

# Changes in Renal Function and Blood Pressure in Patients with Stone Disease

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**Abstract.** Stone disease is a rare cause of renal failure, but a history of kidney stones is associated with an increased risk for chronic kidney disease, particularly in overweight patients. Loss of renal function seems especially notable for patients with stones associated with cystinuria, hyperoxaluria, and renal tubular acidosis, in whom the renal pathology shows deposits of mineral obstructing inner medullary collecting ducts, often diffusely. However, even idiopathic calcium oxalate stone formers have a mild but significant decrease in renal function, compared to age, sex and weight-matched normals, and appear to lose renal function with age at a slightly faster rate than non-stone formers. There is also an increased incidence of hypertension among stone formers, although women are more likely to be affected than men.

**Keywords:** Kidney stones, chronic kidney disease, hypertension, calcium oxalate, glomerular filtration rate

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## STONES AND RENAL DISEASE

Stone disease is, fortunately, a rare cause of end-stage renal disease (ESRD). In the United States, the Renal Data System categories “Nephrolithiasis, obstruction, gouty nephropathy” and “Nephrocalcinosis” accounted for 1.2% and 0.1%, respectively, of cases of ESRD, a total of 6453 patients, from 2000-2004 [1]. This is somewhat lower than the frequency of nephrolithiasis-associated ESRD of 3.2% reported in patients starting dialysis at Necker Hospital (Paris, France) between 1989 and 2000; however, the rate dropped from 4.7% in 89-91 to 2.2% in 98-2000, suggesting that this entity is becoming less common [2].

Urolithiasis may result in loss of function by two general mechanisms: 1) episodic events, such as ureteral obstruction during stone passage, or because of procedures needed for stone removal, and their attendant complications, or 2) continuous events, as a result of a disordered physiology that underlies stone formation [3]. Nephrectomy, at one time a relatively common outcome of stone disease, especially in patients with staghorn calculi – such as from struvite or cystine stones – is uncommon in the era of modern endourologic approaches. However, renal dysfunction may still occur in patients with stone disease, via one or both of these mechanisms. As even moderate renal dysfunction is associated with increased long-term cardiovascular morbidity [4], the issue deserves the attention of those who treat patients with stones.

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## **Nephrolithiasis Is Associated with an Increased Risk of Chronic Kidney Disease**

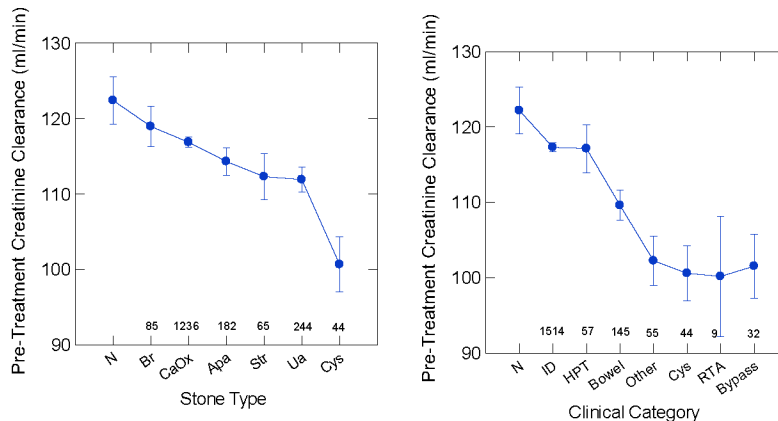
A history of kidney stones may be a risk factor for chronic kidney disease (CKD). In a case control study comparing 548 patients with newly diagnosed CKD from diverse causes to 514 age, sex, and race matched controls, a history of kidney stones was reported significantly more often by the subjects with CKD than by controls (16.8 vs. 6.4% respectively,  $p < 0.001$ ) [5]. Stone formers (SF) had an increased risk of CKD (odds ratio 1.9, 95% CI 1.1-3.4) after adjustment for multiple confounders. Among subjects with hypertension, CKD was 3 times more common among those with stones than those without.

This association between stones and CKD was borne out by data from the Third National Health and Nutrition Examination Survey (NHANES III) [6]. This survey, conducted between 1988 and 1994, was designed to provide estimates of health status in the non-institutionalized U.S. population. Participants were asked if they had ever had a kidney stone. Renal function was estimated using the Modification of Diet in Renal Disease (MDRD) equation, and individuals who reported having ever had a stone were compared to those with no such history. The median body mass index (BMI) among SF in this sample was  $27 \text{ kg/m}^2$ , and initial analysis of the relationship between stone history and glomerular filtration rate (GFR) revealed a significant interaction between stones and BMI. In subjects with  $\text{BMI} < 27$ , history of stones did not increase the relative risk for decreased GFR. However, among subjects with  $\text{BMI} \geq 27$ , SF had a significantly increased risk of having Stage 2 or Stage 3 CKD (using the Kidney Disease Outcomes Quality Initiative definitions for reduced renal function [7]), after adjustment for age, gender, race, systolic blood pressure (BP), diabetes, smoking, cardiovascular disease and health insurance. The odds of having Stage 2 CKD (GFR 60-90 ml/min/1.73 m<sup>2</sup>) was 1.66-fold higher in SF compared to non-SF, while the odds for stage 3 CKD (GFR 30-60 ml/min/1.73 m<sup>2</sup>) was 1.87-fold higher, relative to having a GFR greater than 90 ml/min/1.73 m<sup>2</sup>. Among SF in this survey, 19% had had surgery for stone removal, and 7% had ESWL; neither was associated with increased risk for loss of renal function in this analysis. As well, 40% of patients reported taking medication for stones; use of such medication was also not associated with loss of GFR. Thus, among overweight persons, a history of kidney stones significantly increased the risk of having decreased GFR compared to comparably overweight non-stone formers, after adjustment for multiple confounders.

### **Association of Specific Stone Types with Reduced GFR**

These studies cannot give any detail about association of stone type with loss of function. We have used data from SF investigated at the University of Chicago Kidney Stone Program between 1969 and 2005 to look into such associations [8]. All patients had 3 24-hour urines collected prior to starting therapy, and creatinine clearances were calculated for each of the 1856 patients (581 females) in our program with at least one stone analysis; 153 normal subjects (63 female) were used as a comparison (Fig. 1).

Clinical phenotypes were also determined, including the presence of bowel disease, jejunioileal bypass for obesity, renal tubular acidosis, and hyperparathyroidism. Compared with the controls, virtually all the SF groups had some decrease in renal function, but certain types of patients stand out as being at special risk.



**FIGURE 1.** Pretreatment creatinine clearances by stone type or clinical category, adjusted for age, weight, and gender, shown as means  $\pm$  SEM. Patients are from the University of Chicago Kidney Stone Program. Numbers represent patients in each category; overall, 1856 stone formers, 153 normal subjects. N, normal; Br, brushite; CaOx, calcium oxalate; Apa, apatite; Str, struvite; Ua, uric acid; Cys, cystine; ID, idiopathic; HPT, hyperparathyroid; Bowel, bowel disease with or without surgery; Other, rare diseases such as sarcoidosis, drug stones, eating disorders; RTA, renal tubular acidosis; Bypass, obesity bypass. [reprinted from [8], used by permission from American Urological Association].

One example would be inherited diseases with life-long renal excretion of large amounts of insoluble materials, such as patients with cystinuria. Patients with cystine stones are well known to be at risk for renal insufficiency [9]. The fact that these stones may become quite large, are frequently recurrent, and that cystine SF often require many procedures for stone removal, could explain the virtually universal decrease in renal function among cystine SF. However, loss of renal function appears early in the course of cystine stone formation, and creatinine clearance remains below that of idiopathic SF at all ages. Fortunately, ESRD is a rare occurrence, at least among treated patients, in whom procedure rates diminish, although they continue to be higher than among other groups of SF.

The renal pathology of cystinurics suggests another reason that they may experience decreased renal function [10]. During percutaneous nephrolithotomy (PCNL) it is common to find abnormalities of most or all papillae in these patients, with dilated Bellini ducts containing masses of crystal, although some patients, early in their course, have little damage. Histopathologic analysis of papillary biopsies reveals deposition of cystine crystals, and often apatite crystals, that fill inner medullary collecting duct (IMCD) lumens and result in obstruction of these tubules, with damage to the lining cells. Fibrosis surrounds dilated crystal-filled tubules, and is

associated with glomerular obsolescence. This diffuse tubule plugging seems likely to contribute to decreased renal function, although there is not yet data correlating the extent of plugging with level of GFR.

Patients with renal tubular acidosis (RTA) also exhibit marked decreases in renal function. These patients, like cystinurics, have a systemic disease, and usually have diffuse involvement of all papillae with deposits of apatite, which is seen on X-ray as nephrocalcinosis, and on papillary biopsy as deposits of apatite filling tubule lumens in most papillae [11]. The diffuse involvement of almost all papillae is a striking feature of patients with either cystinuria or RTA.

Excretion of large amounts of oxalate is also associated with a risk for renal insufficiency. Renal failure is seen in many patients with primary hyperoxaluria type I, because of deposition of calcium oxalate in renal tissue, and may occur before the diagnosis of their underlying disease has been made [12]. Acquired hyperoxaluria may also lead to loss of renal function, as in patients with ileal resection or bypass, in whom intra-tubular crystal deposits are also seen [13]. Recent reports suggest that newer bariatric surgery may also carry a risk for hyperoxaluria, and consequently the potential for renal damage because of increased oxalate transport through the kidney [14].

Overall, the worst kidney dysfunction is seen among patients with stone types associated with crystal plugging, seen most often in the IMCD and Bellini ducts, which is often associated with interstitial fibrosis. That these diseases are also associated with formation of large stones, requiring multiple procedures, is also likely to result in renal injury.

Whether surgical treatment for stones may result in injury to the kidney, with resultant loss of GFR, is unclear. There have been rare reports of acute renal failure after extra-corporeal lithotripsy (ESWL) [15], and studies in animals that have undergone lithotripsy document renal damage accompanied by reduction in GFR [16, 17]. In humans, data about the effects on renal function of repeated episodes of lithotripsy is lacking.

Uric acid stones are associated with risk for CKD as well. Recent work has linked this type of stone to the presence of insulin resistance, obesity, and often frank diabetes [18, 19].

### **Routine Calcium Oxalate Stone Formers May Not Have Normal Renal Function**

The groups noted in Fig. 1 to have the greatest decrease in renal function are those in which diffuse tubular obstruction with crystals could lead to a drop in kidney function. However, these diseases are relatively rare, and unlikely to account for the increased risk of CKD in stone formers noted in the large groups described by Gillen [6] or Vupputuri [5]. Therefore, it is of interest that among the University of Chicago cohort, even routine calcium stone formers—those with calcium oxalate (CaOx) stones and without systemic disorders—also had renal function that was slightly, but significantly, below that of normals, adjusted for sex, age and weight ( $115 \pm 1$  vs.

122±2,  $p=0.02$ , SF vs. normal) [8]. The reason is not obvious; we do not have data on procedures or stone numbers, which might have an effect on renal function. Since these patients make up the majority of SF, this abnormality, although in general mild, may still be significant.

Tubule obstruction with crystals is not likely to account for decreased renal function in these patients. Routine CaOx SF have not been found to have intra-tubular deposits of mineral. Instead, subepithelial apatite deposits, Randall's plaque, have been found in all those studied to date [13]. These deposits appear to originate in the basement membrane of the thin limb of Henle, and spread into the interstitium. Tubule epithelium is intact, and interstitial fibrosis is not noted. The impact of these deposits on renal function has not been determined; glomerular anatomy appears normal.

Our cross-sectional data suggests some alterations in the renal function of SF; we wished to know also if SF lose renal function with age at the same rate as non-stone formers. When the rate of loss of GFR with age among the SF in the University of Chicago program was compared with data from studies of normal subjects in the literature, renal function among SF began to decline at a later age than among normals, but after the age of 45 male SF lost renal function more rapidly, compared to normals [20]. The pattern for women was similar, but did not reach statistical significance. Whether loss of GFR with age is truly accelerated among stone formers will need to be confirmed by further study, and the associations with underlying stone type and metabolic abnormalities clarified.

## STONE DISEASE AND HYPERTENSION

One condition that may impact renal function in this group of patients is the reported association between stone formation and hypertension (HTN). A number of epidemiologic studies have suggested that the incidence of hypertension is increased among patients who make kidney stones. Madore et al. have found an association between stone history and development of hypertension in large cohort studies of women aged 34 to 59 years [21], and men aged 40 to 75 [22]; the relationship was not explained by dietary intake of calcium, sodium or potassium, but was stronger in women. We have found a similar association using data from NHANES III [23]. In this cross-sectional survey, SF's were significantly more likely to report a history of HTN (32.7% vs. 24.6%, SF and non-SF, respectively,  $p=0.001$ ). We found that the relationship between stone formation and blood pressure was dependent on sex and BMI; among women in the upper 2 quintiles of BMI, systolic BP among SF was 7.62 mm Hg (95% CI 1.04-14.2,  $p=0.024$ ) and 4.36 mm Hg (95% CI 0.30 to 8.42,  $p=0.036$ ) greater in SF compared with non-SF; diastolic BP was also increased modestly. A similar trend among males did not reach statistical significance.

The association between nephrolithiasis and HTN does not imply a causal relationship. It is possible that renal damage related to stone formation could lead to increased blood pressure; in animals, tubulo-interstitial injury can lead to a salt-sensitive form of hypertension [24]. As we have seen, many stone formers have some degree of tubulo-interstitial injury; whether these SF are particularly prone to HTN has

not been settled. Among cystine SF studied in our program, we did not find higher BP than among routine SF; however, the numbers studied are relatively small, and we cannot know the degree of tubulo-interstitial injury in any given patient, at present. Alternatively, there may be genetic mechanisms that are linked to increased risk for both stones and hypertension. Hypercalciuria may be a link between the two diseases [25].

## IS KIDNEY DONATION SAFE FOR STONE FORMERS?

One of the questions that physicians who care for SF are sometimes faced with is whether such individuals can safely donate a kidney. Because calcium stones are quite common, and onset is usually in early to mid-adulthood in otherwise healthy people, SF may present for evaluation as potential donors for a family member with renal failure. Does stone formation pose an unacceptable risk to these potential donors? Are they at risk for more rapid loss of renal function with age?

There have been no systematic studies looking at SF who have donated a kidney. In order to see if the loss of a kidney would lead to significant risk for CKD among SF, we have studied a group of 115 SF (58 male) who lost a kidney for reasons including obstruction and infection [16]. In a cross-sectional analysis, loss of renal function with age in the single kidney SF was not accelerated, compared to two-kidney SF, among the women, nor among men over the age of 45; loss of GFR may be increased among younger male stone formers who have lost a kidney. Stone recurrence was not increased among the single-kidney patients, who were all being treated for their stone disorder. Overall, from this study one would conclude that donation would not automatically be ruled out for SF, but in view of the accumulating data linking stone formation to some risk for renal impairment, careful screening would be important, and treatment to prevent stone recurrence with careful follow-up should be advised to any such donors.

## ACKNOWLEDGMENTS

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