Citrates in nephrolithiasis

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Summary

Nephrolithiasis is a multisystem disease arising from the synergistic 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 hypocitruria prevalence in nephrolithiasis have been reported in literature. Hypocitruria 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 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 181 KDa, that is synthesized in the Krebs cycle starting from the condensation of acetyl-CoA and oxalacetate, or 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, entero-cytes 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 hypocitruria condition (10). Hypocitruria 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 hypocitruria. 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-

References:

scribed a reduction in urinary citrate excretion in healthy postmenopausal women, as well as a lower citruria 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 (8). 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 hypocitruria 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.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Prevalence</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaeger et al.</td>
<td>8.0%</td>
<td>1986</td>
</tr>
<tr>
<td>Caudarella et al.</td>
<td>12.6%</td>
<td>1991</td>
</tr>
<tr>
<td>Hess et al.</td>
<td>29.0%</td>
<td>1990</td>
</tr>
<tr>
<td>Hosking et al.</td>
<td>29.2%</td>
<td>1995</td>
</tr>
<tr>
<td>Khand et al.</td>
<td>29.2%</td>
<td>1995</td>
</tr>
<tr>
<td>Mossetti et al.</td>
<td>32.7%</td>
<td>2003</td>
</tr>
<tr>
<td>Caudarella et al.</td>
<td>32.8%</td>
<td>1996</td>
</tr>
<tr>
<td>Höbart and Hofbauer</td>
<td>34.0%</td>
<td>1991</td>
</tr>
<tr>
<td>Akinci et al.</td>
<td>46.6%</td>
<td>1991</td>
</tr>
<tr>
<td>Vahlensieck et al.</td>
<td>47.0%</td>
<td>1987</td>
</tr>
<tr>
<td>Pak et al.</td>
<td>55.0%</td>
<td>1987</td>
</tr>
<tr>
<td>Nicar et al.</td>
<td>55.0%</td>
<td>1983</td>
</tr>
<tr>
<td>Fardella et al.</td>
<td>68.3%</td>
<td>1994</td>
</tr>
</tbody>
</table>

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-
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 alkalinization 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 inhibitory power. For example, it has been suggested that Tamm-Horsfall protein (THP) shows a dichotomous behaviour on stone formation, acting either as a 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 citrate has been widely used in patients with recurrent calcium stone disease and in several other pathological conditions associated with calcium stones (Table III). The most frequently used salts are potassium citrate, sodium-potassium citrate, potassium-magnesium citrate and calcium citrate, although potassium citrate is usually the preferential treatment (9). The consequent high urinary citrate concentration and the alkalinization 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 inhibitory power. For example, it has been suggested that Tamm-Horsfall protein (THP) shows a dichotomous behaviour on stone formation, acting either as a 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).

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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 (hypercitruric calcium nephrolithiasis)
- Cystine nephrolithiasis
- Familial or secondary hyperoxaluria
- Hypertrophy in distal renal tubular acidosis
- Hypertrophy associated with inflammatory bowel diseases
- Hypertrophy associated with by-pass or ileal resection
- Hypertrophy associated with chronic diarrhea syndrome
- Drug-induced hypertrophy
- Hypertrophy associated with potassium depletion
- Hypertrophy 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) 2D 3 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 increased intestinal absorption of some metals such as aluminum and lead (36). These Authors suggest renal function in patients with renal stones is not altered by citrate administration.