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Hypocitraturia: its importance as a factor in the development of urolithiasis

Hipocytraturia – znaczenie w rozwoju kamicy układu moczowego

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Abstract

The citrate anion is an endogenous inhibitor of calcium deposits in the urinary tract. Moreover, by urine alkalisation, citrates enhance uric acid and cystine solubility. Hypocitraturia in adults is defined as excretion of citrates with urine below 320 mg/24 h. The most common definitions in children involve citrate excretion in 24 hour urine collection at a level <365 mg/1.73 m^2/24 h in boys and <310 mg/1.73 m^2/24 h in girls. Moreover, the urine citrate/creatinine ratio is also considered: for children aged 0–5 years <0.42 mg/mg and for children older than 5 years of age <0.25 mg/mg. Hypocitraturia is a common metabolic disturbance; such a diagnosis is made in approximately 20–60% of adults and 10–68% of children with urolithiasis. Various factors may affect citrate excretion with urine, the most significant of which is the pH value (of blood, urine or intracellular fluid). Most patients are diagnosed with so-called idiopathic hypocitraturia, although it also accompanies acidosis, including distal tubular acidosis, hypokalaemia, high-protein diet and treatment with certain medications (carbonic anhydrase inhibitors, angiotensin-converting enzyme inhibitors, thiazide diuretics). Patients with hypocitraturia should first and of foremost have dietary modifications introduced. This involves an increase in the dietary amount of fluids and citrus fruit as well as salt and protein restriction. Patients with recurring urolithiasis may also be recommended citrate products, the most common of which is potassium citrate. Citrus juices may be an alternative, but their effect is not as potent and unambiguous as in the case of commercially available citrate products.

Keywords: hypocitraturia, citrates, urolithiasis, children

Streszczenie

Anion cytrynianowy to endogenny inhibitor powstawania złogów wapniowych w drogach moczowych. Ponadto przez alkalizację moczu cytryniany zwiększają rozpuszczalność kwasu moczowego i cystyny. Hipocytraturia definiowana jest u dorosłych jako wydalanie cytrynianów z moczem poniżej 320 mg/24 h. Najczęściej stosowane definicje hipocytraturii u dzieci to wydalanie cytrynianów w dobowej zbiórce moczu <365 mg/1,73 m^2/24 h u chłopców i <310 mg/1,73 m^2/24 h u dziewczynek; używa się też wskaźnika cytrynianowo-kreatyninowego z porcji moczu: dla dzieci w wieku 0–5 lat <0,42 mg/mg, a powyżej 5. roku życia: <0,25 mg/mg. Hipocytraturia to częsta nieprawidłowość metaboliczna – stwierdza się ją u około 20–60% dorosłych i 10–68% dzieci z kamicą. Na wydalanie cytrynianów z moczem wpływ ma wiele czynników, z których najważniejszym jest wartość pH (krwi, moczu oraz wewnątrzkomórkowe). Większość pacjentów ma tzw. idiopatyczną hipocytraturię, choć występuje ona także w stanach kwasicy, w tym kwasicy kanalikowej dystalnej, hipokaliemii, diecie bogatobiałkowej oraz przy stosowaniu niektórych leków (inhibitory anhydrazy węglanowej, inhibitory konwertazy angiotensyny, diuretyki tiazydowe). U pacjentów z hipocytraturią w pierwszej kolejności należy podjąć modyfikacje dietetyczne, polegające na zwiększeniu ilości przyjmowanych płynów i owoców cytrusowych oraz ograniczeniu spożycia soli i białka. U pacjentów z nawrotową kamicą zastosowanie znajdują preparaty cytrynianów, z których najczęściej stosuje się cytrynian potasu. Alternatywnie można stosować soki cytrusowe, jednak ich korzystne działanie nie jest tak silne i jednoznaczne jak w przypadku komercyjnie dostępnych preparatów cytrynianów.

Słowa kluczowe: hipocytraturia, cytryniany, kamica moczowa, dzieci

UROLITHIASIS – HYPOCITRATURIA

According to epidemiological studies, a decreased level of crystallisation inhibitors is one of the most significant risk factors of urolithiasis[1]. Citrates are substances deemed the most important urinary calculus inhibitors. Their reduced urinary excretion (hypocitraturia) may be an isolated defect in patients with urolithiasis, but may also accompany hypercalciuria or hyperoxaluria.

Citrates are inhibitors of calcium oxalate and calcium phosphate crystallisation. Hypocitraturia is identified in approximately 20–60% of adults[2] and 10–68% of children with urolithiasis[3–7]. In the analysis of 113 patients with nephrolithiasis, hypocitraturia was identified in 68% of children, including 81% with a genetically or systemically determined nephrolithiasis (primary hyperoxaluria, cystinuria, Dent disease, 2,8-dihydroxyadenine urolithiasis, tubular acidosis, Lesch–Nyhan disease, Crohn's disease, ketogenic diet) and 65% with idiopathic nephrolithiasis[5]. Moreover, hypocitraturia was noted in 31.7% (19/60) of children with asymptomatic microscopic haematuria[6]. In 63 children with nephrolithiasis, hypocitraturia was the most common (58.1%) metabolic abnormality, even more common than hypercalciuria. The authors put forward a hypothesis that hypocitraturia is becoming the most common risk factor of urolithiasis in the paediatric population due to unfavourable dietary changes[7]. It is the primary risk factor of urolithiasis in preterm infants[8] and in children with very low birth weight[9] as well as in some parts of the world (for example in Turkey)[10].

Citrate excretion is higher in children than in adults. Hypocitraturia in adults is identified with citrate excretion below 320 mg/24 h (=1.67 mmol/24 h)[11]. The diagnostic criteria of hypocitraturia in children according to Hoppe and Kemper are[8]:

1. amount of citrate in 24 h urine collection: boys: <365 mg/1.73 m^2/24 h; girls: <310 mg/1.73 m^2/24 h;
2. citrate/creatinine ratio in a urine sample: 0–5 years of age: <0.42 mg/mg (<0.25 mol/mol); >5 years of age: <0.25 mg/mg (<0.15 mol/mol).

It must be underlined that the reference levels are arbitrary, and the risk of urolithiasis grows continuously with a decreased urine citrate level[12].

Kirejczyk et al. evaluated urinary citrate excretion in 2,334 healthy boys and girls aged 2–18 years. The authors showed that citrate excretion, expressed in absolute values, increases with age and is higher in boys than in girls. Based on these results, they have proposed the following diagnostic criteria for hypocitraturia (defined as citrate excretion <5th percentile in the studied population): boys: 180 mg/1.73 m^2/24 h; girls: 250 mg/1.73 m^2/24 h[13].

Hypocitraturia may be the only risk factor of urolithiasis, but often coexists with other potential causes, usually with hypermagnesuria, but also with hypercalciuria and hyperoxaluria or cystinuria. It therefore seems that the estimation of reciprocal relationships of calculus components and calculus inhibitors (e.g. citrates) may be useful. DeFoor et al. demonstrated that the calcium-to-citrate ratio may occur adequate for this purpose. The ratio amounted to 0.33 in healthy children, 0.41 in children with one episode of urolithiasis and 0.64 in children with recurring urolithiasis[14]. Turudic et al., however, found the oxalate/(citrate × glycosaminoglycans) ratio to be an independent risk factor of calculus formation in children[15].

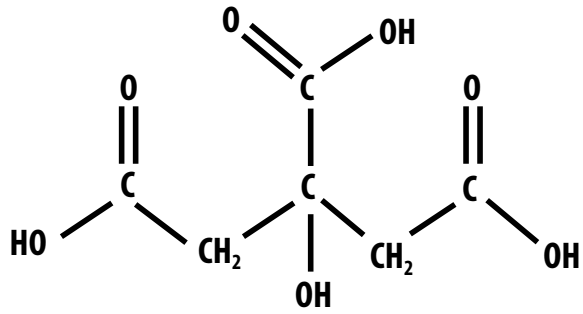

Fig. 1. Chemical structure of citric acid[62, own modification]

CITRATE METABOLISM

Citric acid is tricarboxylic acid (Fig. 1) synthesised in the mitochondria from oxaloacetate and acetyl-CoA with the participation of citrate synthase (Fig. 2). This is the central stage of tricarboxylic acid cycle (also called Krebs cycle or citric acid cycle), which is a common terminal pathway for oxidation of carbohydrates, proteins and lipids[16]. The serum citrate concentration persists at a relatively

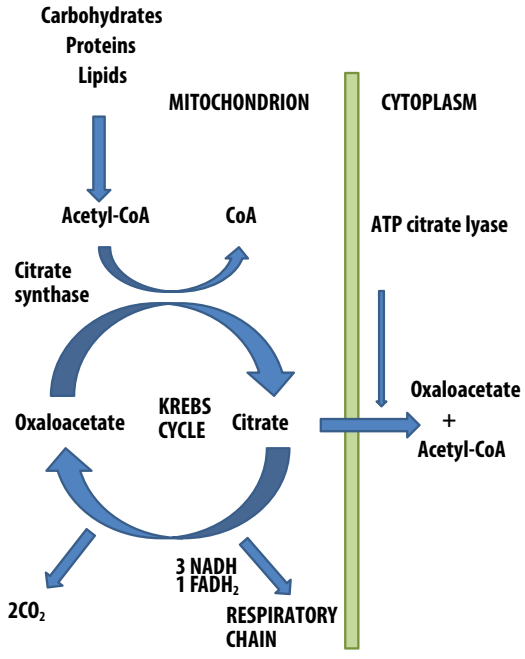

Fig. 2. Metabolism of citric acid[62, own modification]

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stable level: from 0.1 to 0.15 mmol/L[17]. Approximately 90% of citrates in the body are located in bones, which are their main reservoir, with osteoblasts being the basic site of citrate production. Citrates are released to circulation during bone tissue resorption[17]. Most circulating citrates assume the form of complexes with divalent cations, such as calcium and magnesium. It is believed that the most important hormones responsible for maintaining an appropriate blood citrate concentration are parathyroid hormone and calcitonin owing to their impact on bone metabolism[17].

Citrates are filtrated in the renal glomeruli and enter the primary urine. Citrate reabsorption occurs mainly at the level of the proximal tubule[18]. In humans, 65–90% of filtered citrates are reabsorbed[19]. That is why their urinary excretion mainly depends on the degree of proximal tubule reabsorption[18]. The most important protein responsible for citrate reabsorption is sodium-dependent dicarboxylate transporter 1 (NaDC-1), whose expression is noted in the proximal tubule, small and large bowels, liver and brain[19]. NaDC-1 exerts activity towards dinegative citrates but is inhibited by trinegative citrates. Energy needed for citrate reabsorption is provided by the sodium–potassium pump, located on the surface of the basolateral cells of the proximal tubule. Most citrates that cross the apical membrane enter the mitochondria and are used in the tricarboxylic acid cycle[18]. Citrates that remain in the cytoplasm are metabolised by ATP citrate lyase. It catalyses citrate conversion to oxaloacetate and acetyl-CoA using coenzyme A and ATP. Acetyl-CoA is subsequently utilised, for instance in the process of fatty acid and cholesterol synthesis, while oxaloacetate is a substrate for gluconeogenesis[20]. Non-metabolised citrates return to circulation via the renal vein[17].

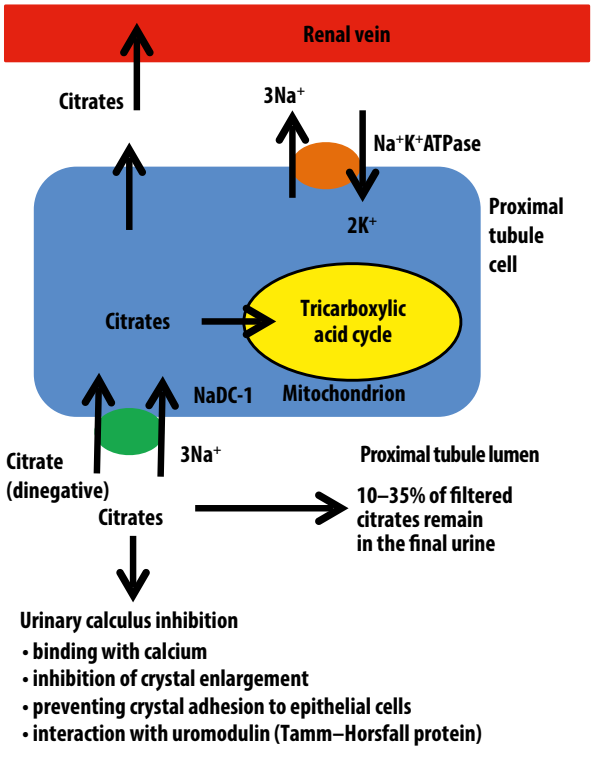

Fig. 3. Citrate renal transport and mechanisms of their anti-urolithiasis action[61, own modification]

Renal citrate reabsorption is regulated by various factors, the most important being pH (of urine, plasma, renal interstitium and intracellular fluid). Acidosis reduces renal citrate excretion, while alkalosis enhances it[21]. One of the mechanisms responsible for the impact of pH is the degree of citrate ionisation. Dinegative citrates transported by NaDC-1 are present in higher concentrations in acidic pH compared to alkaline pH. Chronic acidoses not only enhance the activity of NaDC-1, but also increase its expression. Moreover, these conditions intensify intratubular citrate metabolism[19].

Bowel citrate absorption is also mediated by NaDC-1. Citrate bioavailability following oral administration is 96–98%[21].

MECHANISM OF ANTI-UROLITHIASIS EFFECTS OF CITRATES

The mechanisms of anti-urolithiasis effect of citrates and their renal transport are illustrated in Fig. 3. Citrates are bound with calcium in the renal tubules, thereby forming a non-dissociating but soluble complex. This decreases the pool of free calcium, available for binding with oxalates and phosphates. Citrates also seem to inhibit crystal enlargement (aggregation), which is a process whereby single calcium oxalate crystals combine into a calculus[22]. Additionally, citrates bind with the surface of a calculus. This prevents calcium oxalate adhesion to epithelial cells[23]. Furthermore, the mechanism of action of citrates consists in entering into a positive interaction with another crystallisation inhibitor, namely Tamm–Horsfall protein (uromodulin)[24]. It has also been demonstrated that they reduce the urine level of osteopontin, which is a common component of a calculus. Moreover, they improve uric acid and cystine solubility by increasing urine pH[25].

CLINICAL CONDITIONS LEADING TO HYPOCITRATURIA

Clinical conditions leading to hypocitraturia are presented in Tab. 1.

Idiopathic hypocitraturia, dietary factors and genetic factors

Although factors of idiopathic hypocitraturia are unknown, the proposed aetiology is associated with environmental factors (mostly with high-protein diet)[26] and genetic predisposition. High-protein diet (especially with protein from meat, poultry and eggs) acidifies the system and increases citrate reabsorption at the level of the proximal tubule. It has been shown that low-carbohydrate acidifying diets

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Metabolic acidosis	Distal tubular acidosis Metabolic acidoses of other aetiology (e.g. inborn errors of metabolism) Chronic diarrhoeas Malabsorption syndromes Intensive physical effort
Systemic/renal ionic disorders	Hypokalaemia Hypokalciuria Hypomagnesuria
Hormonal disorders	Hyperparathyroidism Hyperaldosteronism
Dietary factors	High-protein diet High-salt diet Ketogenic diet Diet poor in vegetables/fruit Fasting
Drugs	Carbonic anhydrase inhibitors Angiotensin-converting enzyme inhibitors Thiazide diuretics
Other medical conditions	Glycogen storage disease type I
Genetic factors	Vitamin D receptor (VDR) gene polymorphisms Sodium-citrate transporter (NaDC-1) gene polymorphisms ZNF365 (zinc finger) gene polymorphisms

Tab. 1. Clinical conditions leading to hypocitraturia[61, own modification]

(such as Atkins diet, ketogenic diet or Kwaśniewski diet) also reduce urinary citrate excretion[27].

In addition, fruit-poor diet results in body acidification, a low intake of potassium and low urinary potassium excretion, which correlates with urinary citrate excretion[26,28]. Furthermore, it has been demonstrated that hypocitraturia is linked with a high-sodium diet[29] and fasting[30] (in both cases, probably in the mechanism of mild metabolic acidosis).

A relationship has been noted also between vitamin D receptor (VDR) gene polymorphisms and urinary citrate excretion[31]. The active form of vitamin D, i.e. $1.25(OH)_2D$, modulates NaDC-1 activity by binding with the VDR receptor[32].

Moreover, it has been observed that urinary citrate excretion is correlated with polymorphisms of the sodium-citrate cotransporter (hNaDC-1) gene and zinc finger protein 365 (ZNF365) gene that encodes talanin[34].

Electrolyte and tubular disorders

Metabolic acidoses

Children with chronic metabolic acidosis are at a higher risk of urolithiasis. Children with acidosis caused by increased citrate reabsorption in the proximal tubule excrete lower amounts of citrates with urine as these citrates are used for the regeneration of the alkaline pool in the body.

In the mechanism of chronic metabolic acidosis, hypocitraturia, which entails a higher risk of urolithiasis, also occurs in chronic diarrhoeas (e.g. in cystic fibrosis)[35].

Moreover, hypocitraturia is common in (type 1) distal tubular acidosis. Exacerbation of hypocitraturia is higher in complete tubular acidosis, but may also occur in incomplete distal renal tubular acidosis (dRTA) with the absence of overt metabolic acidosis[35]. It must be noted that other types of tubular acidosis, such as the proximal form (type 2) and hypokalaemic form (type 4), are not associated with hypocitraturia. Nevertheless, this disorder has been identified in children with secondary tubular acidosis, e.g. after treatment with ifosfamide, or in substance addicts "sniffing glue" (chronic toluene poisoning).

Patients with malabsorption syndromes are also diagnosed with hypocitraturia, which is secondary not to impaired citrate absorption, but rather to intestinal carbohydrate loss[36].

Hypokalaemia

Hypokalaemia enhances NaDC-1 activity by leading to intratubular and intracellular acidosis (in the mechanism of transmembrane K^+ and H^+ exchange)[28].

Hypercalciuria and hypermagnesuria

Increased urinary excretion of calcium and magnesium also enhances urinary citrate excretion[37]. Kovacevic et al. showed that potassium and magnesium excretion is positively correlated with citrate excretion[7]. Administration of magnesium increases urinary citrate excretion[38]. Calcium and magnesium bind with citrates in urine, thereby decreasing their pool available for NaDC-1.

Hormonal factors

Parathyroid hormone reduces urinary citrate excretion[17]. Hypocitraturia is detected in approximately 20–40% of patients with hyperparathyroidism[39]. A precise mechanism of action of parathyroid hormone remains unclear. There are no data on its effect on increasing NaDC-1 activity. However, it has been shown that it may inhibit citrate metabolism in tubular cells in the kidneys[40].

Animal studies indicate that renal citrate excretion is increased by calcitonin. Its administration to rats caused a five-fold increase in citraturia[41]. The mechanism of action of this phenomenon and its relevance in humans remain unclear.

Drugs

Hypocitraturia is identified in patients treated with carbonic anhydrase inhibitors. These drugs induce systemic acidosis by inhibiting carbohydrate reabsorption at the level of the proximal tubule. This, in turn, results in increased citrate reabsorption from urine. Drugs from this group include: acetazolamide, topiramate and zonisamide[36]. Hypocitraturia has been noted in 93% of children treated with topiramate[42].

The disorder may also appear secondary to treatment with angiotensin-converting enzyme inhibitors. It is believed that the mechanism of action of these drugs consists in increasing the activity of ATP citrate lyase in cells of the proximal tubule[43].

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Thiazide diuretics reduce urinary citrate excretion probably in the mechanism of hypokalaemia induction[26,44]. Lithium, on the other hand, increases urinary citrate levels by suppressing their reabsorption in the proximal tubule[45].
Vitamin D also affects the activity of NaDC-1[32] and citrate metabolism in tubular cells[19], which results in increased urinary citrate excretion.

Other clinical conditions

The concentration of citrates in the primary urine decreases with a decreasing glomerular filtration in chronic kidney disease. However, an increase in the filtration fraction maintains the stable citrate concentration in the final urine until the stage of severe renal failure[46]. Hyperaldosteronism increases the sodium pool in the body and causes hypokalaemia, thereby inducing hypocitraturia and hypercalciuria[47]. Hypocitraturia (as hypercalciuria and hyperuricosuria) has been identified in patients with glycogen storage disease type I[48]. Despite increased risk of nephrolithiasis in obesity, the relationship between body mass index and citraturia is not clear[26,49]. Physical exercise does reduce urinary citrate excretion, but water reabsorption maintains their relatively stable levels[50].

THERAPEUTIC MANAGEMENT IN HYPOCITRATURIA

The risk of urolithiasis is associated with dietary modifications. Increased intake of fruit and vegetables has a positive impact on urinary citrate excretion[51]. The dual mechanism of action in this case consists in the presence of citrates in these products and in increasing the potassium and magnesium pool. It must also be underlined that ingested citrates are mainly metabolised in the liver to bicarbonates, and they inhibit urinary citrate reabsorption by increasing pH[25].
Oral citrate supplementation reduces the risk of urolithiasis in patients with hypocitraturia[52]. Potassium citrate is the most common supplement. These products increase the alkaline pool and raise urinary pH, thereby reducing the risk of uric acid urolithiasis and cystine urolithiasis. The efficacy of potassium citrate supplementation has also been shown in patients with infection nephrolithiasis[53].
The effects of citrate supplementation have been evaluated in prospective studies in adults with recurring urolithiasis[54,55]. Doses ranged from 60 to 90 mmol/24 h. The efficacy of potassium citrate (administered at a dose of 1 mmol/kg/24 h) for prevention of recurring episodes of urolithiasis has been demonstrated also in children with hypocitraturia[56]. In 82 children with hypocitraturia, recurring episodes of urolithiasis were observed in only 1 of 71 children (1.4%) treated with potassium citrate and in all 11 children who received no supplementation[56]. Undesirable effects of potassium citrates are mild and usually involve the gastrointestinal tract (bloating, nausea, diarrhoea)[57]. They are more common with liquid preparations than tablets. Nevertheless, the rate of citrate absorption from tablets is lower compared to liquid preparations.
The citrate dose depends on patient's body mass and the degree of hypocitraturia and acidosis. Typical doses for adults range from 40 to 60 mmol/24 h. In children, the recommended doses are 0.1–0.2 g/kg/24 h (0.3–0.6 mmol/kg/24 h). They may be significantly higher in patients with distal tubular acidosis, where the minimum dose of potassium citrate is usually 0.2–0.3 g/kg/24 h.
Currently, there are two products with potassium citrate available in Poland. Tablets of 680 mg (1 tablet containing 2.2 mmol) (Litocid) are registered for treatment of adults with calcium urolithiasis and low urinary citrate excretion. A recommended starting dose is 3 × 2 tablets (approximately 50 mg/kg/24 h), which is subsequently modified depending on urine pH. Granules (Citrolyt) contain 46.4 g of potassium citrate monohydrate, 39.1 g of sodium citrate dihydrate and 14.5 g of citric acid monohydrate in 100 g (i.e. 3.16 mmol of citrates in 1 g). The product is registered for treatment of uric acid and urate nephrolithiasis in adults and children over 12 years of age. The initial dosing pattern is: 2.5 g in the morning at 7–8 a.m., next 2.5 g at 2–3 p.m. and 5.0 g at 10 p.m. Further treatment is conducted on the basis of urine pH values.
Patients administered citrates require monitoring of electrolyte levels, urine pH as well as mineral and citrate excretion levels. The urine pH after administration of citrates may increase to the level that is a risk of calcium–phosphate urolithiasis. If urine pH exceeds 7.0, citrate doses must be reduced. Patients with distal tubular acidosis are an exception as their urine pH value is already high before treatment initiation.
Patients intolerant of potassium citrate may ingest citrus fruit. Wabner and Pak showed that drinking orange juice increases the urine citrate concentration to a similar degree to potassium citrate but, by contrast with the drug, does not reduce calcium oxalate excretion[58]. Grapefruit juice, on the other hand, does not reduce risk factors for urolithiasis[59], and may exert adverse effects on drug metabolism by acting on cytochrome P450. Data on the effects of drinking lemonade (water with lemon juice) seem unclear[60,61]. Some researchers note its positive effects on citrate excretion, while others show no such benefits. Lemon juice contains citric acid, which is different from orange and grapefruit juices that contain high amounts of potassium citrate. A large amount of proton ion exerts a negative effect on urine properties and neutralises the positive effect of citrates.

Conflict of interest

The authors do not report any financial or personal affiliations to persons or organisations that could adversely affect the content of or claim to have rights to this publication.

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References

1. Rudman D, Kutner MH, Redd SC 2nd et al.: Hypocitraturia in calcium nephrolithiasis. J Clin Endocrinol Metab 1982; 55: 1052–1057.
2. Pak CY: Etiology and treatment of urolithiasis. Am J Kidney Dis 1991; 18: 624–637.
3. Miller LA, Stapleton FB: Urinary citrate excretion in children with hypercalciuria. J Pediatr 1985; 107: 263–266.
4. Gouru VR, Pogula VR, Vaddi SP et al.: Metabolic evaluation of children with urolithiasis. Urol Ann 2018; 10: 94–99.
5. Bevill M, Kattula A, Cooper CS et al.: The modern metabolic stone evaluation in children. Urology 2017; 101: 15–20.
6. Spivacow FR, Del Valle EE, Rey PG: Metabolic risk factors in children with asymptomatic hematuria. Pediatr Nephrol 2016; 31: 1101–1106.
7. Kovacevic L, Wolfe-Christensen C, Edwards L et al.: From hypercalciuria to hypocitraturia – a shifting trend in pediatric urolithiasis? J Urol 2012; 188 (Suppl): 1623–1627.
8. Hoppe B, Kemper MJ: Diagnostic examination of the child with urolithiasis or nephrocalcinosis. Pediatr Nephrol 2010; 25: 403–413.
9. Sikora P, Roth B, Kribs A et al.: Hypocitraturia is one of the major risk factors for nephrocalcinosis in very low birth weight (VLBW) infants. Kidney Int 2003; 63: 2194–2199.
10. López M, Hoppe B: History, epidemiology and regional diversities of urolithiasis. Pediatr Nephrol 2010; 25: 49–59.
11. Chow K, Dixon J, Gilpin S et al.: Citrate inhibits growth of residual fragments in an in vitro model of calcium oxalate renal stones. Kidney Int 2004; 65: 1724–1730.
12. Curhan GC, Taylor EN: 24-h uric acid excretion and the risk of kidney stones. Kidney Int 2008; 73: 489–496.
13. Kirejczyk JK, Porowski T, Konstantynowicz J et al.: Urinary citrate excretion in healthy children depends on age and gender. Pediatr Nephrol 2014; 29: 1575–1582.
14. DeFoor W, Jackson E, Schulte M et al.: Calcium-to-citrate ratio distinguishes solitary and recurrent urinary stone forming children. J Urol 2017; 198: 416–421.
15. Turudic D, Batinic D, Golubic AT et al.: Calcium oxalate urolithiasis in children: urinary promoters/inhibitors and role of their ratios. Eur J Pediatr 2016; 175: 1959–1965.
16. Krebs HA, Salvin E, Johnson WA: The formation of citric and alpha-ketoglutaric acids in the mammalian body. Biochem J 1983; 32: 113–117.
17. Costello LC, Franklin RB: Plasma citrate homeostasis: how it is regulated; and its physiological and clinical implications. An important, but neglected, relationship in medicine. HSOA J Hum Endocrinol 2016; 1: 1–19.
18. Brennan TS, Klahr S, Hamm LL: Citrate transport in rabbit nephron. Am J Physiol 1986; 251: 683–689.
19. Simpson DP: Citrate excretion: a window on renal metabolism. Am J Physiol 1983; 244: 223–234.
20. Melnick JZ, Srere PA, Elshourbagy NA et al.: Adenosine triphosphate citrate lyase mediates hypocitraturia in rats. J Clin Invest 1996; 98: 2381–2387.
21. Dedmon RE, Wrong O: The excretion of organic anion in renal tubular acidosis with particular reference to citrate. Clin Sci 1962; 22: 19–32.
22. Kok DJ, Papapoulos SE, Bijvoet OL: Crystal agglomeration is a major element in calcium oxalate urinary stone formation. Kidney Int 1990; 37: 51–56.
23. Sheng X, Jung T, Wesson JA et al.: Adhesion at calcium oxalate crystal surfaces and the effect of urinary constituents. Proc Natl Acad Sci U S A 2005; 102: 267–272.
24. Hess B, Zipperle L, Jaeger P: Citrate and calcium effects on Tamm–Horsfall glycoprotein as a modifier of calcium oxalate crystal aggregation. Am J Physiol 1993; 265: 784–791.
25. Habbig S, Beck BB, Hoppe B: Nephrocalcinosis and urolithiasis in children. Kidney Int 2011; 80: 1278–1291.
26. Mandel EI, Taylor EN, Curhan GC: Dietary and lifestyle factors and medical conditions associated with urinary citrate excretion. Clin J Am Soc Nephrol 2013; 8: 901–908.
27. Reddy ST, Wang CY, Sakhaee K et al.: Effect of low-carbohydrate high-protein diets on acid-base balance, stone-forming propensity, and calcium metabolism. Am J Kidney Dis 2002; 40: 265–274.
28. Domrongkitchaiporn S, Stitchantrakul W, Kochakarn W: Causes of hypocitraturia in recurrent calcium stone formers: focusing on urinary potassium excretion. Am J Kidney Dis 2006; 48: 546–554.
29. Sakhaee K, Harvey JA, Padalino PK et al.: The potential role of salt abuse on the risk for kidney stone formation. J Urol 1993; 150: 310–312.
30. Windus DW, Cohn DE, Heifets M: Effects of fasting on citrate transport by the brush-border membrane of rat kidney. Am J Physiol 1986; 251: 678–682.
31. Mossetti G, Vuotto P, Rendina D et al.: Association between vitamin D receptor gene polymorphisms and tubular citrate handling in calcium nephrolithiasis. J Intern Med 2003; 253: 194–200.
32. Pajor AM, Sun N: Protein kinase C-mediated regulation of the renal Na^+/dicarboxylate cotransporter, NaDC-1. Biochim Biophys Acta 1999; 1420: 223–230.
33. Okamoto N, Aruga S, Matsuzaki S et al.: Associations between renal sodium-citrate cotransporter (hNaDC-1) gene polymorphism and urinary citrate excretion in recurrent renal calcium stone formers and normal controls. Int J Urol 2007; 14: 344–349.
34. Medina-Escobedo M, González-Herrera L, Villanueva-Jorge S et al. Metabolic abnormalities and polymorphisms of the vitamin D receptor (*VDR*) and *ZNF365* genes in children with urolithiasis. Urolithiasis 2014; 42: 395–400.
35. Pak CY: Citrate and renal calculi: an update. Miner Electrolyte Metab 1994; 20: 371–377.
36. Welch BJ, Graybeal D, Moe OW et al.: Biochemical and stone-risk profiles with topiramate treatment. Am J Kidney Dis 2006; 48: 555–563.
37. Hamm LL: Renal handling of citrate. Kidney Int 1990; 38: 728–735.
38. Reungjui S, Prasongwatana V, Premgamone A et al.: Magnesium status of patients with renal stones and its effect on urinary citrate excretion. BJU Int 2002; 90: 635–639.
39. Koff SG, Paquette EL, Cullen J et al.: Comparison between lemonade and potassium citrate and impact on urine pH and 24-hour urine parameters in patients with kidney stone formation. Urology 2007; 69: 1013–1016.
40. Alvarez-Arroyo MV, Traba ML, Rapado A et al.: Role of citric acid in primary hyperparathyroidism with renal lithiasis. Urol Res 1992; 20: 88–90.
41. Franklin R, Costello LC, Stacey R et al.: Calcitonin effects on plasma and urinary citrate levels in rats. Am J Physiol. 1973; 225: 1178–1180.
42. Corbin Bush N, Twombley K, Ahn J et al.: Prevalence and spot urine risk factors for renal stones in children taking topiramate. J Pediatr Urol 2013; 9: 884–889.
43. Melnick JZ, Preisig PA, Haynes S et al.: Converting enzyme inhibition causes hypocitraturia independent of acidosis or hypokalemia. Kidney Int 1998; 54: 1670–1674.
44. Pak CY, Peterson R, Sakhaee K et al.: Correction of hypocitraturia and prevention of stone formation by combined thiazide and potassium citrate therapy in thiazide-unresponsive hypercalciuric nephrolithiasis. Am J Med 1985; 79: 284–288.
45. Zhang X, Aggarwal P, Li X et al.: The role of lithium carbonate and lithium citrate in regulating urinary citrate level and preventing nephrolithiasis. Int J Biomed Sci 2009; 5: 215–222.
46. Marangella M, Vitale C, Manganaro M et al.: Renal handling of citrate in chronic renal insufficiency. Nephron 1991; 57: 439–443.
47. Shey J, Cameron MA, Sakhaee K et al.: Recurrent calcium nephrolithiasis associated with primary aldosteronism. Am J Kidney Dis 2004; 44: 7–12.
48. Cochat P, Pichault V, Bacchetta J et al.: Nephrolithiasis related to inborn metabolic diseases. Pediatr Nephrol 2010; 25: 415–424.
49. Ekeruo WO, Tan YH, Young MD et al.: Metabolic risk factors and the impact of medical therapy on the management of nephrolithiasis in obese patients. J Urol 2004; 172: 159–163.
50. Sakhaee K, Nigam S, Snell P et al.: Assessment of the pathogenetic role of physical exercise in renal stone formation. J Clin Endocrinol Metab 1987; 65: 974–979.

51. Meschi T, Maggiore U, Fiaccadori E et al.: The effect of fruits and vegetables on urinary stone risk factors. Kidney Int 2004; 66: 2402–2410.

52. Pak CY, Fuller C: Idiopathic hypocitraturic calcium-oxalate nephrolithiasis successfully treated with potassium citrate. Ann Intern Med 1986; 104: 33–37.

53. Cicerello E, Merlo F, Gambaro G et al.: Effect of alkaline citrate therapy on clearance of residual renal stone fragments after extracorporeal shock wave lithotripsy in sterile calcium and infection nephrolithiasis patients. J Urol 1994; 151: 5–9.

54. Hofbauer J, Höbarth K, Szabo N et al.: Alkali citrate prophylaxis in idiopathic recurrent calcium oxalate urolithiasis – a prospective randomized study. Br J Urol 1994; 73: 362–365.

55. Soygür T, Akbay A, Küpeli S: Effect of potassium citrate therapy on stone recurrence and residual fragments after shockwave lithotripsy in lower caliceal calcium oxalate urolithiasis: a randomized controlled trial. J Endourol 2002; 16: 149–152.

56. Karsli O, Izol V, Aridogan IA et al.: Metabolic risk factors and the effect of metaphylaxis in pediatric stone disease with hypocitraturia. Urolithiasis 2013; 41: 9–13.

57. Mattle D, Hess B: Preventive treatment of nephrolithiasis with alkali citrate – a critical review. Urol Res 2005; 33: 73–79.

58. Wabner CL, Pak CY: Effect of orange juice consumption on urinary stone risk factors. J Urol 1993; 149: 1405–1408.

59. Goldfarb DS, Asplin JR: Effect of grapefruit juice on urinary lithogenicity. J Urol 2001; 166: 263–267.

60. Penniston KL, Steele TH, Nakada SY: Lemonade therapy increases urinary citrate and urine volumes in patients with recurrent calcium oxalate stone formation. Urology 2007; 70: 856–860.

61. Zuckerman JM, Assimos DG: Hypocitraturia: pathophysiology and medical management. Rev Urol 2009; 11: 134–144.

62. Granner DK, Murray RK, Rodwell VW: Biochemia Harpera Ilustrowana. Wydawnictwo Lekarskie PZWL, Warszawa 2018.

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