AKI. This strongly suggests that considerably milder degrees of AKI, including those that cannot be detected with serum creatinine, may result in a rise in NGAL. This overlap is also present in the article by Paragas et al., examining HIV in relation to kidney disease.

These limitations help to frame the challenges that we as a renal community will experience as we seek to validate these biomarkers and implement their use in a way that cardiologists use troponin. First, we must be very careful to approach the development of these biomarkers as a way to augment rather than replace the rather familiar tools of serum creatinine and urine output in detecting new clinical presentations of renal injury such as AKI. We might consider the analogy of how troponin measurements do not replace the electrocardiogram in acute coronary syndrome. Second, we need to validate the level of biomarker elevation that is truly clinically significant. As we examine the literature, clearly we will have increasingly more sensitive abilities to identify patients with subclinical or exceptionally mild disease. With continued research in the development of biomarkers will come the increasingly important task of defining the relevant thresholds for elevation above which therapy should be instituted or additional diagnostic tests triggered. Finally, we need to prioritize studies in which treatment of the patient will be affected and early knowledge of the disease or injury will benefit outcome. Hopefully, the development of strategies to treat AKI more actively and successfully will soon follow the discovery of how to diagnose AKI earlier and earlier.

The second application, as explored in the article by Paragas et al., may have a more immediate impact. Our ability to differentiate between particular histologic lesions using urine studies rather than biopsy will represent a major leap ahead in the early detection of acute kidney injury after cardiac surgery. Clinical nephrologists will be affected and early knowledge of the disease or injury will benefit outcome. Hopefully, the development of strategies to treat AKI more actively and successfully will soon follow the discovery of how to diagnose AKI earlier and earlier.

Before we adopt these biomarkers in such a role, we must not forget that these urine studies are actually intermediate outcomes. They will need to be validated in the rigorous manner as outlined by the McMaster criteria. Although they clearly correlate with the event of interest, we must further understand how a change in their measure represents a change in the event under study. This may seem a daunting task, but if the cardiologists can do it with troponins, then so can we.

DISCLOSURES

None.

REFERENCES


Does Idiopathic Hypercalciuria Trigger Calcium-Sensing Receptor–Mediated Protection from Urinary Supersaturation?

Elaine M. Worcester and Fredric L. Coe

Department of Medicine, University of Chicago, Chicago, Illinois


doi: 10.1681/ASN.2009060580

Kidney stone formation is common, affecting 5 to 6% of the American adult population, and highly recurrent. Approximately 70% of stones are composed predominantly of calcium oxalate (CaOx) with small amounts of calcium phosphate (CaP); another 10% are largely CaP. The physicochemical requirement for stone formation is supersaturation of urine with respect to the stone minerals. In the case of calcium stones, supersaturation is driven by urine calcium concentration, which is a function of calcium excretion and urine volume. For CaP, supersaturation is also controlled by urine pH, because solubility of this salt decreases as urine pH rises; CaP stones are seen largely in patients with urine pH >6.

Biopsies of renal medullary papillae of stone formers, taken during percutaneous nephrolithotomy, demonstrate that stone formers are also characterized by specific patterns of mineral deposition in tissue. Common idiopathic CaOx stone formers have interstitial deposits of CaP in the medullary interstitium, so-called Randall’s plaques, which begin in the thin loops of Henle and extend downward toward the base of the...
papilla, where they can be seen beneath the urothelium.\(^1\) CaOx stones form as overgrowths on plaque, attached to the papillae.\(^2\) When the amount of plaque covering the papillary surface was quantified, it varied directly with urine calcium excretion and inversely with urine volume and pH.\(^3\) The factors that control urinary supersaturation also affect plaque formation, which seems to be critical to the initiation of most calcium stones.

Medullary biopsy of patients with CaP stones have a different appearance. CaP deposits are found in the inner medullary collecting ducts and the terminal ducts of Bellini, associated with fibrosis and papillary deformity,\(^4\) and interstitial plaque abundance is low. The process of stone formation is less clear in these patients because attached stones seem to be uncommon, but supersaturation is still the driving force.

The central importance of supersaturation in stone formation is reinforced by the fact that treatment to prevent recurrent stones relies on lowering supersaturation. One very important means for doing this is increasing urine volume. A randomized trial of 199 first-time calcium stone formers found that risk for stone recurrence during 5 yr of follow-up was significantly decreased (relative risk 0.45; \(P = 0.008\)) by increased fluid intake, which raised urine volume from the pretreatment level of 1 L/d to approximately 2.6 L/d in the study group; urine volume did not change in control subjects.\(^5\) In general, this requires a compliant patient and consistent intake of fluids throughout the day and is often hard to achieve.

In this issue of JASN, Renkema et al.\(^6\) provide evidence that the magnitude of urinary supersaturation produced by hypercalciuria may be partially offset by effects of luminal calcium concentration on water reabsorption and urine pH, mediated through the collecting duct apical cell membrane calcium-sensing receptor (CaSR). They used mice in which the distal tubule calcium channel, TRPV5, was eliminated (TRPV5\(^{-/-}\) mice). These mice have hypercalciuria and also exhibit polyuria and a more acidic urine pH than their wild-type littermates.\(^7\) Expression of renal aquaporin 2 (AQP2) is downregulated in TRPV5\(^{-/-}\) mice compared with controls, a finding consistent with the work of others showing that stimulation of the apical CaSR decreased insertion of AQP2 in collecting duct apical membranes and impaired vasopressin-stimulated water reabsorption.\(^8\) In addition, urine net acid excretion is higher and urine pH lower in the TRPV5\(^{-/-}\) mice than in controls. Urine pH returns to control levels in TRPV5\(^{-/-}\) mice in which the B1-subunit of H\(^{+}\)-ATPase is also ablated. These double-null mice develop CaP crystal precipitation in their collecting ducts, indicating that urine supersaturation with respect to CaP is elevated, as would be expected from the extreme hypercalciuria and alkaline urine pH (despite the persistent polyuria). In vitro studies also provide evidence for a stimulatory effect of apical calcium concentrations, mediated by the effects of CaSR on H\(^{+}\)-ATPase activity in collecting duct cells from both control and TRPV5\(^{-/-}\) mice. The authors suggest that hypercalciuria through the apical collecting duct CaSR stimulates an increase in acid excretion by H\(^{+}\)-ATPase, which, together with polyuria produced by decreased collecting ducts AQP2 membrane insertion, protects against harmful intratubular CaP precipitation in TRPV5\(^{-/-}\) mice.

It is unclear whether stimulation of the collecting duct apical CaSR exerts a protective effect on urine volume or pH in humans. If it did, then it would be expected that stone formers with hypercalciuria should have higher urine volumes and lower urine pH than individuals with normal urine calcium excretion, on average. In some children with enuresis, hypercalciuria is associated with a decrease in nocturnal AQP2 levels in urine; low-calcium diet, which decreases urine calcium excretion, is associated with an increase in urine AQP2 and decreased nocturnal urine volume.\(^9\) No similar data have been reported in adults or stone formers. Reports of urine volume in stone formers with idiopathic hypercalciuria compared with non–stone formers vary; some suggested low urine volume is characteristic of calcium stone formers,\(^9\) whereas others reported that stone formers have similar or slightly higher volumes than non–stone-forming control subjects.\(^10\)

In metabolic studies of urine collected from incident stone formers and control subjects in three large cohorts, stone formers were characterized by higher calcium excretion and lower urine volume.\(^11\) No study has been done to address directly the relationship between urine calcium excretion and urine volume in human adults, and it is hard to remove from many reports the “stone clinic effect,” which causes stone formers to increase fluid intake. Overall, it seems unlikely that hypercalciuria produces a significant increase in urine volume in humans in the absence of hypercalcemia, although a modest effect cannot be excluded.

Urinary pH in humans has a median value of approximately 6\(^{13}\) but varies widely among individuals and during the course of a day. Urine pH may determine the type of stone formed in patients with hypercalciuria. Those who form stones composed predominantly of CaP have 24-h urine pH values that are usually >6.2, whereas urine pH in those with stones composed primarily of CaOx (the large majority of calcium stone formers) is slightly <6\(^{14}\); CaP stone formers, if anything, have more hypercalciuria on average than CaOx stone formers. Patients who are destined to convert from CaOx to CaP stone formation have a higher urine pH on initial evaluation compared with those who do not convert (6.23 ± 0.05 versus 5.94 ± 0.03),\(^15\) with equivalent levels of hypercalciuria. Although CaP stone formers may have abnormalities of urine acidification, in general, no defect in net acid excretion is present in these individuals, and the cause of their relatively alkaline urine pH is unclear. Whether the majority of patients with idiopathic hypercalciuria have a urine pH lower than that of normal individuals has not been studied.

Although the data by Renkema et al. are persuasive, there is reason to believe it may have limited application to humans with hypercalciuria. The TRPV5\(^{-/-}\) mice exhibit extreme hypercalciuria, with mean urine calcium concentrations of 36.7 mmol/L, compared with 6.7 mmol/L in control mice. Untreated human stone formers most often have urine calcium concentrations <6 mmol/L,\(^12\) and the ionized calcium con-
concentration is often only half the total urinary concentration of calcium, because of ligand binding. The EC₅₀ for calcium of the human CaSR is approximately 5 to 6 mM at pH values in the range of human urine, 5.5 to 6.5, so expected concentrations of ionized calcium in urine would have only a weak effect to stimulate the CaSR unless pH were either much higher or much lower than the usual range. High ionic strength also decreases the sensitivity of the receptor.

Although the effects of hypercalciuria to moderate urine volume or pH are not clearly evident in human calcium stone formers, a therapeutic modality that could stimulate urine acidification and increase urine volume would potentially be of benefit in patients with calcium stones, especially those with CaP stones, in whom a potentially destructive deposition of mineral in renal tubules exists as a result of urinary CaP supersaturation. There is no safe way to lower urine pH in these patients. Until such therapy exists, the use of increased fluid intake, low-salt diet, and thiazide remains the mainstay of preventive treatment.

ACKNOWLEDGMENTS

This work was funded by National Institutes of Health grant PO1 DK56788.

DISCLOSURES

E.M.W. and F.L.C. have received consulting fees from Laboratory Corporation of America.

REFERENCES


The SDF-1/CXCR4 Axis Is a Novel Driver of Vascular Development of the Glomerulus

Jürgen Floege, Bart Smeets, and Marcus J. Moeller
Division of Nephrology and Immunology, RWTH University of Aachen, Aachen, Germany


Spatial and temporal control of developing glomerular capillaries is complex and requires coordinated cross-talk between various cell types. Recent advances in our understanding of the processes that regulate glomerular morphogenesis reveal some

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Jürgen Floege, Division of Nephrology and Immunology, Rheinisch Westfälische Technische Hochschule University of Aachen, Pauwelsstrasse 30, 52074 Aachen, Germany. Phone: 011-49-241-8089-530; Fax: 011-49-241-8082-446. E-mail: juergen.floege@rwth-aachen.de

Copyright © 2009 by the American Society of Nephrology