Vitamin D deficiency and kidney hyperfiltration: a mechanism of kidney injury?

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Introduction

Chronic kidney disease (CKD) is a public health problem, given that approximately 13% of adult Americans currently living with CKD (1). CKD is associated with a high risk of hospitalization, cardiovascular events and mortality (2). CKD is associated with multiple metabolic derangements including low 25-hydroxyvitamin D [25(OH)D] levels (3,4). Low 25(OH)D levels are associated with increased risk of mortality compared to normal levels (5,6). Low levels of 25(OH)D have also been linked to the progression of CKD and cardiovascular disease (7,8). However, not all studies concur, and a recent Mendelian randomization study revealed the opposite: genes associated with lower 25(OH)D levels were associated with higher estimated GFR, or better kidney function (9). Low levels of 25(OH)D are also associated with proteinuria; conversely, activated vitamin D compound (paricalcitol) use is associated with less proteinuria (10,11). Recent Kidney Disease Improving Global Outcomes (KDIGO) guidelines on CKD-mineral and bone disorder (MBD) suggest supplementing low 25(OH)D levels (12). A recently published report from the Korean National Health and Nutrition Examination Survey (KNHANES) reveals that low 25(OH)D levels are associated with renal hyperfiltration in healthy adults, adding another piece to this complicated puzzle (13).

Vitamin D metabolism

Vitamin D is a prehormone obtained through the diet or generated by the skin upon exposure to UV radiation. It is subsequently hydroxylated in the liver to become 25(OH)D and becomes 1-alpha hydroxylated in the kidney and other organs to become the more active, 1,25-dihydroxyvitamin D [1,25(OH)2D]. Both compounds then become 24-hydroxylated to an inactive form. To measure an individual's vitamin D status, 25(OH)D levels are measured due to the longer half-life of the compound.

Definition of and prevalence of vitamin D sufficiency and deficiency

Currently, there are several slightly conflicting definitions for 25(OH)D sufficiency and deficiency. The Institute of Medicine's (IOM) definition of vitamin D sufficiency is any level >20 ng/mL (14), but the Endocrine Society's definition is >30 ng/mL (15). The different recommendations may stem from the fact that the IOM was evaluating on a population level whereas the Endocrine Society was making recommendations on an individual patient level. Levels as low as <12 ng/mL are associated with rickets in children and osteomalacia and adults, and most agree that these levels are "deficient" (14). Whichever definition one uses, a significant percentage of the world's population appears to have low 25(OH)D levels. In the United States, recent estimates show that approximately 23% of the population have 25(OH)D levels <20 ng/mL (16). An earlier study of post-menopausal women around the world showed that women in South Korea had lower 25(OH)D levels

(mean 17.6 ng/mL) than most countries (17). The mean 25(OH)D levels combining all the countries studied was 26.8 ng/mL (17).

Vitamin D levels and kidney disease

Low vitamin D levels have been implicated in both progression of kidney disease and proteinuria in national studies in the United States (7,11). Ravani *et al.* showed that serum 25(OH)D was an independent inverse predictor of kidney disease progression and death in 168 patients with early stages of CKD (8). In a cohort of men with HIV infection, lower 25(OH)D levels were associated with a faster decline in eGFR (18). Randomized clinical trials and a meta-analysis have shown that treatment with vitamin D analogs may decrease proteinuria in diabetic nephropathy and other proteinuric diseases (19,20). Large randomized clinical trials are on-going to evaluate cholecalciferol supplementation, albuminuria and progression of diabetic kidney disease (21).

Interestingly, vitamin D itself may affect creatinine generation by muscle and therefore serum creatinine levels. In an elegant study by Agarwal *et al.*, 16 patients with CKD were given paricalcitol, before and after which serial creatinine levels and iothalamate GFRs were performed (22). The patients' creatinine increased but measured GFRs did not change.

The mechanism behind the possible protective role vitamin D may play in kidney disease is thought to be vitamin D suppression of the renin-angiotensin-aldosterone system (RAAS). Other suppressors of the RAAS system, including ACE inhibitors and angiotensin receptor blockers, are proven to slow the progression of kidney disease (23). In mice, the activated form of vitamin D, 1,25(OH)2D, suppresses renin biosynthesis, and vitamin D deficiency stimulates renin production (24). In rats, combining an ACE inhibitor with an activated vitamin D agent decreased proteinuria more than either agent alone (25). Based on its suppression of the RAAS system in animal models, vitamin D supplementation shows beneficial effects on albuminuria, which suggests that vitamin D supplementation may prevent the progression of kidney disease to ESRD like other RAAS blockers.

Renal or glomerular hyperfiltration

Early animal models of diabetic kidney disease reveal renal or glomerular hyperfiltration as an early alteration in the kidney, which causes further damage to the kidney (26). Glomerular hyperfiltration associated with early DM is a risk factor for the development of progressive diabetic nephropathy (27). Glomerular hyperfiltration can be caused by afferent arteriolar vasodilation (as seen in patients with diabetes or after a high-protein meal), and/or by efferent arteriolar vasoconstriction owing to activation of the RAAS system leading to glomerular hypertension. This glomerular hypertension may lead to glomerulosclerosis and put patients at risk for progressive kidney disease. No single definition of renal hyperfiltration has been agreed upon.

25(OH)D levels and renal hyperfiltration in Korean adults: Jhee *et al.*

Jhee *et al.* investigated the association between renal hyperfiltration and vitamin D status in a healthy Korean population. The authors used the 4th, 5th, and 6th editions of the Korean NHANES (KNHANES IV, V, and VI, 2008–2015), a nationwide population-based cross-sectional study from 2008 to 2015. After applying their exclusion criteria, they ended up studying 33,210 subjects with estimated glomerular filtration >60 mL/min^{1}/1.73 m^{2}. They defined vitamin D deficiency as a serum 25(OH)D concentration <20 ng/mL (n=19,888) and severe vitamin D deficiency as <10 ng/mL (n=2,693). Serum 25(OH)D concentrations between 20 and 29.9 ng/mL were defined as vitamin D insufficient (n=8,858) , whereas concentrations ≥30 ng/mL were defined as sufficient (n=1,771) (13). Earlier studies showed that South Korean post-menopausal women have relatively lower 25(OH)D levels compared to women from other countries, so this population may be unique in the low prevalence of vitamin D sufficiency (17).

The mean age of the population was 48.1 [standard deviation (SD) 15.9] years; 56.5% were female. The population was relatively healthy with hypertension in only 18%, diabetes mellitus in 6.6% and proteinuria in only 2.5% (13). In the study, estimated GFR was calculated using the Korean version of the CKD-Epi equation. A logarithm transformed eGFR in the 95th percentile or greater, after adjustment for age, sex, height, weight, and history of hypertension or diabetes was considered to be renal hyperfiltration.

This study showed an association between renal hyperfiltration and severe vitamin D deficiency (<10 ng/mL), adjusted for the variables discussed, in participants with eGFR >60 mL/min/1.73 m^{2}. Interestingly,

as in the Mendelian randomization study by Teumer *et al.*, there was an inverse relationship found between 25(OH)D levels and eGFR; the higher the 25(OH)D levels, the lower the eGFR. This is in contrast to other longitudinal studies where low 25(OH)D levels at one time point are associated with a faster decline in eGFR (9,18).

In this secondary analysis of the KNHANES study, investigators showed a link between lower 25(OH)D levels and higher prevalence of renal hyperfiltration. Strengths of the large cross-sectional cohort include robust data on demographics, anthropometry, nutritional history, and medical history. Limitations of the cohort include lack of directly measured GFR and an ethnically homogenous sample, limiting generalizibility. The investigators found a small but statistically significant association between lower 25(OH)D levels and renal hyperfiltration. The authors appropriately note that analysis is made difficult by the lack of consensus in definitions of both 25(OH)D deficiency and of renal hyperfiltration; the definitions chosen are common but not universal. As with all epidemiologic studies, this investigation does not establish causality, although the authors posit a reasonable mechanistic explanation involving suppression of intrarenal RAAS activation. While this study provides additional support for the role of 25(OH)D deficiency in the development of kidney disease; further studies are needed to show generalizability in other populations and to establish the causality and mechanism of such a relationship.

Additionally, the fact that 1,25(OH)2D treatment may increase creatinine generation and creatinine levels without affecting measured GFR (10) begs the question of whether eGFR should have been used in this analysis. The question of whether the 25(OH)D levels are affecting kidney function or muscle generation of creatinine remains unanswered. It would be nice to see this study repeated with either measured GFR or cystatin C- based eGFR to mitigate the possible effects of vitamin D on muscle and creatinine levels.

In sum, multiple (but not all) studies have shown that low levels of 25(OH)D appear to be associated with a faster progression of kidney disease. In the KNHANES study, extremely low 25(OH)D levels in relatively healthy adults were associated with renal hyperfiltration, which likely causes further damage to the kidney. There is potentially a mechanism, through non-suppression of the RAAS system, of kidney damage. Many of the studies of associations between vitamin D and kidney disease progression are observational and therefore causality cannot be proven. Current, on-going randomized clinical trials will provide evidence about whether or not supplementation with cholecalciferol supplementation over several years may ameliorate diabetic kidney disease, which will help establish causal relationships (21).

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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