

Citrates in nephrolithiasis

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Summary

Nephrolithiasis is a multisystem disease arising from the synergic effects of environmental, hormonal and genetic factors. In Europe an incidence of 2000 stones per million of population has been reported. Kidney stones are mainly composed of calcium (70-80%) with a predominance of calcium oxalate, with or without calcium phosphate. Low urinary citrate excretion is a common feature of idiopathic calcium stone disease. A wide range of hypocitraturia prevalence in nephrolithiasis have been reported in literature. Hypocitraturia is defined as a urinary citrate excretion lower than 320 mg/day. Many factors can modulate citrate excretion. Among them an important role is played by acid-base status, nutritional factors, starvation, hormones and drugs. Estrogen exert an important modulating effect on urinary citrate excretion. Several authors, in fact, have described a reduction in urinary citrate excretion in healthy postmenopausal women, as well as a lower citraturia in males than in premenopausal females. Urinary citrate directly inhibits stone formation by forming highly soluble complexes with calcium in the renal tubule and by increasing intraluminal pH. Idiopathic calcium stone disease, but also other forms of nephrolithiasis, as well as some other pathological conditions can be treated with alkaline citrate. The most common form of these salts is potassium citrate that has been successfully used in the prevention of stone recurrence. In conclusion alkaline citrate represents an effective tool in the prevention of calcium stone formation. Last, but not least, this form of therapy presents few side effects.

KEY WORDS: *nephrolithiasis, nephrocalcinosis, citrates.*

Introduction and physiological elements

Nephrolithiasis is a multisystem disease arising from the synergic effects of environmental, hormonal and genetic factors. The annual incidence of renal stones is between 0.1 and 0.4% and nephrolithiasis shows wide geographical variations (1-3). In Europe an incidence of 2000 stones per million of population has

been reported (4). The lifetime risk of stone formation ranges between 5 and 10% with an expected recurrence rate of almost 50% (4). Up to 70-80% of patients have calcium containing stones with a predominance of calcium oxalate (CaOx), with or without calcium phosphate (CaP) (5).

Citrate is a weak acid, with a molecular weight of 189 kDa, that is synthesized in the Krebs cycle starting from the condensation of acetyl-CoA and oxalacetate, that may derive from exogenous intake. In plasma and in urine (although to a lesser degree) citrate is present mainly as a trivalent anion citrate⁻³; whereas, when the pH becomes more acidic the divalent form of anion citrate⁻², increases significantly (6).

The mean daily intake of citrate with the diet is 4 grams and its intestinal absorption is rapid and almost complete.

Plasma citrate is filtered by the kidney and then reabsorbed, in the proximal tubule mainly in the convoluted and straight segments; in contrast tubular reabsorption does not seem to be present either in the thick ascending tract of Henle limb or in the cortical collecting duct (6). Citrate proximal tubular reabsorption involves a sodium dependent dicarboxylate transporter, that permits the reabsorption across the apical membrane where the citrate is reabsorbed mainly as dicarboxylate anion, although the tricarboxylate is the more common form (7). Furthermore, experimentally in cell culture, a new sodium dependent saturable citrate transport was observed involving a trycarboxylate transporter; in vivo, this trycarboxylate citrate transporter may be located on the basolateral membrane (8). A rate of 10-35% of the filtered load is excreted in the urine. The citrate reabsorbed from the proximal tubule and a small quota deriving from peritubular vessels contribute to the energy supply of the kidney. In fact this ion, via a complete oxidation in the mitochondrial Krebs cycle, participates in the production of ATP. Another destiny of citrate is cytosolic metabolism into Acetyl-CoA and oxalacetate by means of the enzyme ATP citrate lyase (9). The small intestine presents a citrate transporter similar to the sodium dependent dicarboxylate carrier observed in the proximal renal tubule; at least experimentally, enterocytes seem to present a secretion mechanism of citrate (9). After oral intake of alkaline salts, citrate undergoes intestinal absorption and is metabolized inducing an alkaline load that increases the urinary citrate excretion (9). A reduced intestinal alkali absorption may cause a hypocitraturia condition (10). Hypocitraturia is one of the main factors associated with idiopathic kidney stone disease. Moreover citrate has been widely studied for its action in preventing renal stones and it has showed a very high efficacy against calcium nephrolithiasis (11-13). Many physiological conditions, several drugs and some diseases modulate urinary citrate excretion as shown in table I. Acid-base state is one of the main regulators of urinary citrate excretion, with metabolic acidosis inducing hypocitraturia. Also potassium depletion plays an important role in decreasing urinary citrate excretion. Both these conditions enhance ATP citrate lyase activity in the cytosol of renal cortex cells, thus leading to a decreased intracellular citrate concentration and, ultimately, to an increased reabsorption of this ion at the brush border membrane level (9,14). One of the hormones that exerts an important modulating effect on urinary citrate excretion is estrogen. Several authors, in fact, have de-

scribed a reduction in urinary citrate excretion in healthy post-menopausal women, as well as a lower citraturia in males than in premenopausal females (9).

Urinary citrate directly inhibits stone formation by forming highly soluble complexes with calcium in the renal tubule. The first effect of this complex is to reduce urinary levels of supersaturation with CaOx and CaP (4,9). Moreover citrate reduces the spontaneous nucleation, the agglomeration, the aggregation and the crystal growth of CaOx and CaP (9). It could be said that citrate acts as a "poison" on renal stones.

Hypocitraturia: the magnitude of the problem

Low urinary citrate excretion is a common feature of idiopathic calcium stone disease. Several cut-off values have been proposed to classify hypocitraturia (9). In 1983, Nicar et al. (15) defined hypocitraturia as a 24 hour citrate excretion lower than 320 mg (or 1.7 mmol) while other authors fixed the limit below the normal range (12,16-18). These different cut-off values may account for the wide range of hypocitraturia prevalence in nephrolithiasis, since it varies from 8% up to 68.3% in the literature reports (Table II). Another factor which may account for these difference in prevalence is the possibility of considering hypocitraturia as a single metabolic alteration. In fact in a previ-

Table II - Reported prevalence of hypocitraturia in patients with nephrolithiasis.

Authors	Prevalence	Year
Jaeger et al.	8.0%	1986
Caudarella et al.	12.6%	1986
Hess et al.	29.0%	2002
Hosking et al.	29.2%	1985
Khand et al.	29.2%	1994
Mossetti et al.	32.7%	2003
Caudarella et al.	32.8%	1996
Höbart and Hofbauer	34.0%	1991
Akinci et al.	46.6%	1991
Vahlensieck et al.	47.0%	1987
Pak et al.	50.0%	1987
Nicar et al.	55.0%	1983
Fardella et al.	68.3%	1994

Table I - Effect of different factors on urinary citrate excretion.

Factor	Citraturia
Glomerular filtration rate	
Acidosis	
Alkalosis	
Starvation	
Carbohydrates	
Sodium chloride	
Potassium	
Magnesium	
Calcium	
Animal proteins	
Gastrointestinal alkali absorption	
Estrogen	
Parathyroid hormone	
Calcitonin	
Insulin	
Growth Hormone, insulin-like growth factor-1	
Vitamin D ₃ /Calcitriol	
Acetazolamide/ACE-inhibitors/Topiramate/Zonisamide	
Ethacrynic acid/Thiazides/Glucocorticoids	
Transport competitors (succinate, malate, fumarate)	
Metabolic inhibitors (fluorocitrate, malonate, maleate)	
Distal renal tubular acidosis	
Chronic renal failure	
Inflammatory bowel diseases	
By-pass or ileal resection	
Diarrhea and/or malabsorption	
Strenuous exercise (lactic acidosis)	

= Increase; = Decrease

ous paper (16) found a hypocitraturia frequency, considered as a single metabolic derangement, of 12%, whereas, when considering hypocitraturia together with hypercalciuria and/or hyperuricosuria, this rate increased to 32% (19). Last but not least, the evaluation of urinary citrate excretion is highly influenced by food intake. Therefore a relevant difference in daily citrate excretion will occur according to whether patients are on their home diet or on controlled diet (9).

A commonly accepted limit under which hypocitraturia may be diagnosed has been proposed by Pak. This Author suggested a "functional" definition of hypocitraturia which is a citrate excretion lower than 320 mg/day (20).

Notwithstanding the cut-off value adopted, several authors have described a higher rate of hypocitraturia in recurrent stone formers (41%) than in single stone formers (29%), as well as a higher urinary citrate excretion in pre-menopausal females than in males and menopausal females (9).

The daily urinary citrate to calcium ratio has also been used as a risk factor for stone formation. In fact it has been observed that patients with hypocitraturia, as a single metabolic alteration, showed higher urinary citrate excretion than those with several metabolic abnormalities. Moreover a higher rate of hypocitraturia was present also in stone formers with a very active calcium stone disease and/or low urinary citrate/calcium ratio (21-23). Welshman and McGeown found a calcium/citrate ratio in stone formers and normal subjects of 4.52 and 3.02 respectively, while in stone forming females this ratio was 3.54 and 1.41 in healthy females (17). Similar results were obtained in successive studies (9). Finally, Parks et al. examined the citrate/calcium ratio in 13 studies in which patients were maintained on their home diet, and they found a clear difference between renal stone formers and healthy subjects (24). Stone-forming females had higher urinary calcium and lower citrate than control females, whereas stone forming males presented a significantly higher urinary calcium excretion than normal subjects but only a small decrease in citrate excretion. Furthermore, also the studies in which the patients ate controlled diets, showed, generally, a lower urinary citrate excretion in stone formers than in healthy subjects and these differences persisted when the subjects were considered separately according to sex (24). Finally, also in a recent paper (25), dealing with hypercalciuria and bone mass, we have found a higher uri-

nary citrate excretion in females than in males ($p=0.019$) and the prevalence of hypocitraturia in the whole population was 25.5% (unpublished data).

Citrate salts in the treatment of nephrolithiasis

Several studies have pointed out that alkaline citrate is one of the most efficient therapeutic regimens in the treatment of idiopathic calcium nephrolithiasis. In 2001 the Advisory Board of European Urolithiasis Research recommended alkaline citrate, thiazides and fluid intake as the corner-stones in preventing calcium stone formation (26). Oral citrate administration results in an alkali load that, in turn, increases urinary citrate excretion by means of a reduction in the tubular reabsorption of this ion (9). The consequent high urinary citrate concentration and the alkalization of the urine cause several effects that struggle against CaOx and CaP crystallization (4). The increased intraluminal pH induces a dissociation of citrate and the inhibitory macromolecules, resulting in an enhanced inhibiting power. For example, it has been suggested that Tamm-Horsfall protein (THP) shows a dichotomous behaviour on stone formation, acting either as promoter or as an inhibitor of crystallization processes. When urinary citrate increases and luminal pH rises, THP viscosity decreases and its inhibitory effect on calcium oxalate aggregation is enhanced. On the contrary in the absence of citrate THP promotes calcium oxalate aggregation (9). As far back as 1985 Preminger et al. demonstrated that new stone formation continued in 39% of the patients during conservative or placebo trials and 69% of untreated stone formers however, needed at the end surgical treatment. On the other hand only 2% of the patients receiving alkaline citrate required further surgical treatment (27). In the last two decades alkaline salts have been widely used in patients with recurrent calcium stone disease and in several other pathological conditions associated or not with calcium stones (Table III). The most commonly used salts are potassium citrate, sodium-potassium citrate, potassium-magnesium citrate and calcium citrate, although potassium citrate is usually the preferential treatment (9). Both potassium citrate and sodium-potassium citrate, in fact, can ameliorate urinary composition, but the sodium load induced by the latter can increase calcium excretion or a less pronounced reduction of calciuria. In fact citrate has shown to

be able to reduce urinary calcium excretion (4). Furthermore, in patients with hypertension, sodium intake must be restricted, as well as in patients with calcium oxalate lithiasis treated with thiazide. In fact, sodium load induces a hypercalciuria that is uncontrollable with thiazide (9).

Magnesium is an inhibitor of CaP crystal growth and the complexing of magnesium and oxalate induces a decrease in the supersaturation with respect to CaOx. Nevertheless it has been observed that also magnesium excretion is associated with an increased calcium excretion, thus reducing the inhibiting effect of potassium-magnesium citrate on stone formation. Moreover, long-term studies on potassium-magnesium citrate administration are still lacking. However this alkaline citrate appears to enhance thiazide effect on urinary calcium reabsorption when this drug is co-administered. Long-term thiazide therapy, in fact, may result in decreased plasmatic and urinary magnesium and in this very case magnesium supplements appear to be of value (4). Finally promising results have come from Ettinger et al. which found that potassium-magnesium citrate is effective in preventing calcium oxalate stone recurrence (28).

Calcium citrate is generally prescribed as a calcium supplement in the treatment of osteoporosis, while it is not usually used for calcium lithiasis therapy. Calcium citrate increases both urinary citrate and calcium excretion. Notwithstanding the growth of calciuria, this compound provides an alkali load, which in turn, counteracts the increased calcium excretion. Thus the risk of stone formation does not appear to be enhanced. Therefore calcium citrate seems to induce a lower risk of stone formation than all the other calcium supplements (9).

Most of the studies on renal stone prevention have been conducted using potassium citrate as alkaline salt (4). A decrease in urinary calcium concentration has been well documented with this drug (9). In a previous work we were able to demonstrate the ability of potassium citrate to decrease urinary calcium excretion after 9 months of therapy (19), but the same result was not confirmed in a successive paper, where the follow up period was extended to 48 months. In fact, after an increase in urinary calcium excretion during the first year of therapy, calciuria began to decrease slowly, but progressively, in the follow up (29). This result is in agreement with Fuselier et al., who observed a small, but significant, decrease in urinary calcium excretion during treatment periods (30). Ali Tekin et al. evaluated, in an open clinical trial, the effects of oral potassium citrate therapy (22 months) in children with calcium stones and hypocitraturia; these Authors confirmed that potassium citrate reduces the recurrence of renal stones and seems to be a safe treatment. These Authors too, found a decrease in urinary calcium excretion although it remained within the normal range in most cases, so they concluded that potassium citrate seems to influence, to a low degree, calcium excretion (31).

Moreover, in our paper, basal values of citraturia were lower than follow up values (29). However, when patients were subdivided according to urinary citrate excretion, those with the lowest basal citraturia (citraturia lower than 320 mg/24 hours) behaved differently. In fact after a rise in the first year, urinary citrate excretion returned to values similar to or lower than basal value. Also Fuselier et al. observed that in 21% of patients treated with potassium citrate, urinary citrate excretion did not rise. The Authors stated the need for a careful follow-up of the patients treated with potassium citrate in order to identify patients requiring a more aggressive medical therapy and to properly modify the dose of alkali salts (30).

Oxalate, uric acid and creatinine excretion as well as urine volume do not change during the follow up of patients treated with potassium citrate. Moreover potassium citrate does not usually induce an increase in the relative supersaturation ratio of brushite, as it reduces urinary calcium excretion, although an excessive amount of potassium citrate may increase the rela-

Table III - Indications for alkali citrate therapy in different diseases and conditions.

- Idiopathic calcium oxalate stone disease (with or without hypocitraturia)
- Uric acid nephrolithiasis
- Mixed nephrolithiasis (hyperuricosuric calcium nephrolithiasis)
- Cystine nephrolithiasis
- Primary or secondary hyperoxaluria
- Hypocitraturia in distal renal tubular acidosis
- Hypocitraturia associated with inflammatory bowel diseases
- Hypocitraturia associated with by-pass or ileal resection
- Hypocitraturia associated with chronic diarrhea syndrome
- Drug-induced hypocitraturia
- Hypocitraturia associated with potassium depletion
- Hypocitraturia associated with excessive dietary acid load
- Residual renal stone fragments after extracorporeal shock wave lithotripsy
- Osteoporosis (?)

tive supersaturation ratio of brushite (9). Furthermore, in patients with distal renal tubular acidosis, potassium citrate treatment appears to improve calcium balance. In fact it increases intestinal calcium absorption by means of a 1,25(OH)₂D₃ independent mechanism and reduces urinary calcium excretion. According to some authors, the decreased calcium excretion can be explained by an increased calcium reabsorption in the distal tubule induced by metabolic alkalosis (32) as well as by the increased luminal pH (33). The chronic treatment with potassium citrate and other alkaline salts may result in a positive calcium balance. In fact a small but significant increase in bone mineral density in stone forming females has been shown (34). Also Sebastian et al., after treating a group of healthy postmenopausal women with potassium bicarbonate, observed an improved calcium balance through an interaction of bone remodelling phases (35). Several studies in vitro showed that citrate inhibits struvite formation. In fact it causes the chelation of magnesium, the disruption of the hydrogen and ionic binding of this mineral and the coating of the surface of struvite crystal (9). In conclusion alkaline citrate seems to be a rational approach to the treatment of nephrolithiasis in patients with or without hypocitraturia, as it reduces some risk factors involved in stone recurrence. Moreover this form of therapy presents a small number of side effects, mainly gastro-intestinal symptoms (e.g. diarrhea and nausea) and in very few cases hyperkalemia. About the safety of potassium citrate supplementation there is a general agreement in literature; however Coe et al. report some experimental papers showing that citrate increases intestinal absorption of some metals such as aluminum and lead (36). These Authors suggest renal function in patients with renal failure should be carefully evaluated to avoid an increased intestinal absorption of aluminum, particularly if they are treated with aluminum antacids. The same precautions may be of some use also in patients with renal stones.

References

- Pak CY, Resnick MI, Preminger GM. Ethnic and geographic diversity of stone disease. *Urology*. 1997;50:504-50.
- Pak CY. Kidney stones. *Lancet*. 1993;351:1757-1761.
- Scheinman SJ. Nephrolithiasis. *Semin Nephrol*. 1999;19:381-388.
- Tiselius HG. Epidemiology and medical management of stone disease. *BJU Int*. 2003;91:759-767.
- Tiselius HG. Stone incidence and prevention. *Braz J Urol*. 2000;26:452-462.
- Hamm LL. Citrate handling by the kidney. *Kidney Int*. 1990;38:728-735.
- Wright EM. Transport of carboxylic acids by renal membrane vesicles. *Am J Renal Physiol*. 1985;47:127-141.
- Law D, Heering-Smith KS, Hamm LL. Citrate transport in proximal cell line. *Am J Physiol*. 1992;263:C220-225.
- Caudarella R, Vescini F, Buffa A, et al. Citrate and mineral metabolism: kidney stones and bone disease. *Front Biosci*. 2003;8:s1084-1106.
- Sakhaee K, Williams RH, Oh MS, et al. Alkali absorption and citrate excretion in calcium nephrolithiasis. *J Bone Miner Res*. 1993;8:789-794.
- Schwille PO, Scholz D, Schwille K, et al. Citrate in urine and serum and associated variables in subgroups of urolithiasis. Results from an outpatient stone clinic. *Nephron*. 1982;31:194-202.
- Schwille PO, Scholz D, Paulus M, et al. Citrate in daily and fasting urine: results of controls, patients with recurrent idiopathic calcium urolithiasis, and primary hyperparathyroidism. *Invest Urol*. 1979;16:457-462.
- Ratan SK, Bhatnagar V, Mitra DK, et al. Urinary citrate excretion in idiopathic nephrolithiasis. *Indian Pediatr*. 2002;39:819-825.
- Tosukh Wong P, Borvonpadungkitti S, Prasongwatana V, et al. Urinary citrate excretion in patients with renal stone: roles of leucocyte ATP citrate lyase activity and potassium salts therapy. *Clin Chim Acta*. 2002;325:71-78.
- Nicar MJ, Skurla C, Sakhaee K, et al. Low urinary citrate excretion in nephrolithiasis. *Urology*. 1983;21:8-14.
- Hosking DH, Wilson JW, Liedtke RR, et al. Urinary citrate excretion in normal persons and patients with idiopathic calcium urolithiasis. *J Lab Clin Med*. 1985;106:682-689.
- Welshman SG, McGeown MG. Urinary citrate excretion in stone-formers and normal controls. *Br J Urol*. 1976;48:7-11.
- Jaeger P, Portmann L, Jacquet AF, et al. [Indication of the urinary citrate levels in idiopathic renal calculosis]. *Schweiz Med Wochenschr*. 1986;116:371-373.
- Caudarella R, Fabris T, Bernich P, et al. Effect of potassium citrate therapy on some urinary risk factors promoting renal stone formation. *Ital J Mineral Electrolyte Metab*. 1994;8:31-35.
- Pak CYC. Citrate and renal calculi: an update. *Miner Electrolyte Metab*. 1994;20:371-377.
- Conte A, Roca P, Gianotti M, et al. On the relation between citrate and calcium in normal and stone-former subjects. *Int Urol Nephrol*. 1989;21:369-373.
- Cupisti A, Morelli F, Lupatti S, et al. Low urine citrate excretion as main risk factor for recurrent calcium oxalate nephrolithiasis in males. *Nephron*. 1992;71:73-76.
- Vogel F, Leschova P, Schutz W. Some acid-base balance-dependent urinary parameters and calcium-binding anions in stone formers. *Eur Urol*. 1984;10:254-259.
- Parks JH, Ruml LA, Pak CYC. Hypocitraturia. In: Coe FL, Favus MJ, Pak CYC, Parks JH, Preminger GM, eds. *Kidney Stones: Medical and Surgical Management*. Philadelphia: Lippincott-Raven; 1996:905-920.
- Caudarella R, Vescini F, Buffa A, et al. Bone mass loss in calcium stone disease: focus on hypercalciuria and metabolic factors. *J Nephrol*. 2003;16:260-266.
- Tiselius HG. Possibilities for preventing recurrent calcium stone formation: principles for the metabolic evaluation of patients with calcium stone disease. *BJU Int*. 2001;88:158-168.
- Preminger GM, Harvey JA, Pak CYC. Comparative efficacy of "specific" potassium citrate therapy versus conservative management in nephrolithiasis of mild to moderate severity. *J Urol*. 1985;134:658-661.
- Ettinger B, Pak CYC, Citron JT, et al. Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. *J Urol*. 1997;158:2069-2073.
- Caudarella R, Dormi A, Rizzoli E, et al. Chronic treatment with potassium citrate in recurrent calcium urolithiasis. In: VIII International Symposium On Urolithiasis, Dallas, Texas 1996:496-497.
- Fuselier HA, Moore K, Lindberg J, et al. Agglomeration inhibition reflected stone-forming activity during long-term potassium citrate therapy in calcium stone formers. *Urology*. 1998;52:988-994.
- Tekin A, Tekgul S, Atsu N, et al. Oral potassium citrate treatment for idiopathic hypocitruria in children with calcium urolithiasis. *J Urol*. 2002;168:2572-2574.
- Sutton RA, Wong NL, Dirks JH. Effects of metabolic acidosis and alkalosis on sodium and calcium transport in the dog kidney. *Kidney Int*. 1979;15:520-533.
- Miyakawa S, Bomszyk K. Increased perfusate pH stimulates active calcium absorption in the distal tubule (DT). *Clin Res*. 1988;36:523.
- Pak CYC. Physicochemical action and extrarenal manifestations of alkali therapy. In: Robertson WG, ed. *Urological Research*. New York: Plenum Press; 1989:511-516.
- Sebastian A, Harris ST, Ottaway JH, et al. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N Engl J Med*. 1994;330:1776-1781.
- Coe FL, Parks JH, Nakagawa Y. Inhibitors and promoters of calcium oxalate crystallization: their relationship to the pathogenesis and treatment of nephrolithiasis. In: Coe FL, Favus MJ, eds. *Disorders of Bone and Mineral Metabolism*, 2 ed. New York: Raven Press; 2002:741-775.