Is Calcitriol Life-Protective for Patients with Chronic Kidney Disease?

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In nephrology we are frequently confronted with association studies reporting novel biomarkers or mediators. Which among the myriad of potential candidates are amenable to intervention and, thereafter, which do we carry forward into clinical trials? Our group and others have considered the potential of vitamin D. Before commenting on vitamin D in chronic kidney disease, lessons learned from Alfred Sommer’s initial observational studies and subsequent clinical trials with vitamin A—a journey of humility and perseverance—are worthy of reminder.

Alfred Sommer, Dean Emeritus of the Johns Hopkins Bloomberg School of Public Health, received the Lasker Award in 1997 for his seminal work showing vitamin A deficiency is linked to increased risk of mortality and for demonstrating that correcting this deficiency reduces mortality. His series of studies started as simple observations, which led to community-based randomized trials. When Sommer initiated his work, vitamin A deficiency was highly prevalent, yet the connection between vitamin A deficiency and mortality had not been established. With the intent of examining night-blindness and dry eyes, Sommer and his colleagues stumbled across the observation that death rates in children with these ophthalmic conditions were several-fold higher than children without these conditions. When Sommer first published his prospective observational study linking vitamin A deficiency with a 16% increased risk in mortality, the field hardly took notice. As he articulated in a commentary written at the time of winning the Lasker, “The initial report associating vitamin A deficiency with increased mortality was received with deafening silence.” This response, as we know all too well, is common.

Treatment with activated vitamin D, or calcitriol \([1,25(\text{OH})_2\text{D}_3]\), has been used for over three decades to manage the secondary hyperparathyroidism and hypocalcemia accompanying chronic renal disease. This intervention markedly changed the management of renal osteodystrophy, historically a severe debilitating condition. By the late 1990s our attention in nephrology turned to altered mineral metabolism and its relationship to adverse outcomes. The classic role for \(1,25(\text{OH})_2\text{D}_3\) is to maintain calcium homeostasis. As an expected “side effect,” it also raises serum levels of phosphate.

We were keenly interested in understanding the contribution of \(1,25(\text{OH})_2\text{D}_3\) to alterations in serum minerals and whether these alterations associated with increased mortality. In this effort, we accidentally came across a rather strong and consistent association between activated vitamin D therapy and reduced mortality, a finding independent of alterations in serum minerals. Linking vitamin D therapy with altered minerals, and the two with increased mortality, would have “fit the prevailing paradigm” and would have been more easily accepted. Speculating that \(1,25(\text{OH})_2\text{D}_3\) compounds—such as retinoic acid that activates nuclear receptors and leads to changes in gene transcription throughout the body—could have life-saving properties was approaching heresy. The potential mechanisms involved in this observation remain elusive, but more importantly, these observations could have been simply explained by unknown or unmeasured confounders—a fact plaguing any observational study, especially where therapy is involved.

As hypothesis-generating studies, they raised the interest of research groups around the world, most of whom subsequently confirmed these observations in both end-stage and chronic renal failure populations. Others, however, found less consistent findings. The challenges with all of these observational studies include significant population heterogeneity (e.g., mixing incident and prevalent subjects), unknown past use of vitamin D in some cohorts, and examination of populations in which oral vitamin D use is greater than in the United States. Nevertheless, given the preponderance of supportive studies, some might have argued that the calcitriol story was complete. Sommer would have argued, of course, that it was just in its infancy.
ollary observations should also be consistent. For example, if 1,25(OH)_{2}D_{3} therapy confers a beneficial effect, endogenous levels of vitamin D [25OHD_{3} and 1,25(OH)_{2}D_{3}] before correction should themselves be linked with outcomes, especially among those never receiving subsequent corrective therapy. This was found to be true in studies from our group, and more recently from others. We also followed this observation with a study specifically examining African Americans with chronic renal failure, a population with significantly lower levels of 25OHD_{3} and 1,25(OH)_{2}D_{3} compared with whites at the time of initiating chronic hemodialysis. It is well known that African Americans have improved survival over whites after initiation of chronic hemodialysis, and we suggested this survival advantage is explained at least in part by the more frequent use of activated vitamin D therapy in this population. Once again, these were consistent and supportive observations, yet each of which could have been the result of unknown or unmeasured confounders.

What about supportive (or nonsupportive) data from outside the arena of chronic renal failure? Outside the areas of bone disease and cancer, use of calcitriol is largely relegated to chronic renal failure given the predominant location of 25-hydroxyvitamin D_{3} 1α-hydroxylase [CYP27B1], the enzyme that converts 25OHD_{3} to 1,25(OH)_{2}D_{3} in the kidney and its reduced activity in chronic renal failure. Accordingly, hard outcome data examining 1,25(OH)_{2}D_{3} therapy in subjects without renal failure are limited.

Findings linking nutritional vitamin D replacement (e.g., cholecalciferol [vitamin D_{3}] or ergocalciferol [vitamin D_{2}]) with improved survival in the general population, however, are accumulating, and whereas meta-analyses of small randomized trials suggest a survival benefit, large randomized trials are only now underway to confirm these results (JoAnn Mansan, Brigham and Women’s Hospital, Harvard Medical School, personal communication). Even if supportive data outside nephrology existed, one could ask, would they be valid in chronic kidney disease? We have ample experience where therapies found effective in the general population did not translate their benefits to subjects with renal failure. Pursuit of specific studies aimed at subjects with chronic kidney disease is critical.

Patients with chronic kidney disease are profoundly deficient in both 25OHD_{3} and 1,25(OH)_{2}D_{3}, with 50 to 80% of patients at the initiation of chronic hemodialysis showing levels below the lower limits of normal. Therefore, any potential link between vitamin D and outcomes should ideally be tested (and evident) in the extreme population of patients with chronic renal failure, and if found positive, only then pulled back to populations with less severe deficiencies. Such was the case with Sommer, who tested his hypothesis in populations known to be deficient in vitamin A. In fact, and not surprisingly, randomized trials targeting less deficient populations were negative.

We have learned this lesson before, such as from the elegant series of studies first demonstrating the efficacy of statins in patients with familial hypercholesterolemia and only thereafter in progressively less extreme populations. Large-scale studies examining the safety and efficacy of vitamin D compounds with respect to mortality in chronic kidney disease have yet to start but are being planned. The opportunity to test the hypothesis in subjects with a profound deficiency of both 25OHD_{3} and 1,25(OH)_{2}D_{3} remains at our doorstep.

Sommer, unlike many of us, did not stop with simple observations, which was the critical step to his success. As an epidemiologist himself, Sommer acknowledged, “epidemiologists rarely stick to one area of inquiry, and hardly ever are interested in getting to the heart of the matter or reconciling discrepancies.” Contrary to the trend, and much to his credit, he performed a community-based randomized trial in 450 Indonesian villages in which he unequivocally confirmed his initial observations regarding vitamin A. Additional trials by his group and others followed, his results were cemented, and policies for vitamin A supplementation were disseminated around the globe. As his observations and trials gained the interest of the larger medical community, a wide range of experimental studies emerged. Why were deaths from respiratory and gastrointestinal illnesses more common in subjects with vitamin A deficiency? Studies uncovered the critical role of retinoic acid in epithelial cell differentiation, cells that serve an important barrier function in the lungs and intestine.

As a corollary, if calcitriol has life-saving properties, which organ systems and cell types benefit most? The fact that vitamin D receptors occupy nuclear real estate in several cell types throughout the body does not immediately lend itself to a targeted approach. To assist us, we turned to clues from causes of death in patients with chronic renal failure. In most circumstances biology antedates clinical science; however, given the ample supportive observational data linking vitamin D to cardiovascular outcomes, several groups, including ours, were further stimulated to pursue experimental evidence linking 1,25(OH)_{2}D_{3} to cardiac and vascular integrity. We of course also had to be completely open to potential harmful effects. The origins of a direct or indirect link between vitamin D and cardiac structure and function emanated from observations of heart failure in children with rickets and their recovery following therapy with vitamin D, and early experiments examining the cardiovascular effects of vitamin D–deficient animals. Since then, other investigators have examined the effects of vitamin D on the cardiovascular system, including on ventricular myocytes and in vitamin D receptor null mice.

Based on our own observational studies, the prevalence of cardiac hypertrophy in patients with CKD, and the strong link between cardiac hypertrophy and arrhythmia and sudden cardiac death, we were specifically interested in determining whether activated vitamin D attenuates the otherwise reproducible development of cardiac hypertrophy in the Dahl salt-sensitive animal. The analog we tested attenuated the development of cardiac hypertrophy, improved cardiac func-
concentrations of 1,25(OH)2D3 achieved in the klotho renal vitamin D leads to vascular calcification67; however, this effect marker of excess. Experimental studies suggest that activated is likely dose dependent.68

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tion, and normalized the biochemical and molecular parameters of cardiac stress. Other investigators using various animal models also report supportive findings.57–63 Regardless of whether the cardiac effects are direct or indirect—the debate continues—there is improvement in cardiac structure and function with administration of calcitriol. Sommer would now insist we move to human trials, which after innumerable challenges, we were able to initiate (www.clinicaltrials.gov, NCT00497146 and NCT00616902). Clinical observations provoked further experimental studies, and the two were essential to gain support for and subsequently initiate randomized trials.

Is calcitriol safe? The primary side effects of 1,25(OH)2D3 include, but are not restricted to, increased levels of serum calcium and phosphate and oversuppression of parathyroid hormone levels.11 Biologically, the hormone’s primary role is to raise serum levels of calcium, and chronic renal failure is characterized by hypocalcemia. Our concern about altered minerals, excess calcification, and their link to adverse outcomes9,64–66 should cause us to pause, although vascular calcification itself has not met the threshold of a validated surrogate marker of excess. Experimental studies suggest that activated vitamin D leads to vascular calcification52; however, this effect is likely dose dependent.68

Recently the klotho knockout model has shed insight into the mechanisms of vascular calcification and vitamin D in mice.69 This model displays markedly increased expression of renal 1α-hydroxylase (unlike in subjects with renal failure34), elevated 1,25(OH)2D3 levels, elevated phosphate levels, and excess calcification, and this phenotype is rescued by a vitamin D–deficient (or a low phosphate) diet.70 Interestingly, the concentrations of 1,25(OH)2D3 achieved in the klotho knockout animals are 10 to 40 times higher than that seen in subjects with renal failure.27,71,72 In addition, FGF23-null mice have a similar vascular phenotype as klotho-null mice, and vascular calcifications are rescued in the context of a phosphate-deficient diet, regardless of persistent elevations of 1,25(OH)2D3.71 In the animal model more closely resembling the alterations seen in humans with chronic renal failure—klotho and 1α-hydroxylase double knockouts—widespread soft tissue calcification is not seen.74 Nonetheless, altered mineral metabolism remains at least one safety concern with 1,25(OH)2D3 therapy.

What about clinical trials testing the effect of calcitriol on mortality? Unfortunately these data are not available, and only now are groups, including ours, beginning to discuss the feasibility and logistics of such a study. Therefore, what are we to do while we wait? The observational studies for the most part appear consistent. The potential beneficial effects of 1,25(OH)2D3 in various organ systems remain incredibly compelling and only continues to grow. Small-scale trials that advanced several hypotheses related to vitamin D in chronic renal failure should not go unnoticed. For example, intervention with calcitriol improves glucose tolerance25,76 and lipid parameters,77 and reduces erythropoietin requirements.78 In addition to our efforts on cardiac structure and function, ongoing trials are currently testing the role of 1,25(OH)2D3 or a related analog in inflammation (NCT00294866), vascular calcification (NCT00752102), endothelial cell health (NCT00528788), and proteinuria and renal disease (NCT00421733), to name a few.

The biology for nutritional replacement of vitamin D also should not be ignored given the magnitude of 25OHD3 deficiency in chronic renal failure. Recent data on 25OHD3 and antimicrobial peptides are quite compelling,79 and this has not gone unnoticed by the nephrology community (e.g., study NCT00749736) given infection is the second most common cause of mortality in chronic renal failure. Our own group, for example, pursued simple observational studies linking a vitamin D–responsive antimicrobial peptide to infectious mortality in dialysis,80 and we will soon be embarking in small-scale randomized trials to further pursue this hypothesis (NCT00892099). Although always a struggle, many in the nephrology community go beyond hypothesis-generating observational and biological data.

Should we take comfort in knowing survival among prevalent U.S. chronic hemodialysis patients has improved81 and that perhaps use of calcitriol has played a role in this? The two may be completely unrelated. At the forefront should be safety, especially for indications not otherwise approved. We do not have important safety data for the indications we are most interested in, namely mortality. We do, however, have ample experience in routine clinical use of these agents, and we are familiar with strategies to minimize their known adverse consequences.

Although the observational and experimental data are supportive, without randomized trials we will forever be entertaining issues of unmeasured confounding and bias and whether animal data translate to human outcomes. Therefore, although there is cause for significant optimism, we must remind ourselves of the lessons in nephrology and initiate and complete randomized trials before changing practice. Sommer’s journey should remind us that this is not only possible, but also necessary.

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