

## SCAD syndrome: A vicious cycle of kidney stones, CKD, and AciDosis

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correction of plasma and urine pH in patients with reduced renal function and correction of urine pH in patients with normal renal function, may be considered in treating patients with SCAD syndrome.

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**Key words:** Endoplasmic reticulum stress response; End-stage renal disease; pH; Endothelial; Epithelial

**Core tip:** This minireview is written for urology and internal medicine physicians who see kidney stone formers in their daily practice. It is our responsibility to make more serious consideration on the long term outcome of developing end-stage renal disease and cardiovascular diseases in kidney stone formers. The significance of appropriate intervention on acidic condition for these subjects are often neglected. By naming "SCAD syndrome", we can promote more attention on this significant, but sometime forgotten pathological condition.

### Abstract

Cumulative evidence has shown that kidney stone formers are at high risk for developing end-stage renal disease (ESRD) and cardiovascular disease. The aim of this mini-review is to summarize the present knowledge about the close relationships among kidney stone formation, chronic kidney disease (CKD), and plasma and urine acidosis (SCAD). Part of the cause of the positive relationships between higher risk of developing ESRD and cardiovascular diseases in stone formers may be explained by inflammation and cell death due to the components of kidney stones. In CKD patients, acidic urine and loss of anti-crystallization factors may cause stone formation. Acidosis can promote tissue inflammation and may affect vascular tone. Correction of plasma and urine acidosis may improve renal and cardiovascular outcome of stone formers and CKD patients. More intensive and long-term interventions, which include

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### INTRODUCTION

Patients with kidney stones usually visit only urologists. However, cumulative evidence indicates that stone formers are at high risk for developing end-stage renal disease (ESRD) and cardiovascular disease. This review will summarize present knowledge about the relationships among stone formation, chronic kidney disease (CKD), and plasma and urine acidosis. Incorporation of these three pathological conditions is needed for the awareness

of urologists and general physicians. To promote such awareness, we would like to give the name SCAD (stones, CKD, and AciDosis) syndrome to this pathological condition.

## THE RELATIONSHIPS BETWEEN STONE FORMATION AND RENAL INJURY

### Epidemiology

In patients with rare genetic diseases such as hyperoxaluria, cystinuria, Dent disease, and adenine phosphoribosyltransferase deficiency, it is well established that kidney stone formation causes renal damage<sup>[1,2]</sup>. In contrast, little attention has been paid to the pathological role of commonly observed kidney stones in the development of renal damage. As was reviewed by Rule *et al*<sup>[1]</sup> and Gambaro *et al*<sup>[2]</sup>, cumulative evidence has shown a significant association between kidney stone formation and the risk of developing ESRD. Alexander *et al*<sup>[3]</sup> clearly showed in their prospective cohort study that even a single episode of kidney stones can cause a 2.16-fold higher risk for developing end-stage renal failure in both males and females. Hippisley-Cox and Coupland demonstrated a significant association between kidney stones and the development of end-stage kidney failure only in females in their prospective cohort study<sup>[4]</sup>. Chen *et al*<sup>[5]</sup> found an association between sonographically-determined nephrolithiasis and the estimated glomerular filtration rate (eGFR) in their cross-sectional study. Saucier *et al*<sup>[6]</sup> determined in their case-controlled retrospective cohort study that struvite stone formers and uric acid stone formers are more likely to develop CKD. These associations may not be simply explained by renal damage due to occlusion of the tubules or the urinary tract by stones. Alexander *et al*<sup>[7]</sup> discovered that a single kidney stone episode can cause a 1.40-fold higher risk of acute myocardial infarction and a 1.26-fold higher risk of stroke.

### Mechanisms

Part of the cause of the positive relationship between higher risk of developing ESRD and cardiovascular disease in stone formers may be explained by inflammation and cell death due to the components of the stones. Oxalate has been shown to activate inflammatory cytokine signaling pathways, including the interleukin (IL)-2 and IL-6 signaling pathways, in renal tubular cells<sup>[8,9]</sup>. Oxalate has also been shown to induce cellular death in vascular endothelial cells, which is enhanced by hypoxia<sup>[10,11]</sup>. Crystallized uric acid activates toll-like receptors 2 and 4 and promotes inflammation<sup>[12]</sup>. An increase in intracellular uric acid causes oxidative stress<sup>[13]</sup>. In addition, during the process of uric acid generation, xanthine oxidase causes oxidative stress<sup>[14-16]</sup>. Struvite stones are generated at the place of inflammation due to bacterial infection<sup>[17]</sup>. Hamamoto *et al*<sup>[18]</sup> demonstrated the similarity in the mechanisms of pathogenesis for stone and atherosclerosis. They have identified the involvement of osteopontin

in both pathological condition.

## THE RELATIONSHIPS BETWEEN SERUM AND URINE ACIDOSIS AND STONE FORMATION

### Epidemiology

Due to the higher prevalence in stone formers of developing CKD, it is difficult to clearly demonstrate the higher incidence of stone formation in CKD subjects. However, several mechanisms have been identified to help speculate that CKD subjects are at high risk for crystal formation.

### Mechanisms

According to Coe *et al*<sup>[19]</sup>, there are two major pathways for kidney stone formation. One pathway is based on plaque formation in the basement membrane of the thin limbs of loops of Henle. Stone is formed by the overgrowth of plaque and detaches to the tubular space. Plaque formation correlates with urine volume, pH, and calcium. Another pathway is crystallization in the tubular space. Supersaturated solute, including uric acid or calcium oxalate in the urine, forms crystals. The solubility of these solutes is urine pH dependent. These substances are less soluble in low pH conditions. Overall, urine pH has already been established as the major cause of kidney stone formation. In CKD subjects, reduced eGFR is often associated with decreased excretion of calcium and decreased urine concentration capability<sup>[20]</sup>. Indeed, Marangella *et al*<sup>[21]</sup> have demonstrated that subjects with lower GFR may have a lower recurrence rate of calcium stones. Along the same line, metabolic acidosis is often associated with CKD due to the limited capability of acid excretion into urine. But, in contrast to calcium, this does not mean that urine pH is high in CKD subjects, for the following reason. To excrete sufficient acid with limited reduction in urine pH, the kidney uses titration acids, including  $\text{NH}_4^+$  and  $\text{H}_2\text{PO}_4^-$ . These titration acids can also be reduced in the urine of CKD subjects. Therefore, the pH level easily becomes low in the urine of CKD subjects. Related to this idea, Stettner *et al*<sup>[22]</sup> recently showed that sulfatide-deficient mice developed metabolic acidosis with lower urine pH in response to acid overload. Low pH causes the crystallization of uric acid and calcium oxalate by limiting their solubility. Systemic acidosis may also promote stone formation by increasing the solute overload into urine. Acidosis promotes calcium release from bone. Starke *et al*<sup>[23]</sup> showed that, in renal transplant patients, normalization of metabolic acidosis by the administration of potassium citrate has the potential to preserve bone quality, as assessed by bone biopsy. Regarding the molecular mechanism, Geng *et al*<sup>[24]</sup> showed that serum bicarbonate inhibits osteoclast formation though the activation of soluble adenylyl cyclase. Krieger *et al*<sup>[25]</sup> showed that metabolic acidosis directly increases fibroblast growth factor 23 (FGF23)

mRNA and protein in mouse bone. CKD and metabolic acidosis may also affect the expression of the Tamm-Horsfall glycoprotein and other factors that inhibit the growth of crystal<sup>[26]</sup>.

## THE RELATIONSHIPS BETWEEN SERUM AND URINE ACIDOSIS AND KIDNEY INJURY

### Epidemiology

In CKD subjects, high and low serum bicarbonate levels are associated with a risk of mortality and the development of ESRD. Kovesdy *et al.*<sup>[27]</sup> showed in their retrospective cohort study that the group of patients with serum bicarbonate level of 26-29 mmol/L had the lowest mortality rate. The retrospective cohort study of Navaneethan *et al.*<sup>[28]</sup> showed that the group of patients whose serum bicarbonate level was 23-32 mmol/L had the lowest mortality rate. Kanda *et al.*<sup>[29]</sup> showed in their retrospective cohort study that subjects with high serum bicarbonate level (28.8 mmol/L) are less likely to develop ESRD than patients with low serum bicarbonate level (23.4 mmol/L). Recently, several studies have shown the beneficial effect of correcting metabolic acidosis on the decline of GFR in CKD subjects. Susantitaphong *et al.*<sup>[30]</sup> systematically reviewed the effects of sodium bicarbonate in the long term (> 2 mo), and showed an improvement in the eGFR and a lower incidence of initiating dialysis therapy. The beneficial effect of alkali therapy on eGFR in CKD subjects has been shown by the administration of potassium citrate<sup>[31]</sup>.

In non-CKD subjects, acidic urine has been shown to be associated with diabetes and metabolic syndrome (Mets)<sup>[32,33]</sup>. Maalouf *et al.*<sup>[32]</sup> showed a positive association between acidic urine and a number of the components of Mets in non-CKD subjects. These authors speculated that part of this association may be explained by impaired urine buffering capability due to insulin resistance.

### Mechanisms

As was reviewed by Souto *et al.*<sup>[34]</sup>, metabolic acidosis can lead to the development of several risk factors for cardiovascular disease, including inflammation, hypertension and disturbed glucose tolerance, due to decreased insulin sensitivity.

**Effects on inflammation:** Bellocq *et al.*<sup>[35]</sup> and Kellum *et al.*<sup>[36]</sup> showed that acidic condition promotes tumor necrosis factor alpha (TNF- $\alpha$ )-dependent nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) activation in macrophages. More recently, Rajamäki *et al.*<sup>[37]</sup> and Edye *et al.*<sup>[38]</sup> showed pH-dependent secretion of IL-1 $\beta$  and activation of caspase-1 in macrophages. These investigators also have demonstrated the significant role of damage-associated molecular patterns (DAMPs) in this process. Nikolettou *et al.*<sup>[39]</sup> showed that acidosis switches TNF-related apoptosis-inducing

ligand (TRAIL)-induced apoptosis to regulated necrosis in cancer cells. Further investigations are expected to test whether cell death under an acidic condition also shows switching from apoptosis to necrosis. An increase in the proportion of necrosis may promote more inflammation to the injured area. Chen *et al.*<sup>[40]</sup> showed that acidic condition induces the production of cell adhesion molecules, including intercellular adhesion molecule 1 (ICAM-1), E-selectin, and vascular cell adhesion molecule 1 (VCAM-1) in endothelial cells. Acidic condition has been shown to activate complement system. Emeis *et al.*<sup>[41]</sup> and Curley *et al.*<sup>[42]</sup> has shown that acidosis activates C3 and C5. Morita *et al.*<sup>[43]</sup> showed that the administration of sodium bicarbonate in subjects with proteinuria decreases the renal excretion of complement activation products (CAP).

**Effects on vessel function:** The role of acidosis on vascular tone is controversial. As reviewed by Smith *et al.*<sup>[44]</sup>, Smith *et al.*<sup>[45]</sup> and Wray *et al.*<sup>[46]</sup>, extracellular and intracellular decreases in pH have been shown to promote vasoconstriction. However, several studies have shown that acidosis enhances nitric oxide (NO) production and promotes vasodilatation<sup>[47]</sup>. Part of this inconsistency may be explained by oxidative stress. The intracellular acidic condition causes an increase in the fraction of free iron to protein-bound iron in cells, which causes oxidative stress by a Fenton-type biochemical reaction<sup>[48]</sup>. Oxidative stress itself has been shown to promote vasoconstriction. It reacts with NO and generates the highly toxic peroxynitrite anion (ONOO<sup>-</sup>). Enhanced NO production also causes high endothelial permeability<sup>[49]</sup>. Dong *et al.*<sup>[50]</sup> showed that endothelial cells detect the extracellular acidic condition by the proton-sensing G-protein coupled receptor 4 (GPR4), which activates inflammation and the endoplasmic reticulum (ER) stress response.

**Effects on tubules:** In epithelial cells, adaptation mechanisms to acidic conditions have been well investigated. This is because epithelial cells, including in the intestine and the kidneys, are in the location to be exposed to acidic condition even under physiological conditions. Therefore, these cells are resistant to extracellular acidification. Sodium-hydrogen exchangers (Na<sup>+</sup>/H<sup>+</sup> exchangers, NHEs) have an established role in the maintenance of internal pH. Muthusamy *et al.*<sup>[51]</sup> has shown that, in intestinal epithelial cells, acid induces the NHE2 Na<sup>+</sup>/H<sup>+</sup> exchanger to regulate internal pH through the induction of early growth response protein 1 (EGR-1). Preisig *et al.*<sup>[52]</sup> and Kwon *et al.*<sup>[53]</sup> showed an increase in NHE3 and the Na/HCO<sub>3</sub> cotransporter (NBC1) in the renal proximal tubules. Odunewu and Fliegel showed that acute sustained intracellular acidosis activated NHE1 in human embryonic kidney 293 (HEK293) cells and in Madin-Darby canine kidney (MDCK) cells<sup>[54]</sup>. Renal epithelial cells have also been shown to activate glutamine transporters, including SN1<sup>[55]</sup> and mitochondrial



glutamine transporter<sup>[56]</sup>, to increase the production of ammonia, which acts as a titration acid. Ibrahim *et al*<sup>[57]</sup> proposed that, in proximal tubules, a change in intracellular pH may promote the ER stress response followed by the stabilization of corresponding mRNAs for ammoniogenesis. As for the protective mechanism of renal tubular cells against extracellular acidification, Namba *et al*<sup>[58]</sup> have demonstrated the significant role of autophagy in the proximal tubules.

## CONCLUSION

Kidney stone formation, chronic kidney disease or cardiovascular disease, and metabolic acidosis influence each other and form a vicious cycle. Even a single episode of stone formation in a stone former or an asymptomatic stone former may place those persons at higher risk for the development of CKD and cardiovascular disease. More intensive and long-term interventions, which would include correction of plasma and urine pH in subjects with reduced renal function and correction of urine pH in subjects with normal renal function, may be considered in the strategy for treating subjects with SCAD syndrome.

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