If activated vitamin D supplementation is renoprotective, is it because of suppression of the parathyroid hormone (PTH) or selective vitamin D receptor activation?

In the present issue of Hypertension, Alborzi et al present the results of a well-done prospective clinical trial to evaluate the effects of short-term (1-month) treatment with activated vitamin D (paricalcitol) on blood pressure, biomarkers of inflammation, endothelial function, and measures of urinary protein excretion. The results are fascinating. As others have noted previously, there is an unmistakable effect in reducing urinary protein excretion and also on C-reactive protein levels. Yet, intriguingly, there is no apparent effect on blood pressure, measured either in the office or with 24-hour ambulatory blood pressure monitoring, nor was there an effect on renal hemodynamics, vascular function, or PTH levels.

The combination of persistently high PTH levels and low 1,25-dihydroxyvitamin D levels has been reported to be associated with bone loss, cardiovascular disease, immunosuppression, and increased mortality in patients with end-stage kidney disease. Recent studies in patients with chronic kidney disease (CKD) or end-stage kidney disease have suggested that paricalcitol (a selective activator of the vitamin D receptor) is associated with improved mortality. The explanation for this potential benefit is elusive. Some have suggested that vitamin D receptor activation may mitigate the effects of arterial calcification and possibly even prevent or ameliorate factors leading to atherosclerosis. The later benefits may be related to suppression of inflammation, inhibition of bone loss, or possibly attenuation of the activity of the renin-angiotensin system and transforming growth factor (TGF)-β axis.

The cardiovascular disease associated with CKD is, in large part, related to the associated classic Framingham Heart Study risk factors. However, many have suspected that other factors may play a role, and, in particular, levels of PTH and vitamin D may be important. We know that treatment of patients with activated vitamin D analogs suppresses PTH levels. However, is it too much of 1 (PTH) and too little of the other (1,25-dihydroxyvitamin D) that increases the risk for cardiovascular disease? How can we explain the biological benefit of vitamin D receptor activation?

A number of interesting reports suggest that there may be a relationship between 25-hydroxyvitamin D levels and the risk for kidney disease progression. In one study, investigators noted a stepwise increase in the prevalence of albuminuria in patients from the Third National Health and Nutrition Examination Survey with decreased 25-hydroxyvitamin D levels. However, the cross-sectional design of the study did not allow demonstration of temporal or causal relationships between levels of vitamin D and albuminuria. Another study noted that treatment with the activated vitamin D analog calcitriol was associated with significantly greater survival in patients with CKD. However, the retrospective treatment association, although of interest, begs for a prospective clinical trial to test the causality of these associations.

Experimental studies have demonstrated that inadequate vitamin D receptor activation worsens diabetic nephropathy. Zhang et al noted that more fibronectin and less nephrin were expressed in vitamin D receptor knockout diabetic mice compared with diabetic wild-type mice. They also noted that increased measures of the renin-angiotensin system activation and TGF-β levels accompany more severe renal injury in this model. In this same in vitro model, 1,25-dihydroxyvitamin D3 inhibited high glucose-induced fibronectin production and increased nephrin expression in cultured podocytes. Vitamin D analogs also suppressed high glucose-induced activation of the renin-angiotensin system and TGF in both mesangial and juxtaglomerular cells. Other investigators have noted that combination therapy with an angiotensin-converting enzyme inhibitor and a vitamin D analog suppresses progression of renal insufficiency in uremic rats likely through suppression of TGF-β signaling pathways. Paricalcitol has also been demonstrated in experimental models of obstructive nephropathy to inhibit renal interstitial fibrosis possibly by suppressing TGF-β1–mediated E-cadherin suppression of smooth muscle actin and fibronectin induction in renal tubular epithelial cells. As a result of this effect, there was limited epithelial-to-mesenchymal transition.

Thus, there is consistent experimental evidence indicating that there are unique cellular benefits of activated vitamin D. Consequently, there is a rationale to explore the biological consequence of vitamin D supplementation in humans, particularly in those with CKD.

In clinical studies of vitamin D supplementation, Agarwal et al have noted that paricalcitol reduced proteinuria in patients with CKD. More recently, Szeto et al demonstrated that calcitriol had modest antiproteinuric effects in patients with nephropathy and persistent proteinuria despite renin-angiotensin system blockade. Not yet answered in these studies is whether this is an effect related to suppression of PTH, vitamin D receptor activation, or both.

The small but well done study by Alborzi et al helps answer some of these questions. They demonstrate that there...
is not a blood pressure effect to explain the reduction in proteinuria (at least as determined by brachial artery cuff blood pressure measurements). This does not rule out the possibility that perhaps there may be changes in central aortic pressure or even pulse wave velocity that may be of clinical relevance. They also demonstrate no observable effect on endothelial function as determined by brachial artery reactivity. However, this may not be conclusive, because endothelial function can be confounded by the influence by a number of different drugs, such as renin-angiotensin system blockers and statins. It may also be influenced by diet. However, the clear signals in this study are that proteinuria and C-reactive protein are reduced with short-term activated vitamin D supplementation. Unfortunately, we do not know why. PTH levels were not affected. However, they were not high to start with, and there is always inherent variation of levels that could quench any relevant signal of change.

The intrigue associated with these observations stems from the secondary analyses of multiple clinical trials, which indicate a relationship with time-varying albuminuria and kidney disease progression, as well as cardiovascular events (Figure). Therapeutic strategies that reduce proteinuria may provide a biocasure of therapeutic success in reducing the risk for kidney and cardiovascular disease progression. Is there something here about vitamin D supplementation on top of good blood pressure control with a renin-angiotensin system blocker that is important? Future clinical trials will be required to test this important hypothesis. Fortunately, 2 prospective clinical trials are under way to evaluate activated vitamin D supplementation with paricalcitol in patients with CKD and end-stage kidney disease to see if there are measurable clinical benefits. Perhaps these clinical trials may also unravel the mystery as to whether the benefit may be related to vitamin D receptor activation versus PTH level suppression, or both. Importantly, the results of the study by Alborzi et al help start this process.

Disclosures


References

Is Activated Vitamin D Supplementation Renoprotective?
Matthew R. Weir

Hypertension. 2008;52:211-212; originally published online July 7, 2008; doi: 10.1161/HYPERTENSIONAHA.108.115220

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/52/2/211

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/