The Authors Reply

We thank Nickeleit et al.1 for their comment. In their response, they showed that newborn mice with murine polyomavirus (MPyV) IgG antibodies were protected against autologous MPyV infection and did not develop nephropathy, whereas naive animals exhibited very high plasma MPyV loads in plasma and tissue as well as morphologic signs of nephropathy.1 These results clearly show the role of the humoral response in protecting mice against severe polyomavirus infection.

In humans, the role of antibodies in controlling BK virus (BKV) infection has been obscured by the fact that traditional tests that have been used for previous serology studies do not differentiate between different BKV genotypes.2 Recently, Buck and colleagues3 developed a method using reporter pseudoviruses on the basis of individual representatives of the different BKV genotypes that provides an accurate measure of the BKV-specific antibody response. They showed that BKV genotypes represent distinct serotypes with respect to neutralizing antibody responses.4 Using this test, we were able to shed new light on the role of the humoral response against BKV infection and nephropathy in kidney transplantation.5 Similar results have recently been reported for another polyomavirus, the JC virus, that causes opportunistic brain disease progressive multifocal leukoencephalopathy (PML).6 The authors showed that deficient humoral immunity is a common aspect of the pathogenesis of PML and that vaccination could stimulate and expand humoral immunity against JC virus, thus protecting individuals at risk from developing PML.6

Overall, these data provide strong evidence that strengthening the polyomavirus-specific humoral response by passive immunization or vaccination would be an effective antiviral preventive and/or therapeutic strategy.

DISCLOSURES
None.

REFERENCES


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Studying the Effect of Vitamin D Supplementation on Vascular Function in CKD: A Work in Progress

I read with great interest the article “A randomized clinical trial of vitamin D supplementation on vascular function in CKD” published by Kumar et al.1 in the Journal of the American Society of Nephrology.

The study provided a clear demonstration of a beneficial effect of vitamin D supplementation on flow-mediated dilation (FMD).1 As the authors noted, this may mitigate the cardiovascular disease risk in CKD.

However, I think the jury is still out about the consistency of the positive results shown in this study. For example, in contrast to the results of this study, a randomized clinical trial
by Kendrick et al. showed no evidence of change in FMD in the brachial artery after 6 months of daily supplementation with cholecalciferol. Although the trial by Kendrick et al. did not compare cholecalciferol supplementation with a placebo group, the absence of dilation in response to either cholecalciferol or calcitriol was telling. I should also point out that there was a higher number of smokers in the trial by Kendrick et al. (approximately 49%) than in the trial by Kumar et al. (approximately 9%). Smoking is a known risk factor for arterial stiffness and cardiovascular disease. The Cardiovascular Health Study that investigated 5808 patients who were >65 years of age and had CKD revealed that traditional risk factors, including smoking, were associated with the largest absolute increases in risks for cardiovascular deaths among patients with CKD.

I concur with the authors that the exclusion of patients with diabetes was a limitation of the study. This, of course, limits the generalizability to other populations, particularly because type 2 diabetes mellitus is the most common cause of CKD and ESRD worldwide. Incidentally, although the study by Kendrick et al. did include a high percentage of patients with diabetes (38%), there was no difference in the response of vitamin D on FMD by diabetes status.

In conclusion, the finding of this study is important, because it may bring us closer to decreasing the scourge of cardiovascular morbidity and mortality frequently observed in patients with CKD. A broader and more diverse patient population will need to be studied to give us a more complete understanding of the effect of vitamin D on cardiovascular health in patients with CKD.

DISCLOSURES
None.

REFERENCES

See related Letters to the Editor, “The Authors Reply,” on pages 1579–1580.

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The Authors Reply

We thank Dr. Nwaohiri for commenting on our work and agree with the statement that the jury is still out about the consistency of the effect of vitamin D supplementation on vascular function in CKD. Vascular disease in CKD is multifactorial, and the effect of a single intervention will be affected by a variety of patient-related factors as well as study-related factors.

Some important differences between our study and the study by Kendrick et al. could explain the differential findings. In addition to a younger population, a lower proportion of smokers, and exclusion of patients with diabetes, our population was more vitamin D deficient (13.2±4.8 ng/ml [placebo] and 13.4±4.4 ng/ml [cholecalciferol] in our study versus 21.7±7.7 ng/ml [calcitriol] and 23±7.6 ng/ml [cholecalciferol] in the study by Kendrick et al.) and received a higher cholecalciferol dose (5000 versus 2000 IU/d). Importantly, the rise in 25(OH)D and the final achieved levels were greater in the group that received cholecalciferol in our study (mean change: 24.9 versus 11 ng/ml). Furthermore, Kendrick et al. did not notice any change in another important biologic effect of vitamin D: that on parathyroid hormone. It can be speculated that the rise in circulating 25(OH)D level was not enough to lead to significant biologic effect.

Although the uncertainty about the effect of vitamin D on vascular end points remains, evidence in favor of the beneficial effect of correcting vitamin D deficiency in CKD—including the positive effect on cardiovascular health—is growing. Observational studies and clinical trials have documented favorable modulation of vascular and endothelial function after supplementation with native or activated forms of vitamin D. In our study, the cholecalciferol-treated patients also experienced a favorable decrease in pulse wave velocity. Similar results were reported in another recent randomized, placebo-controlled clinical trial. In this study, patients who achieved the highest 25(OH)D levels were the ones with greatest decreases in pulse wave velocity. Also worth noting is that vitamin D supplementation has been generally safe.

Rather than persist with the one size fits all approach, studies are needed to figure out appropriate patient populations, optimal threshold, preferred formulation, and dose and target levels for vitamin D supplementation and evaluate the effects on hard cardiovascular end points so that our patients can derive the benefits from correction of the vitamin D deficiency.

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