

What is cystinuria and what are its symptoms?

Cystinuria is a genetic disease characterized by a buildup of the amino acid cystine in the kidneys and bladder.

These high levels of cystine lead to the formation of cystine stones in the kidneys, ureter, and bladder, which cause various complications, such as hypertension, intense abdominal pain, recurrent urinary tract infections, renal function impairment in up to 70% of patients, and chronic renal insufficiency. These complications can ultimately result in renal failure.

Cystinuria is an autosomal recessive inherited metabolic disorder caused by mutations in the *SLC3A1* and *SLC7A9* genes—autosomal recessive means that two copies of an abnormal gene must be present for the disease to develop. Cystinuria is characterized by deficient re-absorption of cystine and other basic amino acids in the proximal tubules of the kidney, which results in the formation of stones in the kidney, ureter, and urinary bladder; the stones may block the urinary tract. The condition of having abnormally high urinary levels of cystine, lysine, arginine, and ornithine is known as aminoaciduria.

Whereas lysine, arginine, and ornithine are completely soluble, the low solubility of cystine at physiological urine pH (a measure of acidity) induces its precipitation into the distal renal tubules. The elevated cystine concentration there leads to its crystallization and favors the formation of renal calculi, or mineral deposits, in the urinary tract.

Signs and symptoms of the condition are related to the presence of stones and may include nausea, hematuria (blood in the urine), flank pain, and/or frequent urinary tract infections.

There are estimated to be 70,000 and 25,000-35,000 patients with cystinuria in Europe and the United States, respectively.

How is cystinuria treated?

The solubility of cystine in urine is 250 mg/L (1 mmol/L) at the neutral pH level of 7.0, but it increases to about 500 mg/L (2 mmol/L) at a more basic (as opposed to acidic) pH of 7.5. This pH dependence of cystine solubility has determined the medical treatment of cystinuria, which relies on the combination of 1) alkalizing treatments to increase urine pH for higher cystine solubility, 2) hyperdiuresis, which reduces cystine concentration by increasing urine production and excretion, and 3) a protein-poor diet, since proteins are high in cystine.

A hallmark of cystinuria is the persistence or reappearance of crystals, usually followed by a recurrence of lithiasis (stone formation). In order to prevent cystine lithiasis, cystinuric patients require around-the-clock control of their urine pH. Alkalizing treatments avoid cystine stone formation by increasing urinary pH and augmenting cystine solubility and constitute the pharmacological basal treatment of cystinuria.

Historically, sodium bicarbonate was the first-line alkali therapy. However, sodium bicarbonate (and sodium citrate) is not recommended as a treatment for cystinuria, since data demonstrate that sodium increases cystine excretion and thus results in more cystine crystallization. Renal sodium excretion also tends to promote urinary calcium excretion.

Potassium salts do not lead to the adverse consequences observed with sodium salts. Moreover, it is recommended that potassium deficiency be avoided in cystinuric patients since this condition may decrease citrate excretion and cause renal acidosis, which is a buildup of acids in the blood.

Of the available alkali therapies for the management of cystinuria, citrate is the intervention of choice as citrate excretion in urine allows calcium chelating effects, which is potentially an effective way to prevent calcium salt crystallization in urine in alkali conditions (over a pH of 7.5).

There are currently no approved drugs, including potassium citrate/potassium bicarbonate, specifically indicated for the treatment of cystinuria. However, Advicenne has developed a formulation that maximizes absorption of both potassium citrate and potassium bicarbonate along the gastrointestinal tract. In these 2mm prolonged-release granules, potassium citrate is first released to incur limited absorption in the upper gastrointestinal tract. Release starts very slowly, thereby avoiding a potentially painful alkali overload. Diffusion of potassium citrate gradually increases over 3 hours, as the granules reach the duodenum and proximal jejunum, where absorption is more effective. Similarly, granules releasing potassium bicarbonate are designed to limit diffusion during the first hour to avoid abdominal pain. A prolonged release mechanism then ensures effective potassium bicarbonate release and absorption along the entirety of the gastrointestinal tract. Thus, the formulation maintains a sustained release over 12 hours for a twice-a-day administration.