)	
African American	16 (20)	6 (17)	10 (22)	
Asians	16 (20)	11 (31)	5 (11)	
Whites	10 (12)	3 (8)	7 (16)	
Cause of ESRD, no. (%)				0.2105
Diabetes mellitus	48 (59)	22 (61)	26 (58)	
Hypertension	16 (20)	7 (19)	9 (20)	
Glomerulonephritis	10 (12)	2 (6)	8 (18)	
Other/unknown	7 (9)	5 (14)	2 (4)	
Vascular access type, no. (%)				0.04
Arteriovenous fistula	68 (84)	32 (89)	36 (80)	
Arteriovenous graft	4 (5)	3 (8)	1 (2)	
Tunneled catheter	9 (11)	1 (3)	8 (18)	

Responders achieved a 25-D level ≥30 pg/mL after ergocalciferol, and nonresponders did not achieve this level.
ESRD = end-stage renal disease; IQR = interquartile range; SD = standard deviation; 25-D = 25-OH vitamin D.

ment and follow-up periods (data not show). When monthly levels of Hgb, iron sat, ferritin, Ca^{++}, Phos, iPTH and albumin levels were compared between baseline and follow-up periods for these 2 subgroups of patients (EPO ↓ vs. EPO ↑), only ferritin differed significantly in patients who required less EPO. Median ferritin was 939 ng/mL (IQR 686-1,182) during baseline months and 1,068 ng/mL (IQR 953-1,333) during follow-up months (p=0.03).

Median monthly EPO dose was 21,400 U/month (IQR 12,181-35,792) at baseline and 16,825 U/month (IQR 10,488-32,250) during follow-up months in patients who had a baseline 25-D level <20 ng/mL (p=0.23). For patients with a baseline 25-D level ≥20 ng/mL, median EPO dose was 24,133 U/month (IQR 17,667-39,667) at baseline and 21,050 U/month (IQR 15,600-35,250) during follow-up (p=0.25).

Discussion

Most study patients (94%) experienced an increase in 25-D level after ERGO supplementation, but only 44% of patients were able to achieve the target of 30 ng/mL or greater. Nearly one quarter of our study population (those with 25-D levels ≤10 ng/mL) received a total of 350,000 IU of ERGO over a 4-month period, and the remaining patients received a total of 200,000 IU over the same period. Saab et al reported that 95% of patients who received 300,000 IU of ERGO over a 6-month period in St. Louis, Missouri, USA, were able to achieve 25-D levels above 30 ng/mL (15). We were therefore surprised that more of our study patients did not achieve target 25-D levels, especially since our patients were residing in Southern California. One factor that may

TABLE II
MEAN (± SD) AND MEDIAN (IQR) MONTHLY LABORATORY VALUES, IRON AND EPO DOSES FOR RESPONDERS AND NONRESPONDERS

	25-D ≥30 ng/mL (n=36)	25-D <30 ng/mL (n=45)	p Value
Mean baseline Hgb level, g/dL	11.5 ± 0.7	11.3 ± 0.6	0.23
Mean Hgb during treatment, g/dL	11.5 ± 0.9	11.7 ± 0.8	0.55
Mean Hgb during follow-up	11.2 ± 0.8	11.5 ± 0.9	0.21
Median baseline EPO dose, U/month (IQR)	20,208 (14,654-31,000)	22,233 (12,633-39,250)	0.29
Median EPO during treatment period, U/month (IQR)	19,363 (13,231-29,738)	17,500 (13,000-45,250)	0.33
Median EPO dose during follow-up period, U/month (IQR)	19,000 (11,963-29,825)	16,900 (10,500-34,750)	0.48
Mean baseline iron sat., %	36.5 ± 10.2	34.8 ± 11.0	0.47
Mean iron sat. during treatment	36.1 ± 8.7	34.2 ± 7.0	0.27
Mean iron sat. during follow-up	37.1 ± 12.7	35.0 ± 10.8	0.41
Median baseline iron dose, mg/month (IQR)	150 (100-233)	150 (100-267)	0.78
Median iron dose during treatment period, mg/month (IQR)	163 (69-253)	175 (100-300)	0.47
Median iron dose during follow-up period, mg/month (IQR)	113 (88-250)	100 (0-250)	0.32
Median baseline ferritin, ng/mL (IQR)	987 (569-1112)	1,130 (832-1282)	0.067
Median ferritin during treatment period, ng/mL (IQR)	953 (746-1192)	1,130 (878-1,306)	0.0094
Median ferritin during follow-up period, ng/mL (IQR)	1,023 (830-1176)	1,129 (992-1,372)	0.024

EPO = recombinant human erythropoietin; Hgb = hemoglobin; IQR = interquartile range; iron sat. = iron saturation; SD = standard deviation; 25-D = 25-OH vitamin D.

have contributed to this finding is that our patients received ERGO supplementation between the months of November and February, while patients in the aforementioned study received the ERGO between May and October.

Age, race, vintage and cause of ESRD did not differ between responders and nonresponders (Tab. I). We found that women were less likely to be in the responder group than men, but this was probably explained by the finding that women had lower baseline 25-D levels than men. More of the nonresponders used a central venous catheter (CVC) for vascular access (18%) at the time of study start. CVCs are associated with the greatest risk of infection-related and all-cause mortality (18) compared with the arteriovenous fistula or graft. The subgroup of patients who utilized a CVC may have had a higher burden of inflammation, infection or even vascular disease, since we excluded patients on hemodialysis for less than 6 months.

Mean monthly hemoglobin levels were maintained between 11 and 12 g/dL during baseline, treatment and follow-up study periods for all patients. Mean monthly iron saturation levels were also well maintained during these same 3 study periods in both responders and nonresponders. Ferritin levels were significantly higher in nonresponders than responders during treatment and follow-up study periods. This could signify that nonresponders had a higher inflammatory burden than responders. It should also be noted that baseline iPTH levels were significantly higher in nonresponders. The differences we found between responder and nonresponder groups could explain the differences we found in patient response to ERGO supplementation.

While it was not statistically significant, we found a downward trend in the prescribed EPO dose given to all study patients after ERGO supplementation was begun. It would not be expected that all patients would experience a reduction in EPO use after ERGO supplementation since other factors such as secondary hyperparathyroidism, inflammation and infection all impact responsiveness to EPO. More than half of our study patients (57%) experienced a reduction in monthly EPO dose after treatment with ERGO. We found a highly significant difference when baseline use of EPO was compared with use during treatment and follow-up months ($p<0.001$, for both comparisons). Examination of the sub-

TABLE III
BASELINE PATIENT DEMOGRAPHICS ACCORDING TO EPO UTILIZATION AFTER ERGOCALCIFEROL SUPPLEMENTATION

	EPO ↓	EPO ↑	p Value
No. of patients (%)	46 (57)	35 (43)	
Mean age ± SD, years	61.9 ± 12.5	62.3 ± 14.5	0.76
No. of males (%)	24 (52)	14 (40)	0.39
Median vintage, months (IQR)	35.2 (15.6-52.2)	35.1 (22.3-55.9)	0.55
No. of diabetics (%)	30 (65)	22 (63)	0.82
Race, no. (%)			0.44
Hispanics	19 (41)	20 (57)	
African Americans	11 (24)	5 (14)	
Asians	9 (20)	7 (20)	
Whites	7 (15)	3 (9)	
Vascular access type, %			0.26
Arteriovenous fistula	40	28	
Arteriovenous graft	3	1	
Tunneled catheter	3	6	
Baseline 25-D level	16.3±6.8	13.9±7.3	0.13
Follow-up 25-D level	29.1±6.8	27.6±8.3	0.44

EPO = recombinant human erythropoietin; EPO ↓ = patients who utilized less EPO after ergocalciferol supplementation; EPO ↑ = patients who utilized more EPO after ergocalciferol supplementation; IQR = interquartile range; SD = standard deviation; 25-D = 25-OH vitamin D.

TABLE IV
MEAN (± SD) AND MEDIAN (IQR) MONTHLY LABORATORY VALUES COMPARED FOR PATIENTS WHO REQUIRED LESS EPO (EPO ↓) VS. MORE EPO (EPO ↑) AFTER ERGO SUPPLEMENTATION

	EPO ↓	EPO ↑	p Value
Mean baseline Hgb level, g/dL	11.6 ± 0.7	11.2 ± 0.5	0.011
Mean Hgb during treatment, g/dL	12.1 ± 0.6	10.9 ± 0.6	<0.0001
Mean Hgb during follow-up period, g/dL	11.4 ± 0.8	11.2 ± 0.9	0.21
Mean baseline iron sat., %	33.7 ± 8.9	38.0 ± 12.2	0.075
Mean iron sat. during treatment period, %	34.9 ± 8.1	35.3 ± 7.5	0.84
Mean iron sat. during follow-up period, %	37.2 ± 12.2	34.2 ± 10.7	0.25
Median baseline ferritin, ng/mL (IQR)	939 (686-1,182)	1,127 (897-1,272)	0.11
Median ferritin during treatment period, ng/mL (IQR)	1,015 (776-1,256)	1,141 (859-1,236)	0.38
Median ferritin during follow-up period, ng/mL (IQR)	1,068 (953-1,333)	1,103 (928-1,286)	0.85
Median baseline iron dose, mg/month (IQR)	167 (107-263)	133 (92-233)	0.39
Median iron dose during treatment period, mg/month (IQR)	163 (100-333)	175 (88-263)	0.95
Median iron dose during follow-up period, mg/month (IQR)	200 (13-250)	100 (0-175)	0.06
Mean baseline albumin level, g/dL	3.9 ± 0.3	4.0 ± 0.3	0.30
Mean albumin level during treatment period, g/dL	4.0 ± 0.3	3.9 ± 0.3	0.72
Mean albumin level during follow-up period, g/dL	3.9 ± 0.3	3.9 ± 0.3	0.89

EPO = recombinant human erythropoietin; Hgb = hemoglobin; IQR = interquartile range; iron sat. = iron saturation; SD = standard deviation.

group of patients who required an increase in EPO dose after ERGO supplementation revealed a less significant result when mean monthly baseline EPO dose was compared with the dose received during follow-up months (p=0.016).

The mechanism by which ergocalciferol supplementation leads to a reduction in the use of EPO is not known, but 1 mechanism may be related to its role as a substrate for calcitriol in bone marrow. Calcitriol has a direct effect on bone marrow erythropoietic cells (which have specific 1,25-OH_2 vitamin D receptors) and has been shown to regulate the response to human recombinant erythropoietin in vitro and in vivo (19, 20). 25-D deficiency is also associated with higher C-reactive protein and lower hemoglobin concentrations in patients with chronic kidney disease, thus low levels of 25-D may impair erythropoiesis due to inflammation (21).

We were limited by the number of hemodialysis patients available in our dialysis unit, and so the study was not powered to detect a statistically significant reduction in EPO dose in all treated patients. We intended this to be a pilot study to determine whether a larger prospective study might be feasible and yield significant results. Were such a study to be undertaken, we would recommend larger doses of ERGO to assure that patients achieve a minimum 25-D level $\geq$30 ng/mL, if not higher. Women, patients with CVCs and those with evidence of an inflammatory process would need to be monitored closely to assure adequate 25-D levels. We are reassured by our data that ERGO supplementation in hemodialysis patients will not have a negative impact on markers of mineral metabolism.

We conclude that ERGO supplementation in hemodialysis patients may lessen the need for EPO but probably has no impact on markers of mineral metabolism. The reduction in EPO dose after 25-D supplementation did not achieve statistical significance in all patients, but was highly significant in the majority of treated patients. We observed no meaningful trends in any other laboratory value analyzed, including serum hemoglobin, iron saturation, ferritin, calcium, phosphorus, albumin and iPTH. Our findings regarding the impact of ERGO on markers of mineral metabolism are consistent with those of other recent studies.

Our findings should be considered hypothesis generating and should be confirmed with a randomized controlled study to examine whether correction of 25-D deficiency in hemodialysis patients decreases EPO requirement. EPO injections are costly and will no longer be reimbursed separately from the dialysis procedure after the Centers for Medicare and Medicaid Services (CMS) changes to a bundled reimbursement system. It should be anticipated that for-profit dialysis units will reduce their utilization of EPO after reimbursement changes in 2010 occur and that this will likely result in significantly lower Hgb levels in the United States. An inexpensive supplement such as ERGO might keep patients out of harm's way in future years, when for-profit units will need to reduce total patient care costs.

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References

1. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008;117:503-511.
2. Ginde AA, Scragg R, Schwartz RS, Camargo CA Jr. Prospective study of serum 25-hydroxyvitamin D level, cardiovascular disease mortality, and all-cause mortality in older U.S. adults. J Am Geriatr Soc. 2009;57:1595-1603.
3. Adami S, Bertoldo F, Braga V, et al. 25-Hydroxy vitamin D levels in healthy premenopausal women: association with bone turnover markers and bone mineral density. Bone. 2009;45:423-426.
4. Ensrud KE, Taylor BC, Paudel ML, et al. Serum 25-hydroxyvitamin D levels and rate of hip bone loss in older men. J Clin Endocrinol Metab. 2009;94:2773-2780.
5. Mezquita-Raya P, Muñoz-Torres M, Luna JD, et al. Relation

between vitamin D insufficiency, bone density, and bone metabolism in healthy postmenopausal women. J Bone Miner Res. 2001;16:1408-1415.
6. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med. 2007;167:1730-1737.
7. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporos Int. 2009;20:315-322.
8. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005;293:2257-2264.
9. Pittas AG, Harris SS, Stark PC, Dawson-Hughes B. The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults. Diabetes Care. 2007;30:980-986.
10. Del Valle E, Negri AL, Aguirre C, Fradinger E, Zanchetta JR. Prevalence of 25(OH) vitamin D insufficiency and deficiency in chronic kidney disease stage 5 patients on hemodialysis. Hemodial Int. 2007;11:315-321.
11. Clayton P, Singer R. 25-Hydroxyvitamin D levels in prevalent Australian dialysis patients. Nephrology (Carlton). 2009;14:554-559.
12. Jean G, Souberbielle JC, Chazot C. Monthly cholecalciferol administration in haemodialysis patients: a simple and efficient strategy for vitamin D supplementation. Nephrol Dial Transplant. 2009;24:3799-3805.
13. Jean G, Terrat JC, Vanel T, et al. Daily oral 25-hydroxycholecalciferol supplementation for vitamin D deficiency in haemodialysis patients: effects on mineral metabolism and bone markers. Nephrol Dial Transplant. 2008;23:3670-3676.
14. Tokmak F, Quack I, Schieren G, et al. High-dose cholecalciferol to correct vitamin D deficiency in haemodialysis patients. Nephrol Dial Transplant. 2008;23:4016-4020.
15. Saab G, Young DO, Gincherman Y, Giles K, Norwood K, Coyne DW. Prevalence of vitamin D deficiency and the safety and effectiveness of monthly ergocalciferol in hemodialysis patients. Nephron Clin Pract. 2007;105:c132-c138.
16. Eschbach JW, Abdulhadi MH, Browne JK, et al. Recombinant human erythropoietin in anemic patients with end-stage renal disease: results of a phase III multicenter clinical trial. Ann Intern Med. 1989;111:992-1000.
17. Z hang Y, Thamer M, Stefanik K, Kaufman J, Cotter DJ. Epoetin requirements predict mortality in hemodialysis patients. Am J Kidney Dis. 2004;44:866-876.
18. Pastan S, Soucie JM, McClellan WM. Vascular access and increased risk of death among hemodialysis patients. Kidney Int. 2002;62:620-626.
19. Aucella F, Scalzulli RP, Gatta G, Vigilante M, Carella AM, Stallone C. Calcitriol increases burst-forming unit-erythroid proliferation in chronic renal failure: a synergistic effect with r-HuEpo. Nephron Clin Pract. 2003;95:c121-c127.
20. Carozzi S, Ramello A, Nasini MG, et al. Ca++ and 1,25(OH)2D3 regulate in vitro and in vivo the response to human recombinant erythropoietin in CAPD patients. Adv Perit Dial. 1990;6:312-315.
21. Kendrick J, Targher G, Smits G, Chonchol M. 25-Hydroxyvitamin D deficiency and inflammation and their association with hemoglobin levels in chronic kidney disease. Am J Nephrol. 2009;30:64-72.

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