Causes of Hypocitraturia in Recurrent Calcium Stone Formers: Focusing on Urinary Potassium Excretion

Somnuek Domrongkitchaiporn, MD, Wasana Stitchantrakul, MSc, and Wachira Kochakarn, MD

• ***Background:*** **Multiple factors associated with hypocitraturia have been identified. However, limited studies addressing the causal relationship to hypocitraturia are available. We therefore conducted this study to determine factors associated with hypocitraturia and show their causal relationship in recurrent calcium stone formers.** ***Methods:*** **Dietary review and 24-hour urine samples were obtained from all recurrent calcium stone formers referred for metabolic workup in the stone clinic. One month of oral potassium chloride supplementation was prescribed to stone formers to determine the causal relationship between urinary potassium and citrate levels.** ***Results:*** **Eighty-three subjects, 44 men and 39 women, were recruited to participate in this study. Hypocitraturia (citrate < 300 mg/d [<1.43 mmol/d]) was found in 50.6% of subjects. Four independent urinary variables associated with hypocitraturia were identified, including potassium level, net gastrointestinal alkaline absorption, calcium level, and titratable acid. Urinary potassium level was the strongest predictor of urinary citrate level. Hypocitraturic subjects also had lower fruit intake compared with subjects with high urinary citrate levels. Potassium chloride supplementation to a subgroup of this population (n = 58) resulted in a significant increase in urinary citrate excretion (350.73 ± 27.25 versus 304.15 ± 30.00 mg/d [1.67 ± 0.13 versus 1.45 ± 0.14 mmol/d];** $P < 0.02$**), but no alteration in fractional excretion of citrate (19.7% ± 2.7% versus 23.1% ± 2.4%;** $P > 0.05$**).** ***Conclusion:*** **Hypocitraturia was found to be a common risk factor associated with recurrent calcium stone formation and low urinary potassium level, low alkaline absorption, low urinary calcium level, and high titratable acid excretion. Hypocitraturia is predominantly of dietary origin. Estimation of fruit intake should be included in the metabolic evaluation for recurrent calcium stone formation.** ***Am J Kidney Dis*** **48:546-554.**

INDEX WORDS: Hypocitraturia; nephrolithiasis; potassium; alkaline absorption; calcium; titratable acid.

CITRATE IS A TRICARBOXYLIC acid normally excreted in urine. Urinary citrate acts as an inhibitor for calcium oxalate stone formation through several mechanisms. First, urinary citrate binds to urinary calcium, forming a soluble complex and decreasing available free ionic calcium for calcium oxalate stone formation.[1] Urinary citrate also interacts with calcium oxalate crystal as an inhibitor of crystal aggregation[2,3] and crystal growth.[4] Low urinary citrate excretion is a well-accepted risk factor for calcium stone formation.[5] Increased urinary citrate excretion in hypocitraturic calcium stone formers by means of alkaline therapy was recommended to decrease the risk for recurrent calcium stone formation.[6] The incidence of hypocitraturia among calcium stone formers from various studies varies from 20% to 60%.[6] Several causes of hypocitraturia were identified, including renal tubular acidosis,[7] chronic diarrhea and malabsorption,[8] metabolic acidosis,[9] potassium deficiency,[10] low intestinal alkaline absorption,[11] low urinary calcium level,[12] and low urine volume.[13] In addition, a diet rich in animal protein[14] or low in vegetable fiber[13] may be associated with hypocitraturia. Frequencies of these causes of hypocitraturia in calcium stone formers may vary among different populations. However, most previous studies tended to focus on each individual cause of hypocitraturia, rather than perform multifactorial analysis on the relative impact of these factors.[12]

A very high incidence of hypocitraturia was reported in the northeastern part of Thailand, ranging from 40% to 70%.[15,16] Hypocitraturia probably is the most common risk factor found in recurrent calcium stone formers. However, causes of hypocitraturia were never addressed systematically. Given a high incidence of hypocitraturia in our calcium stone formers, we therefore conducted this study to determine the relative influence of multiple associated risk factors for hy-

From the Departments of Medicine and Surgery and Research Center, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

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Address reprint requests to Somnuek Domrongkitchaiporn, MD, Department of Medicine, Ramathibodi Hospital, Mahidol University, Rama 6, Bangkok 10400, Thailand. E-mail: rasdr@mahidol.ac.th

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pocitraturia and show their causal relationships to hypocitraturia.

METHODS

Initial Evaluation

Subjects were enrolled from recurrent calcium stone formers attending the nephrolithiasis clinic for metabolic evaluation of underlying causes of recurrent stone formation between July 2002 and July 2003. All subjects were residents of the central part of Thailand and referred from either the Department of Surgery, Division of Urology, Ramathibodi Hospital, or nearby hospitals. Pediatric patients (<14 years) were excluded from this study. The diagnosis of recurrent stone formation was based on a history of at least 2 episodes of stone formation diagnosed by either spontaneous passing of stone or demonstration of new opaque stone on abdominal radiograph. Compositional analysis of renal stones was based on infrared spectroscopy of spontaneous passing stones, extracorporeal shock-wave lithotripsy, or surgical stone elimination. For episodes in which stones were not available for analysis, the diagnosis of calcium stone was based on abdominal radiograph and ultrasound examination. Patients with the following conditions were excluded from this study: staghorn calculi, failure to eliminate urinary tract infection before the study, impaired renal function (serum creatinine > 1.5 mg/dL [>132.6 μmol/L]), polycystic kidney disease, malformation of the urological system, chronic diarrhea, urinary tract obstruction, renal tubular acidosis, and other systemic diseases that might affect calcium and bone metabolism. Renal tubular acidosis was excluded if a patient could acidify his urine (urinary pH < 5.35) within 8 hours after 0.1 g/kg of ammonium chloride loading.[7] Patients administered medications that might have an effect on electrolyte, calcium, and phosphate levels and acid-base balance also were excluded from this study. If a subject underwent surgery or extracorporeal shock-wave lithotripsy for stone removal, the study was postponed for at least 2 months. One hundred two calcium stone formers attended our nephrolithiasis clinic. Nineteen patients were excluded, including 7 patients with renal tubular acidosis, 3 patients with polycystic kidney disease, 1 patient with medullary sponge kidney, 4 patients with staghorn calculi, 1 patient with single kidney, and 3 patients who failed to follow the study protocol. Only 83 patients, 44 men and 39 women, were eligible for this study. Mean age was 49.5 ± 1.4 years, and mean body weight was 62.7 ± 1.0 kg.

All subjects, following a free-choice diet, were instructed by trained staff to perform two 24-hour urinary collections. Urine samples were kept under mineral oil. Toluene also was added to the collecting vessel as a preservative. The entire urine sample was kept in a refrigerator during collection and transferred to our laboratory the same day the urine collection was completed. Bacterial cultures were performed for all urine samples. Urine samples with heavy bacterial contamination (>10^5 colonies/mL), incomplete collection, or improper specimen handling were discarded. If creatinine excretion was less than 80% of predicted creatinine excretion,[17] the urine collection was considered incomplete and discarded. Additional 24-hour urine collections were requested from subjects until properly collected samples were obtained. After the volume of each 24-hour collection was recorded, 2 aliquots of 60-mL urine samples were kept for further analysis. One aliquot was acidified and used for determination of citrate level. No acid was added initially to the collecting vessels to avoid interference with urinary titratable acid determination. If urine samples were handled according to our instruction, there was no significant difference in urinary citrate concentrations between samples acidified initially and samples acidified after complete collection (8% ± 1.1% difference between the 2 techniques). The following urinary constituents were determined: sodium, potassium, chloride, calcium, phosphate, magnesium, citrate, oxalate, urea, creatinine, ammonium, titratable acid, and net gastrointestinal alkaline absorption according to the formula:

$$(\text{Sodium} + \text{potassium} + \text{calcium} + \text{magnesium}) - (\text{chloride} + 1.8 \times \text{phosphate})$$

Electrolyte excretion is in milliequivalents per day, except for phosphate, expressed in millimoles per day with an average valence of 1.8.[18]

The average amount of each urine constituent from the 2 urine collections was used for further analysis. Serum samples for determination of electrolyte, creatinine, calcium, and phosphate levels were obtained at the time of urine collection. Control values in this study were obtained from 26 age-matched healthy volunteers, 10 men and 16 women, aged 47.1 ± 2.1 years, with a weight of 61.6 ± 2.1 kg, during the same period and using the same protocol.

Dietary Assessment

All subjects were interviewed for their diet by a research dietitian. Subjects, following a free-choice diet, performed 3-day dietary records after instruction and verification. Nutrients were calculated by using the INMUCAL (Mahidol University, Bangkok, Thailand) computer program.[19,20] The database for food composition analysis was based on a Thai food composition table developed by Mahidol University.

Subsequent Study

All subjects were invited to participate in a subsequent study to determine the effect of potassium chloride (KCl) supplement on urinary excretion of citrate. Fractional excretion of citrate (FE-citrate) was determined in this subgroup before starting KCl supplementation. After supplementation for 1 month of 40 mEq/d (mmol/d) of KCl in 2 divided doses, an additional two 24-hour urine collections and determination of FE-citrate were performed again, using the same protocol. Subjects were instructed to maintain the same pattern of dietary intake and activity throughout the study.

FE-citrate was determined after an overnight fast. In the morning, subjects were hydrated with 1 L of fluid before the beginning of the test. Next, a 2-hour urine collection (8:00 AM to 10:00 AM) for determination of creatinine and citrate levels was obtained. During the collection, additional fluid intake (0.5 to 1 L) was encouraged to all subjects. Any subject who excreted less than 200 mL of urine during the period was considered to have inadequate hydration, and an