What I tell my patients about **cystinuria**

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Cystinuria is an inherited condition that causes kidney stones in children and adults. **John A Sayer** and **Charles Tomson** describe the effects of this condition and how to manage it successfully.

Cystine is an amino acid found in high-protein foods such as meat, eggs and dairy. High concentrations of cystine, particularly in acidic urine, result in crystallisation of cystine, leading to the formation of kidney stones (see Box 1). These cystine stones are a rare form of kidney stone, accounting for around 6% of kidney stones in children and around 1% of those in adults.[1]

Cystinuria is estimated to affect 1 in 7,000 people.[2] Despite the condition being present from birth, most people affected will get their first stone in their twenties, although a quarter of patients present in childhood. A UK registry of patients with cystinuria has been established as part of the Registry for Rare Kidney Diseases.[3]

How do cystine stones form?

Normally, the kidneys filter the blood to allow waste products to be removed from the body. The kidneys then reclaim many important substances from the urine for recycling. Cystine is one of the substances recovered normally, so most people have very low levels of cystine in their urine.

People with cystinuria have a reduced ability to reabsorb the filtered cystine, leaving high concentrations of cystine in their urine. This causes crystals to form in the urine, particularly if it is concentrated, acidic or both. These crystals stick together to form kidney stones. Cystine stones are typically pale yellow in appearance, and can have a smooth or irregular surface (see Figure 1).

People with cystinuria also have a reduced ability to reclaim a number of other amino acids – namely, ornithine, lysine and arginine; however, these remain dissolved in the urine and, therefore, do not cause any problems.

Inheritance of cystinuria

Cystinuria is an inherited condition, with two known genes that may carry abnormalities leading to cystinuria: *SLC3A1* and *SLC7A9*. A mutation in either or both of these genes can lead to excess cystine in the urine and a tendency to form cystine stones.

Box 1. You say stones… I say calculi

'Kidney stone' and 'renal calculus' means the same thing – a solid piece of material that forms in the kidneys. The word 'calculus' is derived from Latin, literally meaning 'small pebble', as used on an abacus; the plural of calculus is calculi. 'Nephrolith' is another name for a kidney stone

Cystinuria is inherited in different ways and this can be confusing. Most patients have to inherit two faulty copies of the gene involved (one inherited from their mother and one from their father) to be affected by the condition. This is known as autosomal recessive inheritance and with this pattern, parents, although they carry one copy of a faulty gene each, are usually unaffected. Such people are sometimes called carriers. *SLC3A1* is usually the gene that is faulty with this pattern of inheritance.

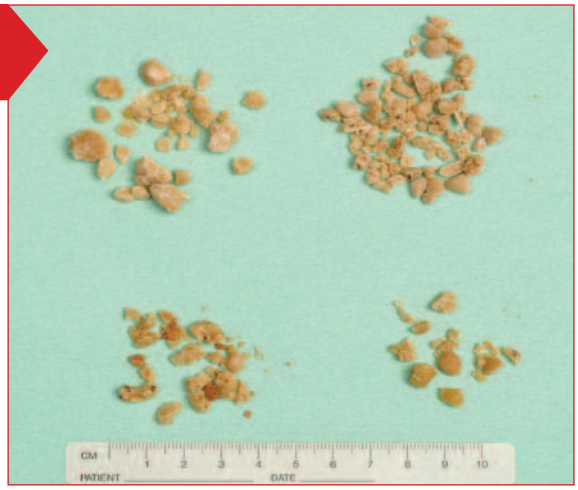
Some patients with cystinuria have just one faulty copy of the gene involved, which is sufficient to cause the disease and for it to be passed down from generation to generation. This is called autosomal dominant inheritance. A faulty copy of *SLC7A9* is usually the gene responsible for this pattern of disease. Genetic testing can be very useful to determine the exact cause and type of cystinuria, and is currently performed within the UK Genetic Testing Network.

Signs and symptoms

Kidney stones are almost always painful. The pain, called renal colic, is severe; it starts in the back and the side and may move down to the groin. Pain typically comes in waves, building up and easing off.

Large stones may block the drainage of urine from the kidney. Cystine can occasionally form huge stones within the centre of the kidney, known as staghorn calculi (see Figure 2). Some patients with cystinuria pass tiny stones that look like grit or sand in the urine; these tend to cause less pain.

The frequency of stone formation varies from patient to patient: some pass stones almost daily, while others only pass one or two stones in their lifetime. We do not yet know why the condition is so



RICHARD COWARD

Figure 1. Cystine stones


CHARLES TOMSON

Figure 2. Staghorn calculus removed from a patient with cystinuria

variable; the severity does not depend on which genetic alterations a patient carries.

Stones which obstruct the flow of urine from a kidney may lead to urinary infection. Repeated infections, obstructions and invasive surgery to remove stones can lead to long-term damage to the kidney but, fortunately, kidney failure is rare. Sometimes, a kidney may be removed due to repeated development of stones or infections, but modern surgical techniques often allow for less invasive, keyhole surgery to remove stones. It is important that kidney function and stone burden are monitored by blood tests and ultrasound scans.

Investigations

It is very important that cystine stones are diagnosed correctly. This is because the treatments for cystine stones differ from those of the more common calcium stones. It is important to check for rare causes of stone formation, including cystinuria, in people who have a family history of kidney stones, those who form kidney stones in childhood or early adult life and those who form a lot of kidney stones.

Diagnosis is often made by a chemical analysis of the stone. Cystine stones are usually made entirely of cystine. Alternatively, the amount of cystine present in a urine sample can be measured, and this is typically high in cystinuria patients. Finally, confirmation of the exact type of cystinuria can be determined from a blood or saliva sample for genetic analysis. Parents, children and siblings can then be screened. A 24-hour urine sample is often collected to serve two purposes: it will give an accurate measurement of urine volume in a stone-forming patient and will allow the estimation of cystine concentration. These two measures can then be used as baseline values to which subsequent measurements can be compared (for example, following dietary interventions and treatments).

Imaging the kidneys can help to detect the position and number of stones. Cystine stones do not show up well with standard X-rays, so a plain X-ray of the abdomen can miss them. An ultrasound scan of the kidney is a good way to monitor stone burden, but stones in the ureters (the tubes between the kidney and bladder) are difficult to spot. A CT scan (see Figure 3) is the best way to see cystine stones but should not be done more often than necessary, as it involves a significant dose of radiation.

Treatments

There is no cure for cystinuria, but this lifelong condition must be managed, so that it causes minimal disturbance to normal living. The aim of treatment is to keep urinary cystine dissolved and prevent its crystallisation and consequent stone formation. In addition, a number of surgical procedures to break up and remove cystine stones are available.

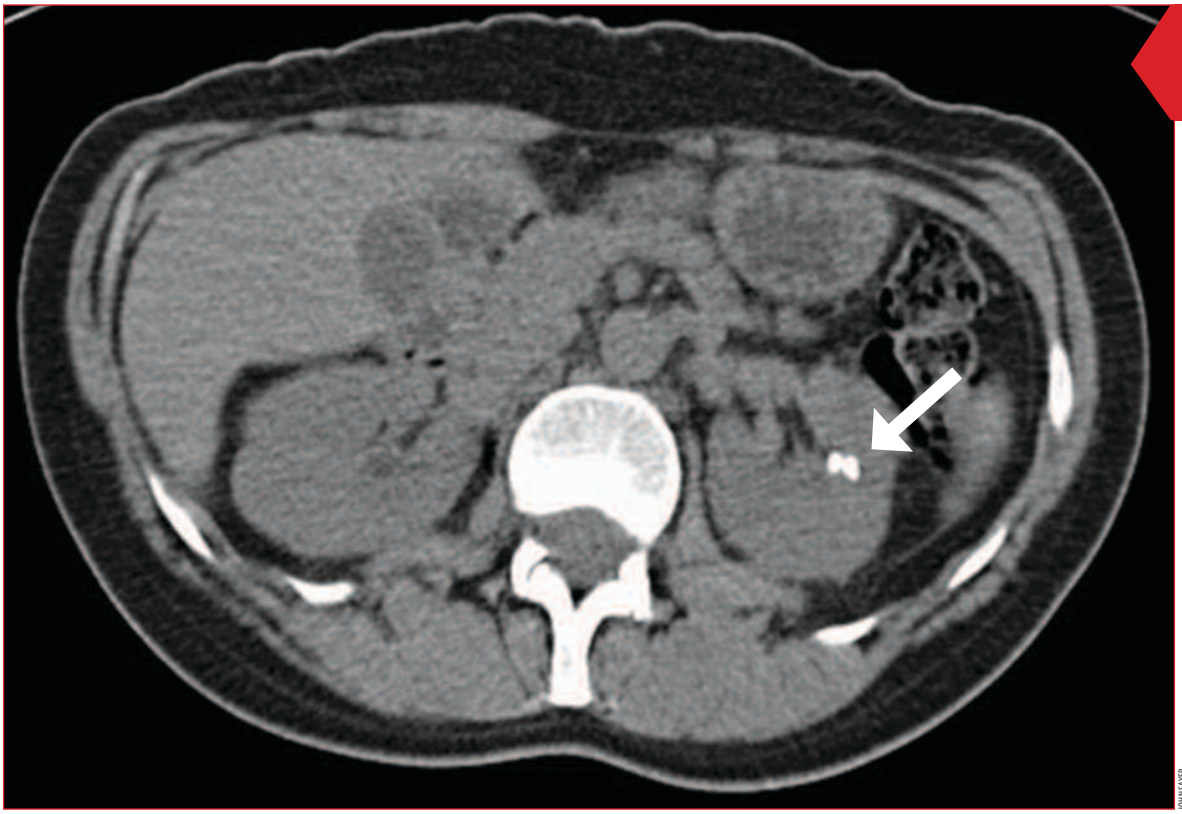
Diet and fluid intake

To help maintain dilute urine, patients are usually advised to drink extra water and other fluids (a total of 4–5 l/24 hours), following a discussion with their doctor to make sure it is safe. The body's natural tendency to concentrate urine happens at night (to allow us a full night's sleep) and this must be overridden to avoid making concentrated urine, which would allow crystals to form. Drinking water in the evening and on waking at night, therefore, allows continuous dilution of the urine.

Carrying a refillable water bottle everywhere may help to ensure that a good fluid intake is maintained throughout the day. Tea, coffee (and other caffeinated drinks) and alcohol all have a tendency to dehydrate, so should be taken in moderation. Certain food types also contain fluid and can, therefore, help achieve a high fluid intake (see Box 2).

In addition to increased fluid intake, a diet low in salt (sodium) is recommended, as too much dietary salt draws extra cystine into the urine.

Depending on our diet, urine can be either acidic or alkaline. Eating less meat and more fruit and vegetables is likely to help reduce stone formation. This sort of diet leads to the formation of alkaline urine, which makes cystine more soluble and less likely to form stones. A vegan diet (which is low in the amino acid methionine, which is converted by the body to cystine) is, in theory, ideal. Reducing intake of meat, fish and cheese is thought to be beneficial, as it reduces the amount of cystine the kidneys have to



■ **Figure 3. A** CT scan showing a cystine stone (indicated by arrow)

JOHN SAYER

Box 2. Foods that contain fluids and help achieve high fluid intake

- Yoghurt
- Fromage frais
- Rice pudding
- Custard
- Porridge
- Ice cream/sorbet
- Melon

handle. Dieticians will be able to advise on this sort of diet; there is also a dedicated cookbook, *Lose a Stone,*[4] to help patients. Drinking water with added lemon juice, which contains potassium citrate, is one suggestion to maintain both a dilute and alkaline urine.

Dietary supplements

As well as dietary manipulations, cystinuria patients are often prescribed agents to make the urine more alkaline. Potassium citrate is commonly used for this, but must be prescribed by a doctor and cannot be used by everyone, especially if they have chronic kidney disease. It comes as a solution and tastes metallic and rather unpleasant. A fizzy form is called Effercitrate, which some patients find more acceptable. In the USA, a capsule form of potassium citrate, called Urocit-K, is available, but this is difficult to obtain in the UK.

Sodium bicarbonate is an alternative to potassium citrate and works in a similar way to alkalise the urine. It is probably not quite as good as potassium citrate because the sodium may increase the amount of cystine in the urine; however, for people who cannot tolerate potassium citrate or a vegan diet,it is a reasonable alternative. To monitor progress of urine alkalisation, urine dipsticks can be used. The aim is to maintain a urine pH between 7 and 7.5. A urine pH greater than 7.5 risks formation of calcium phosphate stones.

Prescription medicines

Some patients with cystinuria may need additional medication to prevent the formation of cystine stones. These medicines require careful monitoring of

Key points

- An early onset of kidney stone disease or a family history of the disease should prompt investigations to look for cystinuria.
- Cystine kidney stones often recur; sometimes they can be large (staghorn calculi).
- A diagnosis can be confirmed by urine tests and stone analysis. Genetic investigations can be helpful in determining the inheritance type of cystinuria.
- An increased fluid intake is important to reduce urinary concentrations of cystine. A diet rich in fruit and vegetables and low in salt and animal protein will reduce the cystine burden, leading to a more alkaline urine and increasing cystine solubility.
- Medical treatment aims to maintain a urine pH between 7 and 7.5 and uses cystine-binding drugs. Multiple surgical options are available if a cystine stone is too big to pass.

blood test results throughout their use and are prescribed by nephrology doctors rather than GPs. These medicines are passed into the urine and bind to cystine, preventing it from forming crystals. There are three main types of 'binding' medicines: penicillamine (brand name: Distamine®), tiopronin or alpha-mercaptopropionylglycine (brand names: Thiola®, Captimer® and Acadione®) and captopril (brand name: Capoten®). Tiopronin may have fewer side effects than penicillamine. It is taken up to three times per day and the dose is adjusted in response to the amount of cystine in the urine. Tiopronin is, however, unlicensed in the UK and has to be imported, which can sometimes lead to supply issues. As it is unlicensed, tiopronin must be prescribed on the sole responsibility of the doctor. Captopril (an angiotensin converting enzyme inhibitor) is a blood pressure medication, which also can be used to bind cystine, although the evidence for this is weak. It is not widely used because the dose required leads to side effects such as low blood pressure.

Surgical treatment

Several procedures are designed to break up and remove cystine stones. Lithotripsy (or extracorporeal shockwave lithotripsy) uses focused ultrasound shock waves to break up stones into grit, which can then be passed in the urine. This is usually a day-case procedure and is performed with the patient awake and without a general anaesthetic. Typically, cystine stones are very hard and may be resistant to treatment with lithotripsy.

Ureteroscopy uses a fine telescope, which is passed into the bladder via the urethra and up the ureter into the kidney. It is performed under general anaesthetic and allows the surgeon to break the stone directly, using a laser. The lasering of cystine stones produces a distinct sulphuric smell (like rotten eggs), which should prompt the diagnosis of cystinuria if it has not already been made.

Percutaneous nephrolithotomy is a minimally invasive type of surgery, usually reserved for large stones. Under general anaesthetic, a telescope is inserted through the skin and muscle of the back into the kidney itself, allowing the surgeon to break up and remove the stone. Rarely, more invasive open or keyhole surgery to remove a kidney, which has been severely damaged by stones, is required ■

Declarations of interest
The authors declare that there is no conflict of interest.

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3. The Renal Association. Cystinuria – Patient Information. http://rarerenal.org/patient-information/cystinuria-patient-information/ (last accessed 01/02/2016)
4. Thomas K, Doherty A. *Lose a Stone.* https://sites.google.com/site/cystinuri-auk/recipes (last accessed 01/02/2016)

Diary dates

■ National Kidney Foundation Spring Clinical Meeting
27 April – 1 May 2016, Boston, USA
Contact: National Kidney Foundation
Tel: +1 212 889 2210
email: clinicalmeetings@kidney.org
website: www.nkfclinicalmeetings.org

■ 11th European International Kidney Cancer Symposium
29–30 April 2016, Barcelona, Spain
Contact: Kidney Cancer Association
email: outreachregistration@niu.edu
website: http://goo.gl/797cAL

■ 53rd ERA-EDTA Congress
21–24 May 2016, Vienna, Austria
Contact: ERA-EDTA Congress Office
Tel: +39 345 0211784
email: registrations@era-edta.org
website: www.era-edta2016.org

■ UK Kidney Week
7–10 June 2016, Birmingham
Contact: British Renal Society
Tel: 01543 442153
email: ukkw@britishrenal.org
website: http://goo.gl/2Bgo4M

■ Renal Physiology Old & New
13–16 June 2016, Gothenburg, Sweden
Contact: Helle Prætorius
email: hp@biomed.au.dk
website: https://goo.gl/ixIbK3

■ 26th International Congress of The Transplantation Society
18–23 August 2016, Hong Kong, China
Contact: The Transplantation Society
Tel: +1 514 874 1717
email: info@tts2016.org
website: www.tts2016.org