

GUEST EDITORIAL

Nephrolithiasis (parts 1 and 2)

The two sections of this CME series cover kidney stone epidemiology, causes and pathogenesis (part 1, in this issue), followed by diagnosis, management and prevention (part 2, to follow). In addition, the practical 'office' work-up and patient advice are presented as online supplementary material not covered in the articles. In the absence of a dedicated stone clinic where a holistic work-up is routine, practising urologists, nephrologists and general practitioners have to be sufficiently educated to be able to manage this common problem in a practical, scientific and cost-effective manner. In order to acquire sufficient knowledge of the problem, practitioners are strongly advised to read not only the two sections, but also the online supplement.

Renal calculus disease was known in the days of Hippocrates (400 BCE), the alchemists (1200 BCE) and the barber surgeons (1400 - 1700 BCE). Indeed, the barber surgeons (so-called because they were actually 'hairdressers'), were frequently called upon to remove renal, ureteric or bladder stones. Their victims seldom survived this ordeal, and hence the wording of the Hippocratic Oath.

In 2001, nephrolithiasis was estimated to occur in ~12% of males and 5% of females. Calcium oxalate stones comprise 80 - 85% of all cases of nephrolithiasis, and recur in 50%. The remaining 15 - 20% are due to uric acid, and cystine, struvite and infective calculi. Calcium oxalate calculi are rarely seen in black South Africans. Although stones are unusual in children, calcium oxalate calculi have increased exponentially over the past 16 years. The risk factors for stone formation are mainly genetic or environmental - especially if associated with inadequate fluid intake and dietary aberrations. The stone types discussed in this CME series are either of calcium oxalate or calcium phosphate, which may present differently in different circumstances, and may have different outcomes. Secondary causes of kidney stones (15% of total) are important, e.g. primary hyperparathyroidism, hypercalcaemia and hypercalciuria from chronic granulomatous disorders, inflammatory bowel diseases and, in recent times, post-bariatric surgery (associated with marked hyperoxaluria).

The pathogenesis of calcium oxalate stone formation involves a multistep process comprising crystal nucleation, growth, aggregation and agglomeration, i.e. a stone. Many factors affect the rate at which these processes occur, even in normal urine. Therefore, there are promoters of stone formation and inhibitors of stone formation. A few of the most important factors of promoters are, firstly, a raised 24-hour urinary calcium excretion. This is largely (but not always) governed by the amount of salt ingested. Five grams of salt ingested per day will yield excretion of 80 - 90 mmol of sodium in the urine. If this salt intake was the rule, 80 - 90% of all calcium oxalate calculi would never form. In addition, the urinary excretion of uric acid, especially in an acid urine (i.e. seen in red-meat eaters), is a potential cause of calcium oxalate crystal precipitation. The uric acid acts as a catalyst, a process known as 'salting out'. The main stone inhibitors are water (as much as to result in 2.2 - 2.5 L of urine per 24 hours) and urinary citrate concentration.

The presence of multiple Randall's plaques seen on computed tomography scans is an important epidemiological factor in stone formation. These are areas of interstitial calcification at the tips of the renal pyramids, and should not be mistaken for stones.

The diagnosis, management and prevention of kidney stones relate mainly to patients with recurrent calcium oxalate or phosphate calculi. As a rule, only patients with recurrent calculi undergo detailed work-up. The management and prevention of an isolated first attack of stone disease are limited to a few tests (e.g. exclusion of primary hyperparathyroidism), and empirical management, i.e. ensuring a fluid intake of ~3 L per day. Routine citrate therapy is not recommended, because only 50% of patients with recurrent calcium oxalate or phosphate stones have hypocitraturia and, more importantly, conversion of an acid to an alkali urine may be associated with conversion of calcium oxalate to a phosphate stone. Calcium phosphate stones have a far more deleterious effect on renal function than the oxalate variety.

However, there are exceptions to the above, and some stone sufferers require a fully detailed work-up and chronic management plan. These include patients <19 years of age, pilots, fire-workers and armed forces personnel, and cases of a first stone in obese patients with type 2 diabetes. Also, if multiple asymptomatic calculi are found on an initial radiological procedure, they are fully investigated. The work-up and management of nephrolithiasis in pregnancy require specific attention to several aspects. The most important aspect of the management is the insistence on a continuously high fluid intake. If this is achieved, 70% of the stones will pass spontaneously.

Routine work-up protocols demand the performance of many blood tests (required for diagnosis, management and follow-up), routine multiple 24-hour urine tests and dietary work-up by a skilled 'stone' dietician.

The surgical management of chronic, symptomatic calcium oxalate stone disease is either extracorporeal shockwave lithotripsy or 'beam' lithotripsy. Many practising urologists follow the 'practical' approach even in recurrent disease. Detailed work-up is not performed, and follow-up is often undertaken by the patient's family physician. This is unacceptable. Lithotripsy is not without complications. Patients with recurring calcium oxalate stone disease often have suboptimal renal dysfunction and, if the stones are calcium phosphate, the deficit may be more severe, even very occasionally resulting in chronic kidney disease. Also, it is not cost-effective.

Many aspects of dietary manipulation have been mentioned. Dietary therapy is of pivotal importance and should be 'tailor-made' for each individual patient, and long-term follow-up is essential.

Patients with confirmed hypocitraturia require special attention. Twenty-four-hour urine collection is a tedious and, in some (e.g. young children), impossible task. However, in symptomatic patients with recurrent stones, it becomes easier. The patient has to follow several strict rules of urine collection and of sample delivery to the pathology laboratory. This is required for accurate citrate estimation, as well as other purposes. In terms of management, it is essential that neither the dietician nor attending practitioner recommends a high fluid intake before all of the tests (and repeats) are available. Doing so would remove one of the most important pathophysiological causes of stone formation, i.e. states of chronic fluid underhydration.

Salt restriction is essential. Eighty percent of all calcium oxalate stone formers have 24-hour urinary sodium levels of >150 mmol. In terms of treatment adherence, it is recommended that repeats

of 24-hour urine collection for sodium (and volume) be performed 3-monthly until adherence is achieved.

In terms of other medications, thiazide diuretics are the preparations most used in patients with 'idiopathic' (i.e. primary) hypercalciuria. This practice must cease. Thiazides, especially in the recommended dose of 50 mg per day to achieve increased renal tubular calcium reabsorption, are potentially toxic. They cause hyperglycaemia or frank type 2 diabetes, the metabolic syndrome (insulin resistance), hyperuricosuria and hypokalaemia. Therefore, they are contraindicated in recurrent calcium oxalate stone disease. In addition, the hypocalciuric effects of thiazides wear off after 6 - 12 months of usage. Indapamide 2.5 mg daily is a more potent urinary calcium-lowering preparation, is safe and its urinary effect never diminishes.

The use of allopurinol has been recommended in all patients with calcium oxalate stone formation, especially in those with chronically low urinary pH readings. Not all agree with this concept. The best approach is to use allopurinol with caution, starting with a low dose, and to watch for significant side-effects – which are very rare.

Finally, and not often mentioned, is the role of medications in producing recurrent renal calculi. Those to be aware of are: the chronic (mis)use of some proton pump inhibitors; some anti-cancer preparations; acetazolamide; topiramate; and mega-doses of vitamin C (as immune boosters/anti-influenza). Obviously, some of the above can either be totally avoided or, if present, considered in the diagnosis and management of recurrent stone disease.

Like most genetic or acquired disorders, kidney stone disease is a heterogenetic condition affected by environmental influences that produce many phenotypically different subtypes associated with certain specific genotypes. The condition is common, and its management is poorly taught and poorly understood. We hope that this two-part series, which describes the basic knowledge required to understand nephrolithiasis, will be of value to all who read it.

The take-home messages are therefore: 'Eat a little of everything and a lot of nothing' (Prof. Sonja Walker, Department of Physiology, University of the Witwatersrand, 1975); and 'Diet imposes patterns of metabolism upon the organism' (J Gillman, Departments of Physiology and Anatomy, Medical School, University of the Witwatersrand, 1951).

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S Afr Med J 2021;111(10):928-929. <https://doi.org/10.7196/SAMJ.2021.v111i10.15991>