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Narrative Review

Blood Pressure, Proteinuria, and Phosphate as Risk Factors for Progressive Kidney Disease: A Hypothesis

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Chronic kidney disease (CKD) affects approximately 500 million people worldwide and is increasingly common in both industrialized and emerging countries. Although the mechanisms underlying the inexorable progression of CKD are incompletely defined, recent discoveries may pave the way to a more comprehensive understanding of the pathophysiology of CKD progression and the development of new therapeutic strategies. In particular, there is accumulating evidence indicating a key role for the complex and yet incompletely understood system of divalent cation regulation, which includes phosphate metabolism and the recently discovered fibroblast growth factor 23 (FGF-23)/klotho system, which seems inextricably associated with vitamin D deficiency. The aim of this review is to discuss the links between high blood pressure, proteinuria, phosphate levels, and CKD progression and explore new therapeutic strategies to win the fight against CKD.
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INDEX WORDS: Chronic kidney disease; vitamin D deficiency; blood pressure; proteinuria; phosphate.

Chronic kidney disease (CKD) is a silent killer. Four of 5 people with advanced CKD are not aware of the disease until death is imminent and kidney replacement therapy (dialysis or kidney transplantation) is unavoidable. Unfortunately, <10% of people requiring replacement therapy have access to it, and more than 1 million people worldwide die of untreated kidney failure each year because dialysis or kidney transplantation is unaffordable in most countries. This represents a huge economic burden, with global costs from 2000-2010 surpassing $1 trillion.[1,2]

Worsening kidney function is associated with a marked increase in cardiovascular morbidity and mortality[1,3] independent of other risk factors. Coexistent hypertension is present in ~80% of patients with CKD and worsens cardiovascular outcomes because only 64% of patients with CKD achieve adequate blood pressure control.[4] As a consequence, only a minority of the hundreds of thousands of patients with stages 3 and 4 CKD reach kidney failure.[5] Proteinuria also is an important prognostic factor in patients with CKD. Although patients with nonproteinuric CKD are at greater risk of cardiovascular mortality than progression to kidney failure, the opposite may be true for the presence of proteinuria. Patients from the REIN (Ramipril Efficacy in Nephropathy) Study who were in the highest tertile of baseline proteinuria (protein excretion ≥3.8 g/d) also experienced the highest rate of glomerular filtration rate (GFR) loss during follow-up.[6]

In addition, although post hoc analysis of RENAAL (Reduction of Endpoints in NIDDM [Non–Insulin-Dependent Diabetes Mellitus] With the Angiotensin II Antagonist Losartan) showed that 85% of patients with proteinuria with protein excretion ≥3 g/d reached the composite end point of doubling of serum creatinine level or end-stage renal disease (ESRD), only 44% of these patients reached the composite cardiovascular outcome.[7]

Besides the well-established role of hypertension and proteinuria in the progression of CKD, accumulating evidence indicates a key role for the complex and incompletely understood system of divalent cation regulation, which includes phosphate metabolism and the recently discovered fibroblast growth factor 23 (FGF-23)/klotho system, which seems inextricably associated with vitamin D deficiency.

The aim of this review article is to emphasize the links between 2 traditional factors of CKD progression, blood pressure and proteinuria (here identified as the first 2 "P" factors for progression), and the more recent subject of phosphate (the third "P" for progres-

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sion) in light of recent findings from experimental and interventional studies.

BLOOD PRESSURE: THE FIRST "P" FOR CKD PROGRESSION

Hypertension, the leading cause of death worldwide,[8] may be either a consequence or a cause of CKD[9] and is a major independent risk factor for both kidney disease and faster rate of GFR loss.[10,11] An increased risk of ESRD beginning at the third quintile of systolic and diastolic blood pressure (127/82 mm Hg) was evident in 332,544 middle-aged men in the Multiple Risk Factor Intervention Trial (MRFIT),[10] and blood pressure values higher than high normal were associated with a progressive increase in risk of ESRD in the Okinawa mass screening program (n = 98,759).[11] There is a large body of evidence that blood pressure reduction may slow GFR loss and reduce cardiovascular outcomes.[12] However, 2 crucial issues in the management of hypertension in patients with CKD are first, whether a specific blood pressure target may maximize renoprotection, and second, whether a specific drug may be beneficial, independent of blood pressure control. Concerning blood pressure targets, few randomized trials[13-16] have been conducted in patients with CKD to confirm the association of findings from these cohort studies.[10,11] In the Modification of Diet in Renal Disease (MDRD) Study, the largest randomized prospective trial performed to date (840 patients, mostly with nondiabetic kidney disease), tight blood pressure control (mean arterial pressure ≤92 mm Hg; ie, blood pressure, 125/75 mm Hg) did not improve the primary outcome of GFR reduction, doubling of serum creatinine level, or ESRD.[13] However, intensive control slowed the progression of CKD when protein excretion >1 g/d,[17] although the greater benefits in GFR decline in these patients may be explained in part by the greater use of angiotensin-converting enzyme (ACE) inhibitors. Similarly, a lower blood pressure goal did not significantly reduce the rate of the composite outcome (GFR reduction ≥50%, ESRD, or death) or the mean GFR slope in 1,094 African American hypertensive patients with mild to moderate CKD from the African American Study of Kidney Disease and Hypertension (AASK),[15] although a trend favoring the lower blood pressure target again was evident in the subgroup with a urinary protein-creatinine ratio >0.22 g/g at baseline (urinary protein excretion >300 mg/d).

In AASK, the ACE inhibitor ramipril afforded 22% and 38% greater reductions in the composite outcome compared to metoprolol and amlodipine, respectively. However, the REIN-2 Study highlights that achieving intensive blood pressure control by add-on therapy with the dihydropyridine calcium channel blocker felodipine on top of ramipril was not beneficial in patients with nondiabetic kidney disease, probably because tighter blood pressure control was not accompanied by a reduction in intraglomerular pressure and proteinuria.[16] Thus, renin-angiotensin-aldosterone system (RAAS)-blocking agents appear to be the key component of renoprotective therapy rather than tight blood pressure control because lowering blood pressure to <130/80 mm Hg does not offer additional renoprotection when achieved with drugs not affecting the RAAS or in patients without significant proteinuria or diabetes.[18] The antiproteinuric properties of RAAS-blocking agents were discovered first by Anderson et al[19] and originally attributed to the hemodynamic effects of reduced intraglomerular pressure through preferential dilation of kidney arterioles. More recently, evidence has been provided that RAAS-blocking agents also ameliorate glomerular sieving function by directly restoring slit diaphragm integrity and increasing negative charge on the glomerular membrane.[20] After the landmark trial on the use of captopril in diabetic kidney disease conducted by the Collaborative Study Group,[21] several clinical trials demonstrated that RAAS-blocking agents may effectively maximize reno- and cardioprotection[5,22] in both diabetic and nondiabetic nephropathies.[23-30]

PROTEINURIA: THE SECOND "P" FOR CKD PROGRESSION

In healthy adults, urinary protein excretion does not exceed 150 mg/d.[31] Until recently, for patients with proteinuria, protein excretion <1 g/d was considered an optimal clinical target due to the low rate of progression toward kidney failure.[32]

More recently, levels of proteinuria as low as protein excretion of 150-500 mg/d are regarded as a risk factor for progression of kidney disease[33] and cardiovascular mortality.[22,34] Both epidemiologic[31,35-37] and interventional studies[6,15,17] consistently show a strong and independent association between increasing values of proteinuria and the risk of progression of kidney disease in both diabetic and nondiabetic patients. Proteinuria was the most powerful predictor of ESRD in a general population screening of more than 100,000 Japanese individuals followed up for 10 years.[35] This strong and graded relationship also was evident for mild increases in protein excretion on dipstick urinalysis. Similar results were evident in a post hoc observational analysis of MRFIT. Dipstick proteinuria with protein excretion of 1+ or ≥2+ was associated with a greater risk of ESRD over 25 years of follow-up (hazard ratios of 3.1 and 15.7, respectively).[37] Moreover, high-normal values of urinary albumin excretion were associated independently with the onset of microalbuminuria or decreased kidney

function in 4,031 patients with type 2 diabetes and normoalbuminuria from the UK Prospective Diabetes Study (UKPDS 74).[38] Finally, a relationship between higher baseline proteinuria and faster reduction in GFR was found in the MDRD Study, as well as the AASK and REIN trials.[6,15,17] The latter study also demonstrated that residual proteinuria reliably predicted long-term kidney prognosis regardless of blood pressure control and treatment randomization and independent of initial values of proteinuria and its reduction during follow-up.[39]

Proteinuria also is a strong predictor of cardiovascular risk[40,41] independent of level of kidney function.[3,42] In a meta-analysis of 10 cohorts involving 266,975 people at increased risk of CKD, lower GFR and higher albuminuria predicted cardiovascular disease and all-cause mortality independently of each other.[43] This independent association between any level of proteinuria and total or cardiovascular mortality was confirmed in more than 1.1 million people with proteinuria identified only by detection of "trace" or greater levels following dipstick analysis[34] and in more than 100,000 individuals with an albumin-creatinine ratio $\geq$10 mg/g.[22] In light of these findings, all attempts have been made to reduce proteinuria by any therapeutic means, including RAAS-blocking agents, low salt intake,[44] smoking cessation, optimal metabolic control, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.[45] Multiple therapies aimed at reducing proteinuria may slow the progression of kidney disease to a greater extent than any single treatment. This was demonstrated effectively by a multimodal intervention strategy, the Remission Clinic program, that used all available lifestyle recommendations and pharmacologic tools to further reduce proteinuria in patients with CKD and severe proteinuria already treated with RAAS-blocking agents.[46-47] We recently confirmed the beneficial effects of this strategy in patients with Alport syndrome.[48]

PHOSPHATE: THE THIRD "P" FOR CKD PROGRESSION

Seminal observations by Ibels et al[49] showed that dietary phosphate restriction prevented proteinuria, kidney calcifications, histologic changes, functional deterioration, and deaths in a murine remnant-kidney model. These findings were confirmed later in patients with CKD treated with a low-phosphorus low-nitrogen diet.[50] A recent post hoc analysis of the REIN Study has further expanded the role of phosphate in CKD progression.[51] The study had a dual objective: (1) assess the relationship between phosphate levels at inclusion and the incidence of kidney events, and (2) assess whether the protective effect conferred by ramipril on disease progression could be altered by serum phosphate levels. The authors observed that an increase of only 1 mg/dL in serum phosphate level, irrespective of other risk factors, was associated with an 85% increase in risk of progression to ESRD. Moreover, patients in higher quartiles of serum phosphate levels showed a significantly lower protective effect from ACE-inhibitor therapy. In patients with serum phosphate levels >4.5 mg/dL, ACE-inhibitor therapy brought almost no benefit. The interactions observed between serum phosphate level, ACE inhibition, and GFR loss did not change appreciably after adjustment for potential confounders, pointing to a specific pathogenic role for this metabolic imbalance in the progression of CKD.

CROSS-TALK AMONG THE 3 "PS" IN THE PATHOGENESIS OF CKD PROGRESSION: WHAT IS ALREADY KNOWN

Dysregulation of phosphate homeostasis may ensue in early stages of CKD long before an increase in serum phosphorus levels. Although phosphate homeostasis previously was thought to be regulated exclusively by 1,25-dihydroxyvitamin D_3 (calcitriol) and parathyroid hormone, the FGF-23/klotho system is now considered the main phosphate-regulating endocrine axis.[52] In the remnant-kidney model of CKD progression,[27] surviving nephrons must excrete an increasing amount of phosphate to maintain normal phosphate levels. This issue is exacerbated further by high dietary phosphate intake, with phosphate bioavailability playing a central role.[53-55] Prolonged phosphate load, rather than plasma levels, has been shown to increase serum FGF-23 levels in nephrectomized rats,[56] suggesting that circulating phosphorus may not adequately reflect phosphorus balance. Through FGF-23–mediated mechanisms, phosphorus also may have an inhibitory effect on the production of nitric oxide,[57] which could reduce or prevent the beneficial effects mediated by nitric oxide activation during ACE-inhibitor therapy. However, the molecular mechanisms underlying the association between prolonged phosphate load and increased levels of FGF-23, which is secreted mainly by bone cells,[58] are largely unknown. The responsiveness of FGF-23 to dietary phosphate is sluggish (hours to days),[59] and phosphate does not directly stimulate FGF-23 expression in osteoblast cultures,[60] emphasizing the importance of other local or systemic regulators.[61] Higher FGF-23 levels increase urinary phosphate excretion by suppressing the expression of the sodium-dependent phosphate cotransporters NPT2a and NPT2c in the kidney proximal tubule[61] and reduce phosphorus absorption in the gut by decreasing calcitriol levels. Unfortunately, lower calcitriol levels also stimulate the RAAS through increased renin production and the

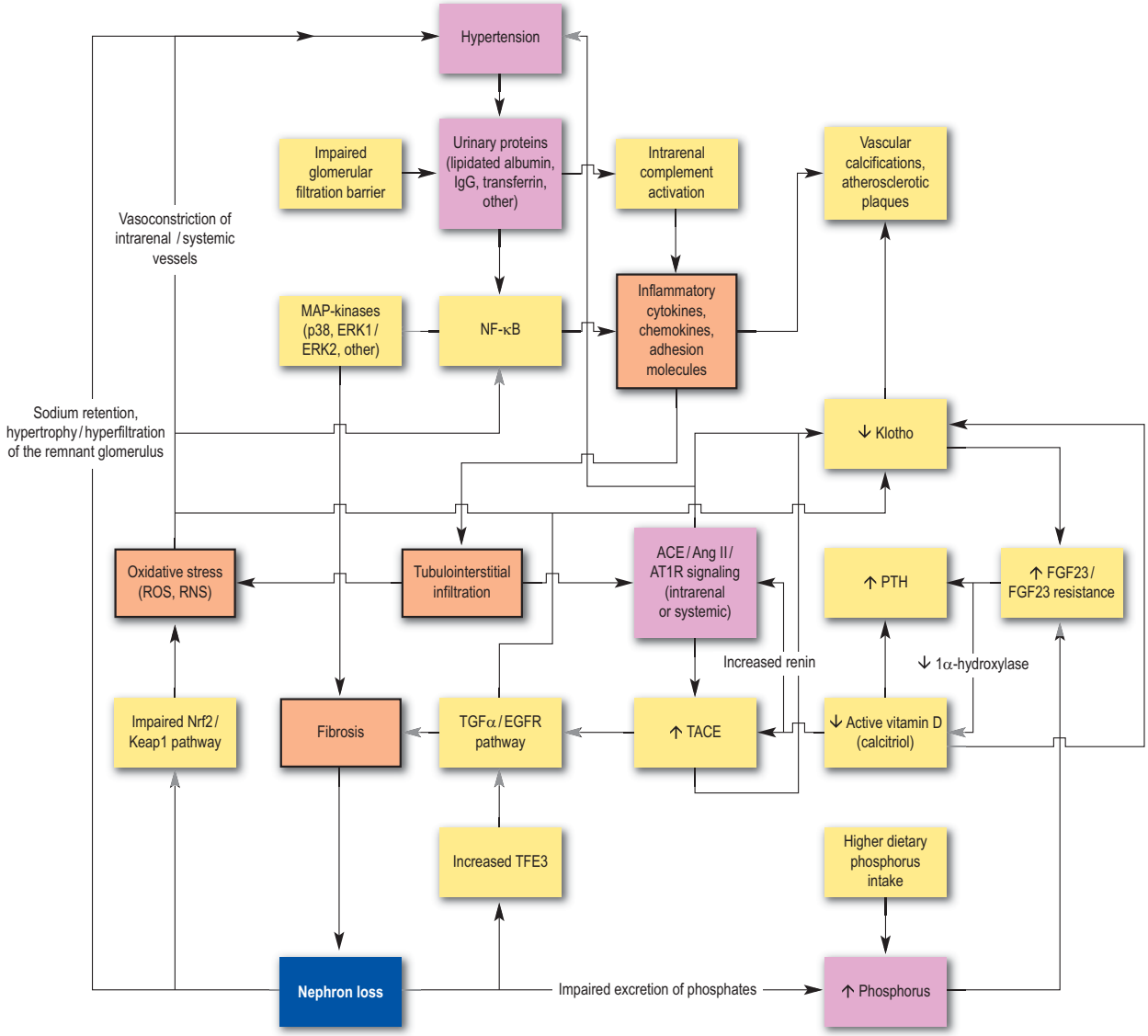

Figure 1. Pathogenesis of chronic kidney disease (hyperglycemia-induced pathways are not shown). Abbreviations: ACE, angiotensin-converting enzyme; Ang II, angiotensin II; AT1R, angiotensin II type 1 receptor; EGFR, epidermal growth factor receptor; FGF, fibroblast growth factor; IgG, immunoglobulin G; MAP, mean arterial pressure; NF-κB, nuclear factor κB; PTH, parathyroid hormone; ROS, reactive oxygen species; RNS, reactive nitrogen species; TACE, tumor necrosis factor α–converting enzyme; TFE3, transcription factor E3; TGF, transforming growth factor.

transforming growth factor α (TGF-α)–converting enzyme/TGF-α/epidermal growth factor (EGF) receptor pathway (Fig 1), leading to an increase in inflammation, urinary protein excretion, and fibrosis. This ultimately accelerates the progression of kidney damage and increases the risk of cardiovascular events.[62-65] FGF-23 also exhibits direct end-organ toxicity on the myocardium and may be involved in the pathogenesis of left ventricular hypertrophy and uremic cardiomyopathy.[66] Lower calcitriol levels also increase parathyroid hormone secretion, which in turn stimulates FGF-23 synthesis[67] and TGF-α secretion,[68] thus generating another vicious circle that could explain in part the increased cardiovascular morbidity and all-cause mortality found in patients with CKD[3] (Fig 1).

The membrane protein klotho is expressed predominantly in kidney and brain and is recognized to have antiaging properties by preventing atherosclerosis plaques and vascular calcifications. Klotho acts as the necessary cofactor for FGF-23 by forming complexes with the FGF receptors and increasing their affinity for FGF-23. The importance of klotho in FGF-23 signaling is supported because its downregulation by angiotensin II, TGF-α–converting enzyme, oxidative stress, nuclear factor κB, and uremic secondary hyperparathyroidism[64,69] results

in end-organ resistance to FGF-23 and increased FGF-23 levels. The latter reduces calcitriol levels and further activates the RAAS. Of note, restoration of klotho by gene transfer improves angiotensin II–induced proteinuria.[70]

As this discussion attests, the FGF-23/klotho system is strongly connected with the RAAS (Fig 1). Abnormal activation of the systemic and local RAAS is found commonly in patients with CKD and deeply influences medium- to long-term control of both blood pressure and proteinuria. Among its well-known hemodynamic and nonhemodynamic detrimental effects, angiotensin II also activates the TGF-α–converting enzyme/TGF-α/EGF receptor pathway,[71] which may exacerbate proteinuria and kidney fibrosis. This may occur through the release of proinflammatory and profibrotic cytokines,[72] including adhesion molecules,[73,74] and reduced vitamin D receptor cell-surface expression.[68]

The cross-talk between phosphorus metabolism, the FGF-23/klotho system, and the RAAS may contribute to the initiation and progression of chronic proteinuric nephropathies that are characterized by a loss of selectivity of the glomerular filtration barrier. In this respect, a recent study highlighted the key role of podocyte detachment and the loss of normal endothelial cell fenestration in 37 patients with type 2 diabetes undergoing kidney biopsy. The percentage of podocyte detachment correlated positively with urinary albumin excretion and negatively with number of podocytes per glomerulus. The percentage of endothelial cell fenestration was associated negatively with glomerular basement membrane width and fractional interstitial and mesangial area and positively with filtration surface area density and GFR. Increasing podocyte detachment is associated with decreased permselectivity of the glomerulus and progressive albuminuria, whereas loss of endothelial cell fenestration is associated with GFR decline.[75] These findings are supportive of previous research in the same field,[76] recapitulated in a recent review.[77] Higher levels of proteinuria may increase the release of profibrotic, proinflammatory, and vasoactive molecules[78-82] with consequent oxidative stress, tubulointerstitial fibrosis, and loss of functional nephrons (Fig 1).[83] These changes cause further nephron injury, increased intraglomerular pressure, impaired filter function, and further loss of proteins in urine, with concomitant activation of the complement cascade.[27,84-86] Progressive nephron loss also causes severe impairment of the Nrf2-Keap1 (nuclear factor erythroid 2–related factor 2/kelch-like ECH-associated protein 1) pathway, with increased oxidative stress and inflammation.[87,88] Inflammation and oxidative stress are linked inseparably and represent major mediators of CKD progression and the associated cardiovascular complications.[62,70,81,89]

INSIGHTS FROM RECENT EXPERIMENTAL STUDIES AND NOVEL THERAPEUTIC TARGETS

In patients with CKD, the vicious cycle between phosphorus metabolism, the FGF-23/klotho axis, and the RAAS likely is activated even in the presence of serum phosphate levels within the normal range. Dietary phosphate restriction can significantly lower FGF-23 levels[53-55] and could be more effective if started before serum phosphate levels increase. Vitamin D receptor agonists may effectively inhibit both the TGF-α–converting enzyme/TGFα/EGF receptor pathway and the RAAS in the parathyroid and kidney[90,91] and reduce vascular calcification, podocyte damage,[63,92-94] and proteinuria through blockade of Wnt/β-catenin signaling.[95] Vitamin D receptor agonists also may upregulate klotho[96] and exert an anti-inflammatory action through the reduction of nuclear factor κB. These actions may explain in part the nephroprotective effects and reduced mortality observed in patients treated with vitamin D receptor agonists independent of serum 25-dehydroxyvitamin D levels.[97-101] Non–calcium-based phosphate binders may correct hyperphosphatemia and ameliorate abnormalities of the mineral metabolism associated with accelerated kidney disease progression and increased cardiovascular risk.[102-104] The finding that phosphate binders reduced proteinuria, an effect that appears to be associated with significant renoprotection in the long term according to recent animal studies (Fig 2),[105,106] along with results of the post hoc analysis of the REIN Study,[51] can be taken to suggest that strategies aimed at lowering phosphate levels might be used in the future to maximize the renoprotective effects of RAAS-blocking agents.

FUTURE PERSPECTIVES

In summary, the complex interactions among the different pathways of CKD progression may explain why the specific renoprotective effects of traditional RAAS-blocking agents are blunted by serum phosphate levels >4.5 mg/dL. This is a major issue because RAAS inhibition currently is the standard therapy for proteinuric nephropathies. In particular, there is a need for additional randomized controlled trials with longer follow-up and hard kidney end points to evaluate the hypothesis that additional therapeutic interventions may be instrumental to improving renoprotection in this high-risk population. In this respect, an ongoing trial will evaluate the renoprotective effects of serum phosphate reduction by noncalcium phosphate binders in patients with CKD with

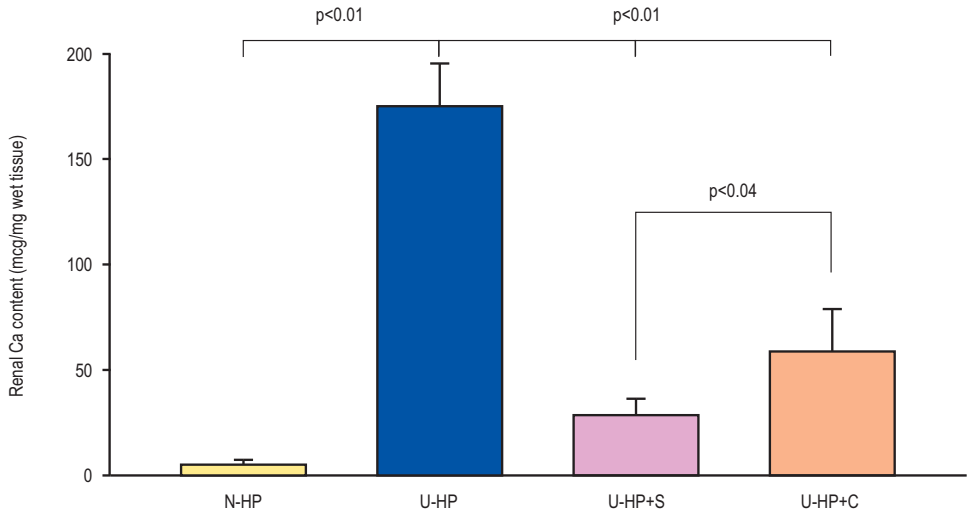

Figure 2. Effects of sevelamer and calcium carbonate on kidney calcium content. Kidney calcium deposition in normal and uremic (5/6-nephrectomized) rats undergoing one of the following experimental protocols for 3 months: (1) normal plus high-phosphorus diet (N-HP); (2) uremic control plus HP diet (U-HP); (3) U-HP plus 3% sevelamer (U-HP+S); and (4) U-HP plus 3% calcium carbonate (U-HP+C). Data presented as mean ± standard error, mean from 7 rats. *P* values indicate statistically significant differences between groups (analysis of variance followed by Bonferroni post hoc). Adapted from Cozzolino et al[106] with permission of the American Society of Nephrology.

reference serum phosphate levels and residual proteinuria despite optimal RAAS-inhibitor therapy according to the Remission Clinic approach.

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