variants that are rare in the general population can be overrepresented in population isolates, because of the lower genetic admixture. Together with the availability of next-generation sequencing technology, which allows the uncovering of millions of rare and very rare mutations, a new paradigm has taken hold in genetics: the ‘common disease, multiple rare variants’ hypothesis, which is contrasted with the old ‘common disease, common variant’ hypothesis. The new hypothesis suggests that the same or very similar variant’ hypothesis. The new hypothesis suggests that the same or very similar phenotype manifestations can occur due to rare mutations on different nucleotides. Within this framework, large and expensive studies, based on tens of thousands of unrelated individuals, may be inefficient to detect the causal variants, while pedigree-based studies provide a powerful design, where a few individuals may be enough to identify the causal mutations. Whether the results from population isolates can then be generalized to larger populations is a matter of debate. However, results such as those presented by Park et al. are reassuring. The possibility to follow the transmission of the genetic pattern across generations in an extended pedigree is a unique way to track genetic variants that could be responsible for the observed phenotypic variations. With the advent of next-generation sequencing technology, pedigree-based studies will become increasingly important in identifying pathways involved in regulation of biological markers.

DISCLOSURE
The authors declared no competing interests.

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CKD. Although the exact mechanism for insulin resistance in CKD remains unclear, a postreceptor defect in the insulin-receptor signaling pathway in skeletal muscle is the likely primary abnormality. A variety of factors, including but not limited to inflammation, oxidative stress, anemia, metabolic acidosis, and vitamin D deficiency, are described as contributing to insulin resistance. Of these, vitamin D requires particular attention because of the kidney’s intricate role in vitamin D metabolism, the high prevalence of vitamin D deficiency in CKD, the availability of safe vitamin D analogs, and the pleiotropy of vitamin D that may cover multiple factors contributing to insulin resistance in CKD, such as inflammation and oxidative stress. Figure 1 summarizes alterations in glucose metabolism in CKD and potential roles for vitamin D compounds.

**Building the evidence pyramid**

Vitamin D has long been implicated as having actions that mediate insulin secretion as well as insulin resistance. Early observations notable for worsening glucose control during the winter and spring in healthy and diabetic subjects were indicative of a possible role for vitamin D signaling in glucose metabolism. A number of cross-sectional studies reported an inverse association between vitamin D status and hyperglycemia. Vitamin D receptor is expressed in pancreatic β-cells, and calcitriol has been shown to improve islet-cell morphology in experimental animals. These investigations combined with the observational data set the stage for RCTs in this field. However, it is noteworthy that intervention trials on vitamin D supplementation using cholecalciferol or ergocalciferol have been largely inadequate to demonstrate any significant effect on glucose metabolism in the general population, whereas a number of small RCTs in hemodialysis patients using calcitriol report significant improvements in glucose metabolism. These conflicting findings could result from different vitamin D formulations as well as differences in study populations. So if vitamin D administration optimizes glucose metabolism in hemodialysis patients, then what will be its effects on glycemic parameters in CKD? Only a well-designed and adequately powered RCT can appropriately address this question. The study by de Boer et al. makes this attempt and contributes valuable information on this topic.

Their trial addressed the effects of paricalcitol administration on glucose metabolism in nondiabetic subjects with stages 3-4 CKD. They followed a crossover design and enrolled 22 CKD subjects with baseline glucose intolerance. The study intervention, 2 μg oral paricalcitol daily for 8 weeks, was compared with a matching placebo with participants and investigators blinded to the randomly assigned sequence of intervention versus placebo. In the intent-to-treat analyses, changes in glucose tolerance assessed by an oral glucose tolerance test were not different between paricalcitol and placebo. Paricalcitol had no effect on measures of insulin sensitivity, insulin secretion, insulin action at adipose tissue, and oxidative stress.

The study was well powered for the primary outcome and was rigorously conducted, maximizing the ability to make accurate inferences about the true state of nature in the study setting (internal validity). However, a number of issues remain regarding the applicability of the findings to CKD patients and interventions in general (external validity). First, patients with overt diabetes, who comprise a significant proportion of CKD patients, were excluded, and as the authors acknowledge, results may be different in these patients. Second, it is possible that there are biological differences between the effects of paricalcitol and calcitriol on glucose metabolism, leaving the door open to study other active vitamin D analogs. Notable differences may exist in vitamin D repletion when cholecalciferol (D₃ compound) is compared with ergocalciferol (D₂ compound), with cholecalciferol being more potent. Among active agents, paricalcitol (D₂ compound) has less affinity for vitamin D receptor and also for vitamin D-binding protein. Can the structural differences between paricalcitol and calcitriol—namely, the absence of a carbon 19-methylene group, the presence of a double bond between carbon 22 and 23, and the presence of an extra methyl group—contribute to differences in their effects on insulin mechanisms and secretion? Third, the majority of the patients were Caucasian and had relatively adequate vitamin D status as measured by 25-hydroxyvitamin D levels. Paricalcitol’s actions on glucose metabolism in the setting of vitamin D insufficiency or deficiency and in other populations including blacks and Hispanics remain unclear and should be taken into consideration in the planning of future studies. Nevertheless, even null findings...
of this study that glucose intolerance is not improved by paricalcitol administration in CKD patients provide essential information for the subject of glucose metabolism in CKD.

**Lessons learned**

A number of lessons are to be derived from the vitamin D RCTs in CKD patients. In addition to factors that address the internal validity of any RCT, such as sample size, intervention adherence, subject retention, and adequate follow-up length, future investigations should pay particular attention to hard clinical outcomes such as mortality or hospitalizations. This is easier said than done, but insisting on such hard outcomes will be an important step in moving the field forward. Intermediate outcomes provide valuable mechanistic insights and make trials efficient; however, their selection in future research needs to be very carefully thought through, especially as they may not be indicative of actual events, as was uncovered in the recently published PRIMO (Paricalcitol Capsule Benefits in Renal Failure-Induced Cardiac Morbidity) trial.11

Given the prevalent use of vitamin D analogs in advanced CKD patients primarily to address secondary hyperparathyroidism, it may also be worthwhile to pursue a pragmatic approach and undertake effectiveness trials rather than efficacy trials, where the emphasis would be on comparative effectiveness with the potential to compare different vitamin D compounds in a diverse population. Large simple trials are more likely to bring us closer to the truth than small complex trials,12 and future efforts in CKD should be directed toward them. Rigorously conducted efficacy studies, such as the one by de Boer et al.,3 with adequate power for a well-conceived objective intermediate outcome are to be encouraged in order to keep reducing critical knowledge gaps in the CKD field and to supply important information regarding study design and method to be applied in larger trials.

**DISCLOSURE**

Ravi I. Thadhani has received a research grant from Abbott Laboratories and is a consultant to Fresenius Medical Care North America. Sagar U. Nigwekar declared no competing interests.

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