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Laterality of nephrocalcinosis in kidney stone formers with severe hypocitraturia

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Abstract

OBJECTIVE—To examine the hypothesis that the distribution of nephrocalcinosis in patients with severe hypocitraturia should be symmetric.

PATIENTS AND METHODS—Patients with profound hypocitraturia defined as a 24-h urine citrate <50 mg at the time of initial presentation were identified from the metabolic stone clinic database at our academic medical center. Two independent blinded reviewers evaluated all of the abdominal radiographs for the segmental distribution of macroscopic nephrocalcinosis.

RESULTS—A total of 44 patients met study criteria, with an equal distribution of males and females and a mean age of 55.4 ± 13.7 years. Mean urinary citrate was 28 ± 11 mg/day. Nephrocalcinosis was present in at least one renal segment in 22 patients (50%). Of the 22 patients with nephrocalcinosis, 9 patients (41%) had unilateral nephrocalcinosis and 13 patients (59%) had bilateral nephrocalcinosis. Of the 35 kidneys with nephrocalcinosis, 14 kidneys (40%) had nephrocalcinosis in only one renal segment, 13 kidneys (37%) had nephrocalcinosis in two segments and eight kidneys (23%) had nephrocalcinosis involving all three segments.

CONCLUSIONS—Despite the systemic nature of severe hypocitraturia, nephrocalcinosis is frequently asymmetric and focal in nature. This suggests that local factors intrinsic to the renal medullary interstitium, such as vascular injury, must play a role in the formation of nephrocalcinosis. Further study to elucidate these intrinsic local factors may further improve the treatment and prevention of urinary stone disease.

Keywords

Nephrocalcinosis; hypocitraturia; nephrolithiasis; laterality

INTRODUCTION

While nephrolithiasis is the condition in which renal calculi are freely mobile in the renal collecting system, nephrocalcinosis is the deposition of calcium in the renal cortex or medulla before the opening of the ducts of Bellini into the renal collecting system [1].

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CONFLICT OF INTEREST

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Although these entities are closely related, one may form in the apparent absence of the other. Traditionally, nephrolithiasis and nephrocalcinosis have been thought to result from systemic conditions. Their formation depends upon both the delivery of minerals such as calcium, phosphate and oxalate, and local factors such as pH, osmolality, and the relative absence of a variety of inhibitory molecules and proteins [2]. Citrate is well known to be one such inhibitory molecule and, indeed, hypocitraturia is an established risk factor for nephrolithiasis [3,4]. One would hypothesize that systemic conditions that cause urinary calcification through alteration of the serum and urinary mineral environment should result in bilateral, symmetric, and diffuse calcification within the kidneys. In anecdotal clinical practice, however, such calcification is frequently unilateral and focal in nature. Indeed, it has been shown that among patients with the condition of cystinuria, up to 29% of patients require only unilateral intervention for stones [5]. In anecdotal clinical practice, however, such calcification is frequently unilateral and focal in nature. The current study was designed to examine the hypothesis that the distribution of nephrocalcinosis should be approximately symmetric.

PATIENTS AND METHODS

Patients with profound hypocitraturia defined as a 24-h urine citrate <50 mg at the time of initial presentation were identified in a database from the metabolic stone clinic at the University of California San Francisco. As a specialty clinic at a tertiary care referral center, almost all patients presented after their first symptomatic episode of nephrolithiasis. Patients with Type I distal renal tubular acidosis identified by a serum bicarbonate <20 mEq/L and urine pH > 5.3 were excluded from the study. Only patients with 24-h urinalysis data obtained as part of a metabolic stone evaluation and plain abdominal radiographs available for review were included in the study. All 24-h urinalyses were performed by Litholink (Chicago IL, USA). Other data including age, gender, past medical history, past surgical history and serum laboratory studies were extracted from patients' medical records when available.

Two independent reviewers (MLS and BHE) evaluated all of the abdominal radiographs for the presence of macroscopic nephrocalcinosis. Each reviewer was blinded to the other's diagnoses. A representative image of nephrocalcinosis is shown in Fig. 1. Kidneys were divided anatomically into three segments – upper pole, lower pole and interpolar – and the anatomic distribution of nephrocalcinosis was noted. Discrepancies between the two reviewers were resolved by consensus. Differences in mean 24-h urine values between patients with and without nephrocalcinosis were evaluated with the student's *t*-test.

RESULTS

The study database included 460 patients with initial metabolic evaluations between 2001 and 2008. A total of 44 patients met the study criteria. There was an even gender distribution with 50% of patients being male. Mean age was 55.4 ± 13.7 years. The characteristics of the patients' 24-h urinalyses are presented in Table 1. Normal values were provided by Litholink and are based upon their proprietary assays. These normal values are in accordance with generally accepted normal values [6]. The urine collections were adequate

24-h collections as shown by a mean 24-h urinary creatinine excretion of 1592 ± 539 mg for men and 1036 ± 402 mg for women.

Consistent with the selection criteria, mean 24-h urinary citrate was low at 28 ± 11 mg. In addition, mean 24-h urinary sodium and calcium were in the normal ranges at 130 ± 68 mmol and 103 ± 78 mg, respectively. Mean 24-h urine volume was also in the normal range at 1.8 ± 0.7 L. Mean 24-h urine oxalate was slightly elevated at 44 ± 24 mg. A comparison of the 24-h urinalyses of patients with and without nephrocalcinosis is presented in Table 2. No statistically significant differences were noted between patients with and without nephrocalcinosis. The mean supersaturations of calcium phosphate in both nephrocalcinosis formers and non-formers were both in the normal range (0.70 ± 0.63 and 0.56 ± 1.00 , respectively; normal 0.5–2.0). Although nephrocalcinosis formers had a higher mean supersaturation of calcium phosphate, this difference was not statistically significant with a *P* value of 0.580. The mean supersaturation of uric acid in nephrocalcinosis non-formers was in the abnormal range at 1.28 ± 0.96 compared with 0.91 ± 0.79 for nephrocalcinosis formers (normal 0–1). However, this difference was not statistically significant with a *P* value of 0.171.

The presence and distribution of nephrocalcinosis in the study population is presented in Table 3. Nephrocalcinosis was present in at least one renal segment in 22 of the 44 patients (50%) included in this study and in 64 of the 266 renal segments (24%) evaluated. Of the 22 patients with nephrocalcinosis, 9 patients (41%) had unilateral nephrocalcinosis and 13 patients (59%) had bilateral nephrocalcinosis. Of the 35 kidneys with nephrocalcinosis, 14 kidneys (40%) had nephrocalcinosis in only one renal segment, 13 kidneys (37%) had nephrocalcinosis in two segments, and only 8 kidneys (23%) had nephrocalcinosis involving all three segments. On a population basis, the overall distribution of nephrocalcinosis was symmetric with equal numbers of left and right renal units being affected by nephrocalcinosis.

DISCUSSION

Nephrocalcinosis, which may be routinely diagnosed through abdominal imaging, can result in relatively frequent referrals to the urologist from primary care physicians and emergency room physicians for urinary stone disease. Nephrocalcinosis, however, is not synonymous with nephrolithiasis, which can produce the symptoms of renal colic because of partial or complete obstruction of the urinary tract. Nephrocalcinosis has been associated with multiple renal tubular disorders such as distal renal tubular acidosis and diuretic-induced hypercalciuria [2]. Although no studies have been able to identify a causal link between the two, conditions that result in nephrocalcinosis frequently also result in nephrolithiasis. Because of this association, nephrocalcinosis could perhaps be considered a precursor to the more symptomatic condition of nephrolithiasis. A true understanding of the mechanism for the development of this precursor condition has not been elucidated.

Citrate is one well-known inhibitor of the crystallization of calcium salts, and hypocitraturia is a known risk factor for nephrolithiasis [4]. Causes of hypocitraturia are systemic in nature and include distal renal tubular acidosis, metabolic acidosis, such as that secondary to

chronic diarrhea, high acid-ash diet and diuretic-induced hypokalemia [7]. These systemic disorders theoretically should affect kidneys bilaterally and symmetrically. Despite the fact that nephrocalcinosis is thought to be caused by systemic processes, a significant proportion of the patients demonstrating nephrocalcinosis in this study had only unilateral involvement. Furthermore, the segmental distribution within affected kidneys varied greatly. This suggests that nephrocalcinosis is commonly asymmetric both between and within renal units and is consistent with anecdotal clinical practice in which patients frequently present with stones only on one side. Therefore, despite the systemic nature of hypocitraturia, local etiological factors may be responsible for the laterality and asymmetry of renal calcifications.

The nature of the cellular events that result in nephrocalcinosis and nephrolithiasis have not been precisely delineated. Various sites within the renal parenchyma may have distinct precipitating factors leading to calcification. Several theories implicate epithelial crystal adhesion, tubular obstruction, and/or vascular obstruction of the vasa recta as the initiating events in the development of urinary calcifications [8]. Proposed mechanisms for the specific development of nephrocalcinosis in the medullary interstitium include *de novo* crystal deposition and translocation of intratubular crystals through transcytosis or epithelial overgrowth [9]. More broadly, commonalities between the processes of osseous and extra-osseous vascular calcifications have been identified [10]. These extra-osseous vascular processes may, in many respects, be similar to the etiology of renal calcifications such as nephrocalcinosis.

Indeed, one possible explanation for the asymmetry of nephrocalcinosis lies in a potential vascular etiology [11]. The tips of the renal papillae lie in a hypoxic and hyperosmolar environment where the blood supply from the descending vasa recta repeatedly branches into capillary plexuses [12]. The resulting hypoxic and turbulent flow may predispose these vascular structures to injury. Epidemiological data do show increased rates of both atherosclerosis and nephrolithiasis in affluent countries [13], suggesting that an atherosclerosis-like reaction associated with diet and lifestyle can lead to renal calcification. In addition, factors such as differential renal and segmental perfusion may also contribute to the asymmetry of nephrocalcinosis. Nuclear scintigraphy studies by Schwartz, *et al.* have demonstrated that body position affects renal perfusion [14] and, correspondingly, 76% of patients are found to form stones on the side that is dependent during sleep [15]. This suggests that stone development may be accelerated by vascular injury owing to hyperfiltration much the same way hypertension accelerates atherosclerosis.

Under stress conditions such as neonatal prematurity and renal transplantation, renal tubular epithelium is known to express crystal-binding molecules not present in intact epithelium. These conditions are associated with ischemia and reperfusion injury [16,17] as well as nephrotoxic drugs such as cyclosporine [18]. Multiple molecules have been implicated as crystal-binders including hyaluronic acid, osteopontin [19,20], sialic acid-containing proteins [21], nucleolin-related protein [22], annexin A2 [23] and phosphatidylserine [24]. The upregulation of these molecules through vascular injury may be a contributing factor in the cascade toward the formation of renal calcifications and may provide a link between systemic disorders and the formation of asymmetric nephrocalcinosis.

To our knowledge, no other studies have examined the laterality of nephrocalcinosis, although this study is not without its limitations. It was a retrospective study that involved a relatively small sample size. While visually significant macroscopic differences between renal units were noted, this study was limited by the sensitivity of plain radiographic films. This study evaluated only the presence and not the severity of renal calcifications. It is possible that, given more time, many of these patients might have developed bilateral and symmetric nephrocalcinosis. However, the fact that patients generally presented to the stone clinic after their first symptomatic collecting system stone argues that these patients were not in an early stage of urinary stone development. In addition, the slightly elevated mean calcium phosphate supersaturation in nephrocalcinosis formers indicates a potential predisposition to calcium phosphate stone formation. It has been suggested that calcium phosphate may provide the nucleus for subsequent stone growth of any composition and therefore may predispose a patient to nephrocalcinosis. If this condition were present, this would suggest a potential physiological difference in mineral metabolism between nephrocalcinosis formers and non-formers [25–27]. However, in this study, the difference in mean supersaturation of calcium phosphate between nephrocalcinosis formers and non-formers was not statistically significant.

Despite these limitations, this study demonstrates that the asymmetry of nephrocalcinosis is not uncommon. Although metabolic disorders such as hypocitraturia are appropriately thought of as systemic problems, this study provides further evidence for the critical role that other local factors must play in the development of nephrocalcinosis. These factors may include vascular injury owing to hypoperfusion or hyperperfusion leading to the induction of stress-induced crystal-binding molecules. Indeed, these local factors may contribute to the progression of nephrocalcinosis within the renal parenchyma to the Randall's plaques attached to renal papillae frequently seen on ureteroscopy. Further study of the causative mechanisms of nephrocalcinosis that can account for its relatively frequent asymmetry is needed and may provide further insight into the formation of urinary calculi beyond the current theories of disordered urinary milieu.

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What's known on the subject? and What does the study add?

Systemic urinary stone-forming conditions such as hypocitraturia or cystinuria should theoretically lead to symmetric and diffuse stone formation. Small studies have shown that some patients with such conditions produce stones primarily on one side. No studies, however, have attempted to quantify the frequency at which such patients form stones asymmetrically.

This study demonstrates that despite having a severe systemic condition such as hypocitraturia, patients frequently have asymmetric and focal nephrocalcinosis. This suggests that additional intrinsic local factors such as renal perfusion or vascular injury must also play a role in stone formation.

FIG. 1.
Representative plain abdominal radiograph demonstrating asymmetric nephrocalcinosis.

TABLE 1

The 24-h urine composition in patients with severe hypocitraturia

	Men	Women	Overall	Normal
Volume (L/day)	1.7 ± 0.9	1.8 ± 0.6	1.8 ± 0.7	0.5–4.0
Calcium (mg/day)	111 ± 82	96 ± 68	103 ± 78	Male <250, female <200
Citrate (mg/day)	26 ± 13	30 ± 10	28 ± 11	Male >450, female >550
Creatinine (mg/day)	1592 ± 539	1036 ± 402	1302 ± 545	
Magnesium (g/day)	88 ± 43	75 ± 36	81 ± 40	30–120
Oxalate (mg/day)	46 ± 25	42 ± 24	44 ± 24	20–40
pH	5.8 ± 0.6	6.0 ± 0.9	5.9 ± 0.8	5.8–6.2
Phosphorus (g/day)	0.9 ± 0.3	0.7 ± 0.3	0.8 ± 0.3	0.6–1.2
Potassium (mmol/day)	59 ± 33	48 ± 31	54 ± 32	20–100
Sodium (mmol/day)	131 ± 75	128 ± 63	130 ± 68	50–150
Sulfate (mg/day)	38 ± 15	33 ± 18	35 ± 16	20–80
Uric acid (g/day)	0.58 ± 0.18	0.53 ± 0.22	0.6 ± 0.2	Male <0.80, female <0.75

TABLE 2

The 24-h urine composition in patients with and without nephrocalcinosis

	Nephrocalcinosis present	Nephrocalcinosis absent	<i>P</i>
Volume (L/day)	1.8 ± 0.7	1.8 ± 0.7	0.839
pH	6.2 ± 1.0	5.7 ± 0.5	0.059
Citrate (mg/day)	28 ± 12	29 ± 11	0.811
Sodium (mmol/day)	133 ± 54	144 ± 80	0.602
Calcium (mg/day)	120 ± 76	80 ± 66	0.085
Uric acid (g/day)	0.54 ± 0.18	0.55 ± 0.21	0.928
Oxalate (mg/day)	44 ± 24	49 ± 26	0.484
Potassium (mmol/day)	60 ± 35	47 ± 25	0.167
Phosphorus (g/day)	0.8 ± 0.3	0.8 ± 0.3	0.574
Magnesium (g/day)	87 ± 36	77 ± 43	0.390
Sulfate (mg/day)	34 ± 17	37 ± 17	0.623
Creatinine (mg/day)	1310 ± 625	1310 ± 400	0.997
SS* Calcium oxalate	5.9 ± 3.8	5.7 ± 6.7	0.897
SS* Calcium phosphate	0.70 ± 0.63	0.56 ± 1.00	0.580
SS* Uric acid	0.91 ± 0.79	1.28 ± 0.96	0.171

* SS, supersaturation.

TABLE 3

Distribution of nephrocalcinosis in patients with severe hypocitraturia

	<i>n</i> (%)
Nephrocalcinosis present	22 (50%)
Nephrocalcinosis absent	22 (50%)
Total patients	44 (100%)
Unilateral nephrocalcinosis	9 (41%)
Bilateral nephrocalcinosis	13 (59%)
Total patients with nephrocalcinosis	22 (100%)
One segment nephrocalcinosis	14 (40%)
Two segment nephrocalcinosis	13 (37%)
Three segment nephrocalcinosis	8 (23%)
Total renal units	35 (100%)