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The effects of changing vitamin D levels on anemia in chronic kidney disease patients: a retrospective cohort review

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Key words

vitamin D – anemia – erythropoiesis

Abstract. Background: Investigate whether changes in vitamin D levels affected erythropoiesis stimulating agent (ESA) requirements in chronic kidney disease (CKD) patients with anemia. **Methods:** A retrospective cohort study of nondialysis-dependent patients with CKD of all stages. Patients were anemic and on ESA with at least 2 documented 25-hydroxylated vitamin D (D25) levels drawn 4 months apart. Patients were grouped based on the change in their D25 levels. The primary end point evaluated was absolute change in the ESA doses needed to maintain target hemoglobin levels between 11 and 12 g/dl. **Results:** A total of 153 patients met the inclusion criteria for analysis. With the exception of the normal-to-low D25 group, patients showed a trend toward lower ESA doses with time. The low-to-normal vitamin D group showed a significant reduction in dose of 24% (1,415 units, $p = 0.025$). The normal-to-low group, however, showed a 22% increase in dose of 1,270 units (NS). Levels of Ca, PTH, and iron indexes were similar across all groups. **Conclusion:** Our retrospective cohort study demonstrates an ESA sparing effect in patients with vitamin D deficiency after repletion to normal levels. Conversely, there was a trend toward increased ESA requirements in patients who became vitamin D deficient from a previously normal state.

shown that D25 deficiency is associated with lower hemoglobin levels and greater rates of anemia [10]. Clinical observations in end-stage renal disease (ESRD) patients have demonstrated that high doses of active vitamin D (1,25-hydroxyvitamin D) compounds improve anemia [11, 12]. Increased immature erythroid precursor proliferation and synergy with erythropoiesis-stimulating agents (ESA) has also been suggested with 1,25-hydroxyvitamin D therapy in ESRD [13]. A 500-fold higher concentration of 1,25-hydroxyvitamin D has been observed in bone marrow compared to plasma [14]. At the molecular level, 1,25-hydroxyvitamin D has been shown to produce an up-regulation of erythropoietin receptors [15]. D25 is a direct precursor to 1,25-hydroxyvitamin D and the most accurate marker of total body vitamin D levels.

We undertook this study to explore the association between changes in D25 levels and changes in ESA dosing in chronic kidney disease (CKD) patients not on dialysis. Specifically we sought to determine whether a change in D25 level in CKD patients at 2 separate time periods resulted in a change ESA dose between the two time periods.

Introduction

Vitamin D is recognized to play a multitude of biologic roles, including the improvement of muscle strength [1, 2], promotion of cell differentiation [3, 4, 5], modulation of the immune system [5, 6, 7], inhibition of renin synthesis [8], and inhibition of insulin production [9].

We sought to examine whether 25-hydroxyvitamin D (D25) is associated with erythropoiesis. A previous observation had

Methods

A retrospective cohort review within the Los Angeles medical center and its satellite clinics of the Kaiser Permanente Southern California (KPSC) health system was conducted in the time period January 1, 2006, to July 31, 2007. Study subjects were captured through the CKD anemia management program at the Los Angeles medical center of KPSC. CKD (predialysis) patients with ane-

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mia in the nephrology department are routinely referred to a clinical pharmacist who assists in management of ESA dosing and iron repletion. Routine protocol requires regular evaluation of iron saturation and ferritin to ensure patients are adequately iron replete prior to and during ESA administration. Hemoglobin (Hb) values are routinely measured, and ESA doses are adjusted on a protocol basis with a target of Hb of 11 – 12 g/dl.

Patients were included in the study if they had CKD and were not on dialysis, had two or more D25 levels drawn within the specified time period, and required use of ESA for the treatment of their anemia. All patients in the study cohort were receiving epoetin alfa (EPO) as the ESA agent and doses described herein refer to EPO. The time period between the two D25 levels had to be a minimum of 4 months apart. The 4-month time period was chosen because it was longer than the average red blood cell turnover period in a healthy individual. If a subject had more than two D25 levels known in the study period, only the first two D25 levels were used as long as they were separated by at least 4 months. The time of the first D25 level drawn was labeled T1 and the second D25 level was labeled T2.

The main objective of the study was to examine EPO dose change between time T1 and T2. Hb levels and EPO dose evaluation needed to be within 1 month from T1 or T2 for inclusion in the study analysis.

To minimize possible confounders for anemia, we excluded subjects who had at least one occurrence of any form of blood loss anemia, diagnosis of HIV, or diseases affecting the bone marrow. Patients with blood loss anemia were identified through ICD-9 coding for any types of GI bleeding 578.9, 537.83, 569.85, 537.83, 537.84, 530.82, 456.0, 562.11, 562.12, 562.02, 562.02, 578.0, 455.8, 578.1, 569.3, 531.3, 531.3, 531.0, 531.6, 531.4, 532.2, 532.0, 532.6, 532.4; intra-abdominal hemorrhage 459.0; gynecological bleed 623.8, 626.XX, 627.1, 621.4, 628.0; genital-urinary tract hemorrhage 599.89; or procedural coding for transfusion of packed red blood cells (210302, 366823). A physician chart review was performed to determine if the blood loss event occurred at the specified time interval of July 1, 2005, to July 31, 2007, which includes the study time interval and 6 months prior. If the occurrence of the

blood loss event coincided with the study time period or 6 months prior to the study time period, the subject was excluded from the study. In addition, patients were excluded if they had an ICD-9 diagnosis of the following at any time period: multiple myeloma 203.00, 238.6; thalassemia of all types 282.4; myelodysplastic syndrome, myeloid metaplasia 238.7 and myelofibrosis 289.8. HIV patients were identified by crosslinking the medical record numbers of the study patients with the KPSC's HIV registry database, which has been internally validated.

Study patients were categorized according to their D25 change during T1 and T2 into the following groups:

- L to L: low D25 level at T1 and low D25 level at T2
- L to N: low D25 level at T1 and normal D25 level at T2
- N to N: normal D25 level at T1 and normal D25 level at T2
- N to L: normal D25 level at T1 and low D25 level at T2

Low D25 level was defined as < 30 ng/ml. Normal D25 level was defined as ≥ 30 ng/ml. The Nichols Advantage 25-hydroxyvitamin D assay is used in KPSC for the measurement of D25. The assay reports 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, and total 25-hydroxyvitamin D levels. The total D25 level was used as the result of interest for this study. Anemia was defined as Hb < 11 g/dl.

To further describe EPO requirement for each patient, we calculated an EPO-resistant index (ERI) by dividing weekly EPO dose (units) by weight (kg) then dividing that product by Hb (g). The ERI has been a method used to evaluate the dose response effect of EPO therapy in CKD patients [16, 17].

Demographic variables of age, gender, race/ethnicity, estimated glomerular filtration rate (eGFR), diabetes mellitus, and use of activated-vitamin D analogs were obtained for the four groups. eGFR is an automated calculation performed by KPSC computer database and is reported simultaneously with the serum creatinine laboratory result. It is calculated by using the abbreviated modification in renal diseases (MDRD) equation [18]. The diagnosis of diabetes mellitus was retrieved using KPSC's diabetic registry data where a subject was identified as diabetic if he or she

Table 1. Characteristics of the 4 vitamin D cohorts (n = 153).

| Group | L to L | L to N | N to N | N to L | p value |
|---|--------|--------|--------|--------|-------------|
| Sample size | 59 | 37 | 35 | 22 | |
| Mean age | 64.0 | 68.4 | 68.4 | 70.0 | 0.04 |
| Gender (% females) | 49.2 | 56.8 | 45.7 | 50.0 | 0.82 |
| Race by % | | | | | |
| Black | 32.4 | 22.0 | 25.7 | 22.7 | 0.90 |
| White | 48.7 | 45.8 | 45.7 | 63.6 | |
| Hispanic | 24.3 | 27.1 | 25.7 | 22.7 | |
| Asian | 16.2 | 23.7 | 22.9 | 13.6 | |
| unknown | 2.7 | 6.8 | 5.7 | 0 | |
| % 1,25-Vit D analog usage | 33.6 | 21.6 | 25.7 | 31.8 | 0.48 |
| Average eGFR | 27.2 | 30.0 | 27.9 | 26.5 | 0.71 |
| Mean time between D25 measurements (days) | 217 | 171 | 183 | 202 | 0.08 |
| % Diabetes | 88.1 | 62.2 | 65.7 | 68.2 | 0.02 |
| % Transplant pts | 11.9 | 18.9 | 14.3 | 4.6 | 0.45 |

Descriptive characteristics of the study population by D25 cohorts with comparisons; by ANOVA. Differences in mean age and prevalence of diabetes were observed between groups. Gender, race, and renal function were similar across the cohorts.

has one of the following conditions: any diabetes medications dispensed, has an inpatient hospital admission with diabetes mellitus (ICD-9 code 250.xx) recorded as the primary or secondary discharge diagnosis, or has an HbA_{1c} of $\geq 6.7\%$. Patients using activated vitamin D analogs were identified by matching a patient's active medication list with the word terms "calcitriol, calcijex, rocaltrol, paricalcitol, zemplar, doxercalciferol, or hecatorol".

The primary analysis for this study was the average absolute change in EPO dose in each group at time T2 compared to time T1.

When laboratory data were available concurrently with T1 and T2, the average calcium level, iron saturations, ferritin level, parathyroid hormone level (PTH), and eGFR were evaluated. This was performed to determine if any of these variables changed appreciably as an alternative explanation for the change in EPO requirement.

Statistical analysis

Paired t-test was used to test if EPO dose, hemoglobin, PTH, calcium, phosphorus, iron

saturation and ferritin were significantly different between T1 and T2 in each group. Kruskal-Wallis nonparametric analysis of variance (ANOVA) was used to detect if there were significant group differences in EPO dose, hemoglobin, PTH, calcium, phosphorus, iron saturation, and ferritin. χ^2 -test was used to determine significance between two categorical variables. All statistical results were generated with SAS Version 9.13 (SAS Institute, Inc. Cary, NC, USA) statistical software and results with p values < 0.05 were considered statistically significant.

Results

In the study period January 2006 to July 2007 of Kaiser Permanente Southern California health system, a total of 322 patients were identified in the CKD anemia management program at the Los Angeles medical center and its satellite clinics. Of those, 163 subjects had 2 documented D25 levels at least 4 months apart and met the inclusion criteria for the study. Ten patients were excluded (9 due to recent GI bleeding and 1 due to myelodysplastic syndrome).

Table 2. Summary of average ESA dose change among the four groups (n = 153).

| D25 change group | N | Av D25 level T1 | Av D25 level T2 | Av Hb T1 | Av EPO dose T1 | Av EPO dose at T2 | Av EPO dose change | p value (paired t-test) |
|------------------|----|-----------------|-----------------|----------|----------------|-------------------|--------------------|-------------------------|
| L to L | 59 | 17.5 | 18.3 | 11.5 | 5,668 | 4,962 | -706 | 0.15 |
| L to N | 37 | 18.0 | 41.8 | 11.7 | 5,924 | 4,509 | -1,415 | 0.02 |
| N to N | 35 | 43.9 | 43.3 | 11.8 | 3,800 | 3,364 | -436 | 0.23 |
| N to L | 22 | 34.9 | 23.0 | 11.9 | 5,657 | 6,927 | 1,270 | 0.26 |

The average dose and change in EPO dose for each D25 cohort is shown along with the mean D25 levels. The L to N group had the only statistically significant change in EPO dose using paired t-test.

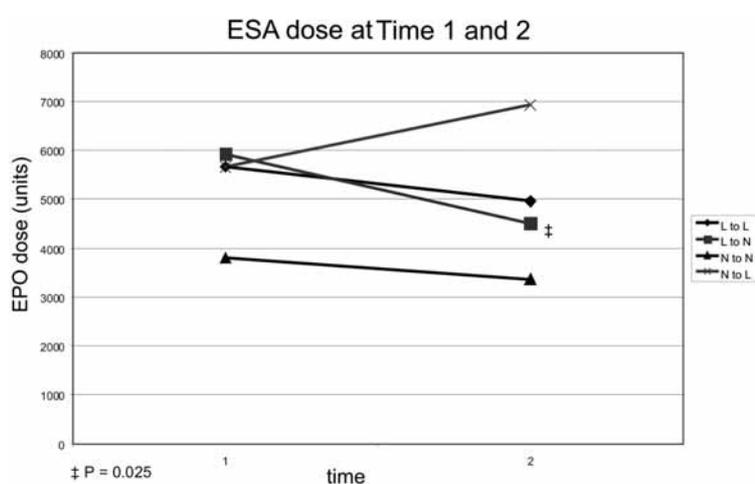


Figure 1. The ESA dose of each cohort at Time 1 and Time 2 are displayed. The N-L group was the only group that showed a trend toward increased ESA need at Time 2. L-N group was the only group to show a statistically significant decrease in ESA need at Time 2.

tients were L to L, 37 patients were L to N, 35 patients were N to N, and 22 patients were N to L.

Baseline characteristics are described in Table 1. There were no statistical differences in variables such as race, gender, and average eGFR. Mean time between D25 levels ranged from 171 to 217 days; thus, the average evaluation period was greater than 5 months within all 4 groups. The average age in the L to L group was 4–6 years younger than in the other groups. There was also a higher proportion of diabetes mellitus in the L to L group. The patients identified as taking 1,25-hydroxyvitamin D (calcitriol, paracalcitol, doxercalciferol) ranged from 21 to 33% by group.

Primary analysis

Three of the four groups showed a reduction of EPO dose between T1 and T2 (Figure 1 and Table 2). The only group to show a statistically significant change in EPO dose was the L to N group with an average reduction of 1,415 units per week ($p = 0.025$). The other two groups that exhibited a trend towards reductions in EPO dose was the L to L and N to N group, but these dose reductions were modest and not statistically significant. The only group to show an upward trend in EPO dose was the N to L group with an increase in dose of 1,270 units per week ($p = 0.26$). The ERI changed similarly to the EPO dosing, paralleling the changing EPO dose requirements of the 4 groups. Although the comparisons were not statistically significant, the N-L and L-N groups showed the greatest differences in ERI at T2 compared to T1.

Table 3. EPO resistance index (ERI) at T1 and T2 by groups.

| D25 change group | N | ERI T1 (units/kg/g) | ERI T2 (units/kg/g) | p value |
|------------------|----|---------------------|---------------------|---------|
| L to L | 59 | 6.27 | 5.89 | 0.19 |
| L to N | 37 | 6.96 | 5.12 | 0.70 |
| N to N | 35 | 4.58 | 4.06 | 0.51 |
| N to L | 22 | 6.45 | 7.83 | 0.47 |

EPO resistance index (ERI) at T1 and T2 for each group calculated by weekly EPO dose divided by weight (kg) then divided by Hb (g). Comparison using t-test showed no statistically significant difference at T1 vs. T2 in each group. Nevertheless, N-L showed an increase in ERI at T2 and conversely the L-N group showed a decrease consistent with the EPO dosing (Table 2).

The 153 subjects were stratified into the four specified groups according to their D25 levels at two different time periods. 59 pa-

Table 4. Mean laboratory variables at T1 and T2 by groups.

| Laboratory variable | L to L | | p value | L to N | | p value | N to N | | p value | N to L | | p value |
|---------------------|---------------|---------------|---------|---------------|---------------|---------|--------------|---------------|---------|---------------|---------------|---------|
| | (N) | | | (N) | | | (N) | | | (N) | | |
| | T1 | T2 | | T1 | T2 | | T1 | T2 | | T1 | T2 | |
| PTH | 194.5 (42) | 204.8 (52) | 0.45 | 127.6 (25) | 126.2 (26) | 0.75 | 92.7 (12) | 123.1 (20) | 0.31 | 117.7 (13) | 149.3 (15) | 0.68 |
| Calcium | 9.0 (50) | 8.9 (49) | 0.40 | 9.2 (27) | 9.2 (29) | 0.44 | 9.4 (29) | 9.3 (25) | 0.25 | 9.4 (19) | 8.9 (17) | 0.03 |
| Iron saturation | 29.3 (47) | 29.8 (48) | 0.49 | 28.6 (31) | 29.4 (30) | 0.85 | 27.6 (31) | 30.7 (29) | 0.28 | 28.1 (20) | 35.5 (17) | 0.06 |
| Ferritin | 434 (49) | 498 (47) | 0.04 | 381 (31) | 408 (30) | 0.34 | 450 (31) | 406 (30) | 0.48 | 423 (19) | 410 (17) | 0.87 |
| GFR | 27.2 (55) | 25.6 (58) | 0.13 | 30.0 (37) | 27.5 (36) | 0.22 | 27.9 (34) | 27.9 (34) | 0.95 | 26.5 (22) | 25.1 (22) | 0.35 |
| Hb | 11.5 (59) | 11.6 (59) | 0.83 | 11.7 (37) | 11.8 (37) | 0.76 | 11.8 (35) | 11.9 (35) | 0.41 | 11.9 (22) | 11.9 (22) | 0.88 |

Laboratory values drawn at the same time (T1 and T2) of D25 draws where available. Hb, iron studies, and calcium were similar across cohorts and within each cohorts time frames. In the N-N cohort, PTH levels increased (non-significant) and calcium levels decreased ($p = 0.03$) which may potentially be a confounder for higher EPO requirement. Paired t-test used for comparison between T1 and T2 values.

Analysis of other variables that may affect EPO dose changes between T1 and T2

Iron saturation levels and ferritin levels did not significantly change between T1 and T2 with no group showing evidence of iron deficiency. Calcium levels were constant from T1 to T2 and did not differ significantly between groups. There was a trend of higher PTH values in the N to N group and the N to L group, but none of the four groups showed a significantly elevated mean parathyroid hormone level to suggest severe secondary hyperparathyroidism. The average Hb values were constant from T1 to T2 in all four groups and were within the target range of 11 – 12 g/dl. eGFR did not change significantly from two time periods, except for a slight reduction of eGFR in the L to N group from 30 to 27.5 ml/min/1.73 m².

Discussion

The results of our study suggest that there may be an ESA sparing effect with the normalization of D25 levels in CKD patients who are initially D25 deficient. The group with low D25 that initially then later normal-

ized their D25 levels (L-N) showed the greatest reduction in ESA dose (24% decrease). Conversely, the ESA dose trend in the group with initially normal D25 levels but subsequent low D25 levels (N-L) had an increase in ESA requirements on average by 1,270 units/week (22% increase).

Due to the retrospective nature of our study, we cannot eliminate the possibility of unmeasured confounding variables that may have affected the changes in ESA dosing. D25 states were reported at two separate time points (T1 and T2) but how those levels were achieved individually was not identified. Changes in D25 could have occurred with intake of over-the-counter or prescription vitamin D supplements, change in sun exposure, or dietary modification. We sought to minimize any known confounders by excluding patients who had any form of blood loss anemia, bone marrow disorders, or HIV. The four groups showed similar baseline characteristics with the exception of age and number of patients with diabetes. These differences were largely due to the L to L group being younger with a higher percentage of diabetics.

We also identified and measured variables that may influence patients' anemia level and

their ESA requirements, such as the degree of hyperparathyroidism, iron deficiency, and changes in eGFR when available concurrently with D25 levels. None of the subjects was found to have exceedingly high PTH, low or high iron indices, or significant changes in their eGFR to account for the changes in ESA dosing. There was an increase in iron saturation in the N to L group from 28.1% to 35.5%, but this change should have theoretically reduced ESA need rather than increasing it.

Previously, Saab et al. [19] demonstrated an ESA sparing effect after treatment of patients with ESRD with ergocalciferol as a secondary analysis. Other clinical studies investigated the administration of high-dose 1,25-hydroxyvitamin D analogs and their effects on anemia, rather than the use of D25. These studies included patients with ESRD already on dialysis compared to this study which evaluated CKD patients not on dialysis.

Using Hb levels to assess the anemia would have been a more direct measure of anemia but not feasible due to recommended and widespread use of ESA for CKD patients with anemia. A previous study in CKD and non-CKD individuals revealed that mean Hb was lower in individuals with D25 deficiency compared to D25 replete individuals in both those who used ESA and those who did not [10]. Our current study used change in ESA dose as a surrogate end point for anemia since the participants were all CKD with target Hb levels near 11 g/dl. There is tight adherence to the ESA dose titration protocol based on a patient's Hb trend by the clinical pharmacy team at our facility. The reliability of ESA dose change is also evident in the fact that the measured average Hb values of all four groups were within the range of 11 – 12 g/dl. These values did not change appreciably from T1 to T2. Our study also classified D25 as normal or deficient instead of evaluating the correlation between D25 and EPO. The rationale for this is that once an individual reaches a sufficient D25 level, further increases would not be as beneficial as for someone who had a deficient D25 level and became replete. Thus, simply determining a correlation between D25 changes and anemia undermines our hypothesis that D25 sufficiency is important for improving anemia rather than higher D25 being better.

The use of activated 1,25-hydroxyvitamin D analogs was prevalent in our study population, which was not surprising. However, 1,25-hydroxyvitamin D analog use did not seem to confound our results for two reasons. First, there were no significant differences in rate of patients who used 1,25-hydroxyvitamin D analogs among the four groups. Although we did not have the exact dosages of 1,25-hydroxyvitamin D analogs, previous observations have demonstrated a class/drug effect of active vitamin D on erythropoiesis and not necessarily a dose-dependent effect [11]. Secondly, the L to N group, which was the only group to show a statistically significant reduction in ESA dose, had the lowest percentage of patients on calcitriol (21.6%).

Possible mechanisms

We propose that repletion of D25 has a beneficial role in red blood cell production, even in patients with advanced CKD and lack of renal 1- α -hydroxylase activity. 1,25-hydroxyvitamin D receptors and localized 1- α -hydroxylase activity are present throughout the body and in different tissues [20]. Repleting D25 stores can provide an adequate bone marrow substrate to allow local conversion of D25 to 1,25-hydroxyvitamin D in an autocrine or paracrine fashion.

D25 repletion may confer more clinical benefit in improving anemia than 1,25-hydroxyvitamin D. In the hematopoietic layer of the bone marrow, levels of 1,25-hydroxyvitamin D have been observed at 500-fold higher concentrations than plasma [14]. Administration of 1,25-hydroxyvitamin D may not provide high enough local levels of 1,25-hydroxyvitamin D levels in the bone marrow to yield a biologic effect on erythropoiesis.

Another hypothesis is that vitamin D plays a role in reducing inflammation commonly seen in patients with CKD. Vitamin D has been shown to reduce markers of inflammation such as C-reactive protein [13, 21, 22], which may ameliorate the anemia effects from chronic disease. Given its retrospective nature, our study did not have C-reactive protein levels on all of our patients because it is not routinely performed as part of anemia and CKD care. We did calculate ERI, which in some studies has been used to associate in-

flammation and malnutrition [16, 17]. The ERI and ERI changes did correspond with D25 levels, suggesting the role of inflammation as a mechanism or confounder. Other studies have also shown that the correction of secondary hyperparathyroidism, either via 1,25-hydroxyvitamin D therapy or parathyroidectomy, may be a mechanism responsible for anemia improvement in CKD [23, 24, 25, 26, 27]. Finally, the effect of vitamin D on producing a favorable calcium concentration conducive for erythropoiesis has been postulated as a mechanism for anemia improvement [28].

Future

Because of the retrospective nature of this study, we cannot establish a causal relationship between D25 repletion and improvement of anemia. This study merely suggests an association between these two entities. Further prospective interventional studies on D25 therapy and anemia outcomes appear warranted.

Conflicts of interest

J.J. Sim has ongoing research funding from Novartis Pharmaceuticals.

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