

# Hypocitraturia and its role in renal stone disease

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■ For more than 50 years, low urinary citrate (hypocitraturia) has occurred in some patients with renal stones; however, only recently has more interest been generated in the role of hypocitraturia in renal stone disease and the beneficial effect of citrate therapy for the prevention and treatment of nephrolithiasis. The authors review the metabolism of citrate, the clinically relevant history of hypocitraturia, and current literature dealing with the effectiveness of citrate therapy in the management of nephrolithiasis.

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TEPHROLITHIASIS is a common medical problem worldwide. In the United States, it affects 3% to 5% of the population, with a higher incidence in men. Acute stone "events" account for 1 per 1,000 hospitalizations annually. If left untreated, renal stones recur in more than 60% of patients.

Renal stone formation is believed to result from changes in the physiochemical characteristics of the urine. A balance between the stone-forming constituents and the naturally occurring stone inhibitors, as well as normal urine pH, are both in part responsible for the prevention of renal stone formation.<sup>2</sup> A number of stone inhibitors have been identified, but pyrophosphate, magnesium, and citrate account for up to 77% of the inhibition; interestingly, citrate alone accounts for about 50% of this inhibitory activity.<sup>3</sup>

### METABOLIC AND PHYSIOLOGIC ASPECTS

Citrate forms the most abundant organic acid in the urine. It is freely filtered in the glomerulus and then 75%

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is reabsorbed in the proximal convoluted tubules, where it is metabolized in the abundant mitochondria of the proximal tubular cells.<sup>4</sup> In humans, 10%–35% of the filtered citrate is excreted in the urine, a much larger fraction than in rats or dogs.<sup>5</sup> The major influence on citrate excretion is the systemic acid-base balance; metabolic alkalosis increases urinary citrate excretion while acidosis decreases it. Other factors that alter the rate of urinary citrate excretion are listed in the *Table*.

Normal adults excrete approximately 600 mg of citrate per day.<sup>6</sup> Hypocitraturia is defined as a 24-hour urinary citrate excretion of less than 320 mg.<sup>7</sup> Using this definition, the frequency of hypocitraturia in patients with nephrolithiasis has been estimated to be between 19% and 63%.<sup>8,9</sup>

Hypocitraturia contributes to calcium stone formation by enhancing urinary calcium saturation through reduced formation of citrate-calcium complex and by promoting spontaneous nucleation and crystal growth through reduced inhibitor activity. Therefore, a citrate supplement would seem to be a physiologically rational treatment for patients with hypocitraturia and calcium nephrolithiasis by creating a urinary chemical environment that is less conducive to stone formation. 10,11

Since it is recognized as an important natural inhibitor of calcium-containing renal stone formation, citrate may reduce urinary calcium saturation by forming a soluble

TABLE CONDITIONS AND DRUGS THAT ALTER CITRATE EXCRETION

Decrease excretion	Increase excretion
Systemic acidosis	Systemic alkalosis
Hypokalemia	Estrogen
Intestinal malabsorption	Vitamin D
Urinary tract infection	Parathormone (primary hyperparathyroidism)
Moderately severe renal failure	Growth hormone
Calcitonin, lithium, vitamin D, acetazolamide	Heat
Magnesium	Ethacrynic acid

complex with calcium and inhibiting growth of calcium phosphate and calcium oxalate crystals. 11,12 Recently, low urinary citrate (hypocitraturia) has been associated with calcium nephrolithiasis. Hypocitraturia and calcium stones have been noted in idiopathic stone disease, as well as renal tubular acidosis, hyperparathyroidism, and inflammatory bowel disease.

# HISTORICAL ASPECTS

Hypocitraturia in patients with renal stones was reported as early as 1931 by Ostberg. Boothby and Adams in 1934, Kissin and Locks in 1941, and Scott and associates in 1943 reported similar findings. In 1949, Conway et al<sup>6</sup> showed that only nephrolithiasis patients with infected urine had a reduced excretion of citrate and concluded that postrenal bacterial destruction of citrate led to the difference in citrate excretion between controls and patients with stones. Hodgkinson<sup>8</sup> reported that healthy young females excrete more citrate than young males, that there is no difference in citrate excretion between patients with sterile and nonsterile urine, and that the reduced citrate excretion by nephrolithiasis patients appears to be the result of altered renal function.

In 1976, Welshman and McGeowan<sup>13</sup> studied citrate excretion in 164 patients with idiopathic nephrolithiasis, 158 patients with various nonrenal diseases, and 108 young adults (ages 17–30) representing normal controls. They found that (a) patients with nephrolithiasis (males and females) excreted significantly less citrate than either patient controls or young-adult controls; (b) females in the young-adult control group had significantly

higher urinary citrate and urinary calcium excretion than the young-adult males; (c) there was no significant difference in citrate excretion between male and female nephrolithiasis patients; (d) citrate excretion rose with increasing calcium excretion, and (e) the mean ratio of citrate excretion to calcium excretion was greater in the young female controls than in female lithiasis patients over the age of 50.13 The difference was thought to be due to an estrogen effect.

In 1980, Rudman et al<sup>9</sup> studied hypocitraturia in 16 patients with gastrointestinal malabsorption. They found that all patients with malabsorption had hypocitraturia and that the hypocitraturia was a result of a subnormal filtered load of citrate and abnormally high net tubular reabsorption of the anion. Those patients also had hypomagnesemia and hypomagnesuria. Treatment with orally administered citrate raised both the serum concentration and the filtered load of citrate to normal fasting levels, but did not influence the abnormally high net tubular reabsorption and therefore did not correct the abnormally low urinary citrate excretion. Magnesium sulfate given intramuscularly restored the net tubular reabsorption of citrate to normal; however, a magnesium sulfate supplement had no effect on serum citrate or its filtered load. These investigators concluded that full correction of hypocitraturia in patients with gastrointestinal malabsorption can only be achieved by combined treatment with orally administered citrate and parenteral magnesium sulfate.

### THERAPEUTIC ASPECTS

Potassium citrate therapy seems to prevent stone formation by several mechanisms. First, it decreases urinary calcium saturation by forming a soluble complex with calcium.<sup>14</sup> It also inhibits spontaneous nucleation of calcium salts and crystal growth of calcium phosphate<sup>3</sup> and calcium oxalate.<sup>9</sup> In addition, it increases the urinary pH,<sup>15</sup> thus reducing uric acid stone formation, and prevents calcium stone formation complicating uric acid lithiasis. Finally, citrate therapy, by creating a higher urinary pH, seems to enhance the action of other stone inhibitors (such as pyrophosphate).<sup>14</sup>

In 1983, Pak et al<sup>11</sup> reported that long-term potassium citrate supplementation was effective in the treatment of calcium renal stones occurring alone or with other metabolic disturbances (i.e., absorptive hypercalciuria, enteric hyperoxaluria, renal tubular acidosis, uric acid stones, and uric acid stones complicated by calcium stones.<sup>11,16</sup> In their 53 patients, urinary citrate and pH

increased significantly during potassium citrate therapy. These same investigators also noted that

- 1. Overall new-stone-formation rate in all their patients declined from 5.14–7.41 to 0.35–1.33 stones per patient per year during a mean treatment period of 1.08 to 1.42 years.
- 2. Forty-two percent of patients with pre-existing radio-opaque stones showed radiological evidence of fewer stones following at least eight months of potassium citrate therapy; in 39%, the stones disappeared, but not, apparently, due to their passage.
- 3. Potassium citrate therapy was effective for preventing new stone formation in patients who experienced a relapse while undergoing other forms of therapy (i.e., thiazides and/or allopurinol or conservative treatment [diet changes and increased fluid intake]); stones continued to develop in 12 of the 53 study patients (eight with absorptive hypercalciuria, two with hyperuricosuric calcium lithiasis, and one each with renal tubular acidosis and no metabolic abnormality) while they were treated with conventional drug therapy, the stone formation rate following potassium citrate therapy decreased from 5.14 to 1.33 stones per patient per year and remission was induced in 91.7%.

Preminger et al<sup>20</sup> compared the efficacy of potassium citrate therapy in 54 patients with hypocitraturia alone or with other metabolic abnormalities (i.e., absorptive hypercalcuria, diarrheal syndromes, renal tubular acidosis, and hyperuricosuria) with that of 11 reported conservative or placebo trials. New stone formation was virtually eliminated by potassium citrate therapy, a remission rate of 96%, whereas only 61% of patients treated conservatively experienced disease remission.

In another study, Pak et al<sup>10</sup> used potassium citrate to treat 89 patients with recurrent calcium nephrolithiasis for 1 to 4<sup>1</sup>/<sub>3</sub> years (36 patients were also given other drugs). In all of these patients, there was a sustained and significant increase in urinary pH, citrate, and potassium. The authors observed that individual stone formation decreased in 97.8%, remission was achieved in 79.8%, and the need for surgical intervention for newly formed stones was eliminated.

In 1985, Pak et al<sup>17</sup> also studied the effect of adding potassium citrate to the ongoing thiazide treatment that was not having any effect on 13 patients who had hypercalciuric nephrolithiasis. Urinary citrate excretion rose to normal and urinary pH significantly increased. Ten patients (76.9%) experienced remission (i.e., stopped

forming new stones) and 13 (100%) had a reduced stone formation rate over  $1.76 \pm 0.53$  years per patient.

Therapy with potassium citrate has been successful not only in the management of calcium stone disease but also in the treatment of uric acid lithiasis presenting with or without calcium nephrolithiasis. Pak et al<sup>18,19</sup> demonstrated that treatment with potassium citrate of patients with uric acid lithiasis (with or without calcium stones) produced a sustained rise in urine pH to the high normal range. Urinary citrate levels rose to the normal mean value. Other changes included significant decreases in the urinary saturation of calcium oxalate and the amount of undissociated uric acid. Moreover, remission was apparent in 94% of the patients with pure uric acid stones and in 84.2% of the patients with hyperuriocosuric calcium oxalate stones; stone formation rate declined by 99.2% in the former group and by approximately 80% in the latter group.

At the Cleveland Clinic's renal stone subclinic, 160 of approximately 400 patients had their urinary citrate excretion determined over the past three years. Seventy-eight (49%) patients had a 24-hour urinary citrate measurement of less than 320 mg. Forty-five of the 78 patients with hypocitraturia (57.6%) had no other metabolic abnormalities; the remaining 42% had hypocitraturia associated most frequently with hyperoxluria, hypercalciuria, and hyperuricosuria. We are currently studying the effect of oral potassium citrate therapy for patients with idiopathic hypocitraturia on the urinary citrate excretion, the rate of new stone formation, and the rate of stone disease remission.

## CONCLUSION

Current evidence suggests that hypocitraturia plays a major role in the pathogenesis of calcium nephrolithiasis. Therefore, the measurement of urinary citrate should be a part of the metabolic evaluation of patients with recurrent renal stone disease. A more aggressive approach to treating patients with hypocitraturia by using orally administered citrate is also recommended.

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