Title
Vitamin D Therapy and Reduced Mortality in Chronic Kidney Disease—Reply

Journal
JAMA Internal Medicine, 168(18)

ISSN
2168-6106

Authors
Kovesdy, Csaba
Ahmadzadeh, Shahram
Anderson, John
et al.

Publication Date
2008-10-13

DOI
10.1001/archinte.168.18.2046-a

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COMMENTS AND OPINIONS

Vitamin D Treatment in Chronic Kidney Disease: What We Really Need to Know

We read with great interest the article by Kovesdy et al[1] about the association between activated vitamin D (calcitriol) treatment and mortality in chronic kidney disease (CKD). The results are certainly of interest, but as the study is purely observational, these data must be confirmed on prospective randomized studies. At the end of the article, the authors are calling for such randomized studies comparing activated vitamin D and analogues. We have another proposal and working hypothesis that would involve a study comparing active vitamin D (1,25-dihydroxyvitamin D_3 [1,25{OH}2-D3]) with native vitamin D (25-hydroxyvitamin D [25{OH}D]). Indeed, 25(OH)D can bind and directly activate vitamin D receptor. Even if 25 (OH)D is 200 to 400 times less active than activated vitamin D, many studies suggest important physiological roles for native vitamin D, even in patient's receiving hemodialysis.[2] On one hand, circulating 25(OH)D plasma concentrations are 500 to 1000 times higher than 1,25 (OH)2-D3. On the other hand, recent studies have well described that 1α-hydroxylation of 25(OH)D is not restricted to the kidney but also exists in other tissues (notably in parathyroid and bones) and could have an important autocrine and paracrine effect.[2,3] The physiological basis for native vitamin D use in patients with CKD is thus strong, while deficit or insufficiency in 25(OH)D concentration is very frequent in these patients.[4]

Moreover, a recent observational study published by Wolf et al[4] shows a correlation between 25(OH)D concentration and early mortality in incident hemodialysis patients. From these results, it will be of interest to know if the patients treated with activated vitamin D and nontreated patients in the study by Kovesdy et al[1] study had similar 25(OH)D concentrations at baseline.

Regarding physiological and clinical data, we are calling for large prospective randomized studies comparing activated vitamin D and native vitamin D. Because native vitamin D is less expensive than activated vitamin D and analogues, such a study could probably only be initiated by the National Institutes of Health or another independent structure owing to the high economic risk for pharmacological firms if native vitamin D was shown to be better.

Pierre Delanaye, MD
Jean-Marie Krzesinski, MD, PhD
Etienne Cavalier, MD

Correspondence: Dr Delanaye, Service de Dialyse, University of Liège, CHU Sart Tilman, 4000 Liège, Belgium (pierre_delanaye@yahoo.fr).

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Vitamin D Therapy and Reduced Mortality in Chronic Kidney Disease

The study by Kovesdy et al[1] showed that treatment with activated vitamin D (calcitriol) therapy significantly increased survival in patients with CKD not receiving dialysis. However, baseline data between treated and untreated groups was not comparable regarding the bone and mineral abnormalities. The baseline parathyroid hormone (PTH) level was high in the calcitriol group (152 pg/mL vs 75 pg/mL), and more patients in the calcitriol group were using calcium and phosphate binder, indicating that more patients in the calcitriol group had secondary hyperparathyroidism. Thus, a simple explanation of observed benefit with calcitriol therapy is by correcting secondary hyperparathyroidism.

Secondary hyperparathyroidism contributes significantly to progression of the kidney disease and increase in mortality.[2] Previous studies suggest a decreased progression of CKD with better management of associated mineral and bone disorders.[3] To suggest a benefit of ac-

tivated vitamin D independent of PTH lowering, the subgroup data regarding calcitriol use in patients with normal PTH levels should be provided. Also, the mean follow-up after starting the calcitriol therapy should be studied to justify its use in reducing mortality. This may highlight the beneficial effects of vitamin D therapy beyond bone health in patients with CKD.[4]

Hari Kumar K. V. S., MD
Kirtikumar D. Modi, MD, DM
Ratan Jha, MD, DM

Correspondence: Dr Kumar, Department of Endocrinology, Medwin Hospitals, Nampally, Hyderabad, Andhra Pradesh, India (hariendo@rediffmail.com)

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In reply

Kumar et al point out that the benefit of calcitriol therapy seen in our study may have been related to PTH level lowering, based on the observation that treated patients in our study had higher initial serum PTH concentrations, which declined subsequently.[1] This discrepancy in PTH levels among the 2 groups is probably due to the observational nature of our study and the fact that the indication for calcitriol therapy in our cohort was treatment of secondary hyperparathyroidism. This may lead to confounding by medical indication, making it apparently difficult to assess the impact of calcitriol on those with normal PTH levels, as Kumar et al suggested. Our subgroup analyses, however, showed that the benefit of calcitriol was equally present in patient groups with lower (<103 pg/mL) and higher (≥103 pg/mL) PTH levels (to convert to nanograms per liter, multiply by 0.1053), suggesting a PTH-independent mechanism.[1] Furthermore, as mentioned in our article, the PTH levels of the group treated with calcitriol remained higher than those in the untreated group throughout the study period,[1] thus it is difficult to postulate that the observed survival benefit was solely related to the lowering of PTH levels, even though higher PTH levels are associated with increased mortality in this patient population.[2]

There are several other potential mechanisms of action that could explain a benefit of vitamin D receptor activation beyond lowering PTH level.[3] As Delanaye et al point out, this receptor activation can occur not only through the action of the activated vitamin D molecule but also via its precursor, native vitamin D (25[OH]D). The role of this precursor in the treatment of patients with CKD remains largely unanswered, though. While physiologically plausible, there is currently only scant proof that such therapy with 25 (OH)D can even lower PTH levels effectively in CKD.[4] The study by Wolf et al[5] indeed showed an association between lower 25(OH)D levels and mortality in hemodialysis patients, but the deleterious effect of this deficit was abrogated by subsequent treatment with activated vitamin D; therapy with 25(OH)D could not be examined in that study. No 25(OH)D levels were available for analyses in our study.[1] Given the extremely complex nature of vitamin D receptor activation,[3] we agree with Delanaye et al that further studies are necessary to clarify the role of 25(OH)D replacement relative to therapy with activated vitamin D.

Csaba Kovesdy, MD, FASN, CPI
Shahram Ahmadzadeh, MD
John Anderson, MD
Kamyar Kalantar-Zadeh, MD, MPH, PhD

Correspondence: Dr Kovesdy, Department of Medicine, Salem VA Medical Center, 1970 Roanoke Blvd, Salem, VA 24153 (csaba.kovesdy@va.gov).

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Notice of Duplicate Publication: "Potentially Harmful Effect of a Testosterone Dietary Supplement on Prostate Cancer Growth and Metastasis" (*Arch Intern Med.* 2008;168[2]:235-236)

Editor's Note

The article by Shariat et al, published in the January 28 issue of the *Archives* (2008;168[2]:235-236), is nearly identical to an article by the same authors published in another journal in January 2008. Before publication, the authors provided verification through our manuscript submission Web site that the article had not been published elsewhere and was not under consideration by another publisher, and they also received a letter of acceptance from the *Archives* with a reminder of our policy regarding duplicate publication. Their response to this Notice of Duplicate Publication follows.

I acknowledge the receipt of your letter regarding the duplicate publication in the *Archives of Internal Medicine*[1] and *Clinical Cancer Research*.[2] First, I sincerely apologize for our careless actions that resulted in duplicate publications. It was never our intention to produce a duplicate publication. This was a result of a misunderstanding and lack of communication between one of the coauthors and me.

This case report was submitted in the spirit of scientific conduct to raise awareness of potentially harmful ef-