surrounding the central focus of the report of Sørensen et al., 5 most particularly those posed by the proposed role for TLR signaling, are presented in Figure 1.

DISCLOSURE
The authors declared no competing interests.

REFERENCES

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Short-term effects of vitamin D receptor activation on serum creatinine, creatinine generation, and glomerular filtration

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Vitamin D Receptor activation may have pleiotropic effects in a variety of tissues. Experimental studies with vitamin D receptor activation demonstrate an ability to delay progression of renal disease. In humans, vitamin D receptor activation reduces albuminuria. Yet some clinical studies demonstrate that patients receiving vitamin D supplementation have an elevation in serum creatinine and a decline in estimated glomerular filtration rate. These observations may be explainable by an effect of vitamin D receptor activation on creatinine metabolism.


Vitamin D receptor activation has been demonstrated to have multiple effects in a variety of tissues. These pleiotropic effects may limit bone loss, but also reduce mortality in patients with kidney disease, and possibly attenuate the rate of progression of renal disease. The explanation for these benefits is elusive but may involve not only diminished levels of parathyroid hormone but perhaps attenuation of hormonal and proinflammatory systems that may promote scarring and fibrosis (Figure 1). Despite the observed benefits with regard to mortality in patients with kidney disease, and the reduction of albuminuria, which is a perceived surrogate of renal protection, a lingering concern is the evidence in a number of patients of a decline in estimated glomerular filtration rate. Might the pleiotropic effects of vitamin D receptor activation possess both beneficial and detrimental effects on kidney function?

Experimental studies have demonstrated that inadequate vitamin D receptor activation worsens diabetic nephropathy through increased fibronectin production and decreased nephrin expression. Moreover, vitamin D receptor activation suppresses high-glucose-induced activation of the renin–angiotensin system and transforming growth factor-β. In other experimental models of nephropathy, vitamin D receptor activation attenuates renal interstitial fibrosis and limits epithelial-to-mesenchymal transition.

In clinical studies, vitamin D receptor activation facilitates an antiproteinuric response that is incremental to blood pressure reduction and renin–angiotensin system blockade. Yet the increase in serum creatinine observed during these studies raises important questions about the overall long-term benefit of vitamin D receptor activation for kidney function.

A number of important clues in the clinical literature provide perspective. First, the effect of vitamin D on serum creatinine was reversible after the cessation of therapy. Second, in small studies, the reduction in creatinine clearance associated with vitamin D therapy was not seen in patients who had simultaneous measurement of glomerular filtration rate. Third, other older studies, albeit small, have suggested that vitamin D receptor activation may alter creatinine metabolism and/or its handling by the kidney. Consequently, the small but well-done study by Agarwal et al. (this issue), in which they examined the effect of vitamin D receptor activation on creatinine metabolism and measured glomerular filtration rate, and its reversibility, is quite important.
Although only 16 patients with chronic kidney disease were studied, Agarwal and colleagues\(^9\) were able to demonstrate that a 7-day course of paricalcitol (2 µg daily) resulted in an increase in serum creatinine and urine creatinine, while creatinine clearance did not change. Simultaneous measurement of glomerular filtration rate with iothalamate was not altered by paricalcitol therapy. Moreover, within 4 days of cessation of vitamin D therapy, the observed changes in creatinine generation and serum creatinine reversed back to near the baseline. In parallel with these changes were effects on both urea nitrogen excretion rate and serum urea nitrogen, indicating an early anabolic response to vitamin D receptor activation. Thus, there may be parallel effects of vitamin D receptor activation on protein and creatinine metabolism. These observations are not entirely surprising given older reports indicating that muscle tissue is a target of vitamin D receptor stimulation.\(^10\) Small clinical studies have demonstrated that vitamin D treatment improves myopathy in patients with bone loss and results in increased muscle strength and gait and reduces falls.\(^11\) It is conceivable that some of the beneficial impact of vitamin D receptor activation on survival in patients with chronic kidney disease could be related to its anabolic effects to improve skeletal and myocardial muscle function. This may be particularly important in patients with early evidence of either skeletal or myocardial muscle dysfunction. One has to wonder whether vitamin D receptor stimulation could even prevent muscle atrophy in patients with chronic kidney disease.

The importance of this small and straightforward study by Agarwal et al.\(^9\) is that vitamin D receptor activation must be considered, at least in the short term, as a factor that can influence creatinine metabolism. Thus, changes of serum creatinine, or a serum creatinine-based estimation of glomerular filtration rate, needs to be cautiously considered in patients receiving activated vitamin D. As we have learned with renin–angiotensin system blockers, which can induce a functional change in glomerular filtration rate that can be misinterpreted as nephrotoxicity, so can vitamin D receptor activation alter creatinine metabolism in a manner that could be misperceived as potential nephrotoxicity. However, as the authors appropriately point out, one should interpret these observations with care given that this is a small, short-term study. The observations that they provide in this important paper should prompt planning for longer-term trials of the overall influence of vitamin D receptor activation on protein and creatinine metabolism in patients with chronic kidney disease. These anabolic effects may help explain why vitamin D receptor activation may have beneficial effects on mortality in patients with chronic kidney disease.

**DISCLOSURE**

The author declared no competing interests.

**REFERENCES**