Vitamin D deficiency: a nontraditional risk factor in polycystic kidney disease?

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Polycystic kidney disease comprises a number of genetically disparate disorders including autosomal dominant polycystic kidney disease (ADPKD), autosomal recessive polycystic kidney disease (ARPKD), and nephronophthisis (NPHP). These cystic disorders are characterized by the development and expansion of numerous renal cysts with ultimate loss of renal function. While ARPKD and NPHP are relatively rare genetic diseases, ADPKD affects an estimated 12.5 million individuals worldwide. As such, ADPKD represents a significant health and economic burden in society. Since the introduction of renal replacement therapies, cardiovascular disease is the leading cause of death among affected patients (3). Early onset of hypertension in ADPKD and ARPKD increases morbidity and risk for mortality in these conditions. The expansion of renal cysts in ADPKD results in compression of the renal parenchyma and vasculature, and the resultant ischemia has been implicated in activation of the renin-angiotensin aldosterone system (RAAS) (9). There is significant variability in both severity and rate of disease progression especially with respect to ADPKD. However, traditional and nontraditional risk factors affecting both renal and cardiovascular disease progression have not been completely delineated. One potential risk factor is vitamin D deficiency. 25-Hydroxyvitamin D (25-OHD) is the main storage form of vitamin D, and the circulating level is a measure of vitamin D status. Conversion of the storage form into the active form of the vitamin, 1,25 dihydroxyvitamin D [1,25(OH)2D], occurs primarily in the kidney and is regulated in keeping with the endocrine function in calcium/phosphorous homeostasis. However, 1,25(OH)2D is also synthesized in many extrarenal tissues, where it serves autocrine/paracrine cell-specific functions with local control by growth factors, cytokines, and other factors. Vitamin D deficiency is prevalent among patients with chronic kidney disease (6). Studies based on participants in the National Health and Nutrition Examination Study (NHANES III) demonstrated that subjects with vitamin D deficiency (25(OH)D level <15 ng/ml) have a higher incidence of end-stage renal disease (ESRD) (4). In a cross-sectional analysis of NHANES III participants, lower levels of 25(OH)D were associated with increased proteinuria (1). There is a well-established link between vitamin D deficiency and hypertension, and not surprisingly also the incidence of cardiovascular events as reviewed by Holick (5). The active form of vitamin D, 1,25(OH)2D, is a potent downregulating hormone of renin expression in the kidney (2). Moreover, angiotensin II is also a growth factor for renal tubular cells (10). Thus vitamin D deficiency by contributing to RAAS activation and potential epithelial cell proliferation may be implicated in exacerbation of both renal and cardiovascular complications in patients with PKD.

In a recent issue of the American Journal of Physiology-Renal Physiology, Rangan et al. (8) investigated the role of vitamin D deficiency on modulation of PKD severity. The authors used Lewis PKD (LPK) rats, a hypertensive rat model with phenotypic characteristics of ARPKD resulting from mutation in the never in mitosis gene-a related kinase 8 (Nek8) gene, an ortholog of human NPHP9. LPK and normal Lewis rats were maintained on diets supplemented with or without cholecalciferol (vitamin D-deficient diet) for periods ranging from 7 to 13 wk. The ad libitum-fed vitamin D-deficient animals who were treated between postnatal week 3 and week 20 had a significant increase in systolic blood pressure, heart weight/body weight ratio, and urine protein/creatinine compared with the non-vitamin D-deficient cystic animals. The total kidney weight/body weight ratio decreased in the deficient animals at 20 wk and also in the non-cystic Lewis control animals who received the vitamin-deficient diet. Similar results were observed in LPK rats maintained on a vitamin D-deficient diet between ages 10 and 20 wk. However, renal function impairment and interstitial monocyte accumulation were also noted in these vitamin D-deficient animals. As the vitamin D-deficient animals had a significant weight gain that might confound the outcome, Rangan et al. (8) repeated the experiments in pair-fed animals treated between ages 3 and 10 wk with a normal or vitamin D-deficient diet. During this early treatment period, no exacerbation of renal function was noted in the vitamin D-deficient animals.

The outcome of this study suggests that sustained vitamin D deficiency may adversely affect blood pressure, heart and potentially renal function in PKD. While the current investigation did not demonstrate an effect of vitamin D deficiency on worsening renal structure, we have previously demonstrated an association between circulating vitamin D levels and total kidney volume in a cross-sectional analysis in young patients with ADPKD (4). Thus this thought-provoking study underlines the need for future prospective clinical trials in human patients with PKD. It is also relevant in view of our ever increasing health care costs that 25(OH)D deficiency may be corrected by supplementation at a cost of just cents per day.

REFERENCES


