Impact of Long-Term Potassium Citrate Therapy on Urinary Profiles and Recurrent Stone Formation

Marnie R. Robinson, Victor A. Leitao, George E. Haleblian, Charles D. Scales, Jr.,* Aravind Chandrashekar, Sean A. Pierre and Glenn M. Preminger†

From the Comprehensive Kidney Stone Center, Division of Urologic Surgery, Duke University Medical Center, Durham, North Carolina

Purpose: Potassium citrate therapy has become one of the cornerstones of medical stone management. We elucidated the long-term effects of potassium citrate on urinary metabolic profiles and its impact on stone formation rates.

Materials and Methods: We performed a retrospective cohort study in patients treated at the Comprehensive Kidney Stone Center at our institution between 2000 and 2006. Patients with pre-therapy and post-therapy 24-hour urinary profiles available who remained on potassium citrate for at least 6 months were included in the analysis.

Results: Of the 1,480 patients with 24-hour urinary profiles 503 met study inclusion criteria. Mean therapy duration was 41 months (range 6 to 168). Overall a significant and durable change in urinary metabolic profiles was noted as soon as 6 months after the onset of therapy. These changes included increased urinary pH (5.90 to 6.46, $p < 0.0001$) and increased urinary citrate (470 to 700 mg a day, $p < 0.0001$). The stone formation rate also significantly decreased after the initiation of potassium citrate from 1.89 to 0.46 stones per year ($p < 0.0001$). There was a 68% remission rate and a 93% decrease in the stone formation rate.

Conclusions: Potassium citrate provides a significant alkali and citraturic response during short-term and long-term therapy with the change in urinary metabolic profiles sustained as long as 14 years of treatment. Moreover, long-term potassium citrate significantly decreases the stone formation rate, confirming its usefulness in patients with recurrent nephrolithiasis.

Key Words: kidney, nephrolithiasis, metabolism, potassium citrate, recurrence

Abbreviations and Acronyms

CT = computerized tomography

KCit = potassium citrate

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† Correspondence: Division of Urologic Surgery, Box 3167, Room 1572D White Zone, Duke University Medical Center, Durham, North Carolina 27710 (telephone: 919-681-5506; FAX: 919-681-5507; e-mail: glenn.preminger@duke.edu).

POTASSIUM citrate is an oral alkalinizing agent that has been used for more than 25 years in patients with nephrolithiasis. While previous studies, including randomized, controlled trials, have confirmed the effectiveness of this medication, there are sparse data on the impact of KCit during a prolonged duration of treatment. Therefore, we retrospectively evaluated the long-term effects of KCit monotherapy as well as KCit combination therapy on urinary metabolic profiles in stone formers seen at our institution. We also investigated the long-term and durable effects of KCit therapy on the stone formation rate in these patients. We hypothesized that KCit would have significant effects on urinary metabolic profiles and decrease the stone formation rate during short-term and long-term use.

METHODS

We retrospectively reviewed the Comprehensive Kidney Stone Center database at our institution. All patients who were evaluated at the center at least once be-

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tween 2000 and 2006 were identified. From those individuals we identified a cohort of patients who underwent initial urinary metabolic evaluation, were initiated on KCit therapy, were on the medication at least 6 months and had subsequent 24-hour urinary metabolic profiles available. Patients with renal tubular acidosis or cystinuria were excluded from analysis. Urinary metabolic profiles consisted of a 24-hour urinary collection that was measured for total volume, pH, calcium, magnesium, phosphorus, sodium, potassium, creatinine, uric acid, oxalate and citrate. Demographic information on each patient was collected, including age at last visit, gender and race. In addition, the daily dose of KCit, duration of KCit treatment, urinary metabolic abnormalities and additional medications that alter urinary metabolic profiles were collected from the medical record.

It should be noted that patients were provided with general recommendations to decrease stone formation. All patients were counseled to increase the fluid intake to 3 l per day (which translates to 2 l urine), maintain a low salt diet and have a moderate red meat and calcium intake. Based on their metabolic profile some patients were provided with additional recommendations, such as decreasing dietary oxalate in those with hyperoxaluria.

Of the overall study population 50% were chosen by selecting patients with the medical record numbers in the earlier portion of the alphabet to be included in subset analysis of the stone formation rate before and after the

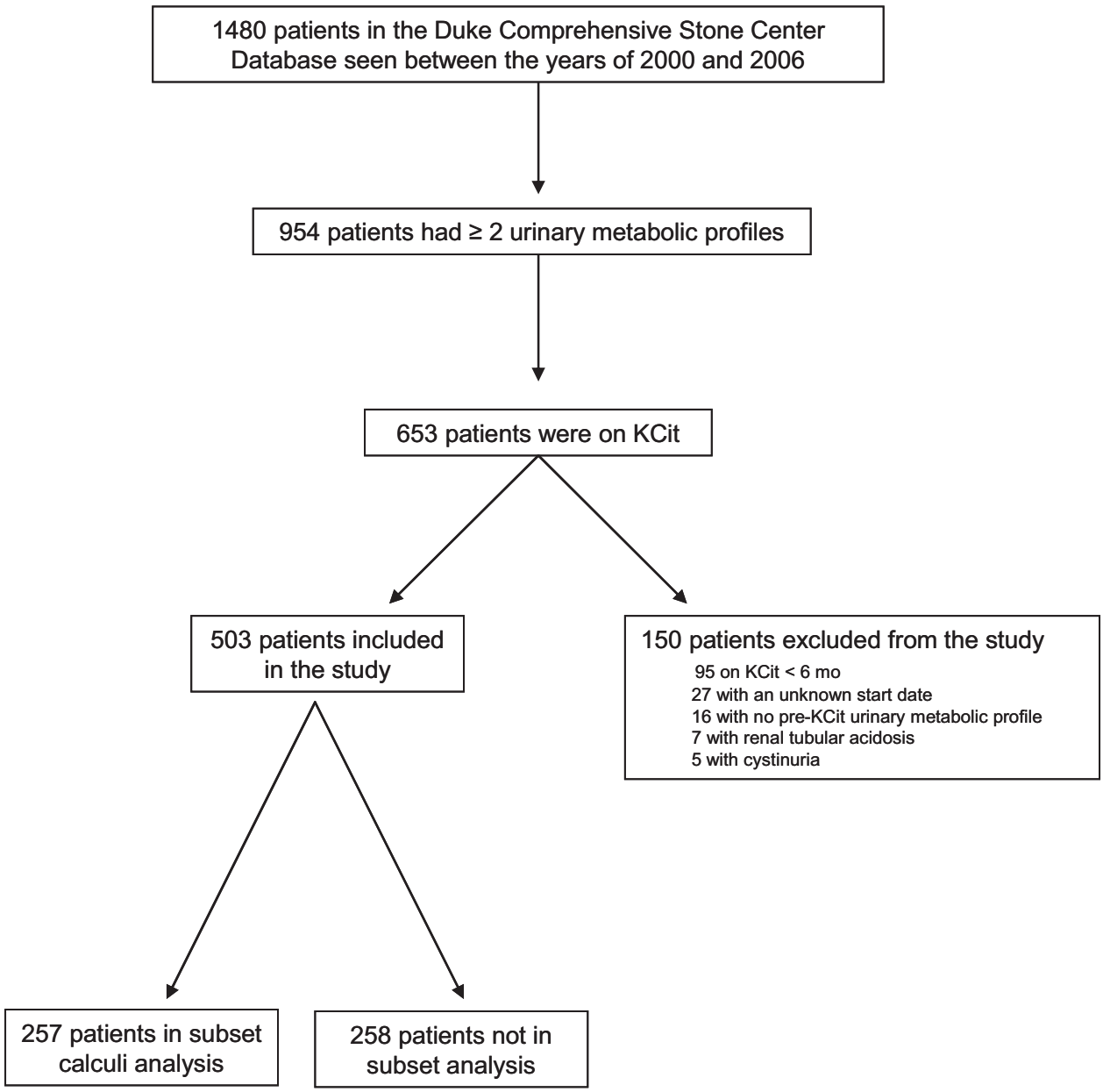

Figure 1

Table 1. *Study population demographics*

	Overall	KCit
No. pts	503	269
% Male	62%	62%
Av ± SD age	55.6 ± 14.9	55.4 ± 15.5
Metabolic abnormalities:		
Av ± SD No.	2.4 ± 0.8	2.2 ± 0.8
% Hypocitraturia	75	80
% Low urine vol	61	66
% Hypercalciuria	45	25
% Gouty diathesis	40	39
% Hyperuricosuria	12	7
% Hyperoxaluria	4	2
% Other	2	2

initiation of KCit therapy. The number of new stones formed or the growth of existing stones per patient per year was used to calculate the stone formation rate. The number of new stones formed was determined by combining the stone passage rate according to the patient history with documentation of existing stone growth or new stone formation by a care review of baseline and followup imaging, including tomography and noncontrast renal CT. Pre-KCit and post-KCit urinary metabolic profiles in patients in this subset analysis with accurate stone composition data available were compared. Additional subset analysis was performed in patients who were only on KCit for medical management for urinary stone disease, eliminating patients who were on other medications that affect the urinary metabolic profile. All of these subset analyses were designated as post hoc analyses.

Statistical analysis was performed using SAS®, version 9.1. Significant changes between pre-KCit and post-KCit urinary metabolic profiles were identified by the paired t test. The unpaired t test was used to determine significant changes in urinary metabolic profiles between patient subsets. The Pearson correlation was used to determine the association of the change in urinary pH and the change in urinary citrate. Two-sided testing was done with a prespecified α of 0.05. No explicit correction was performed for multiple analyses. This study was performed with approval of the Duke University Medical Center internal review board.

RESULTS

We reviewed a total of 5,348 urinary metabolic profiles in 1,480 patients in the Comprehensive Kidney Stone Center database at our institution. Of the patients 954 had 2 or more urinary metabolic profiles available, of whom 653 were placed on KCit medical therapy. A total of 150 patients were excluded from analysis because 95 were on the medication for less than 6 months, 43 had an unknown start date or did not have a pre-KCit urinary metabolic profile available, 7 were diagnosed with renal tubular acidosis and 5 were diagnosed with cystinuria. A total of 503 patients were included in the study cohort (fig. 1).

The patient population was 62% male and 38% female with an average ± SD age of 55.6 ± 15 years (range 10 to 87). Each patient had an average of 2.4 ± 0.8 metabolic abnormalities on the baseline metabolic profile. In patients initiated on KCit therapy the most common diagnoses were hypocitraturia, low urine volume, hypercalciuria and gouty diathesis (table 1). Metabolic abnormalities included in the other category were urinary diversion and enteric hyperoxaluria. The median dose of KCit was 20 mEq twice daily. Average treatment duration was 40.6 ± 31.1 months (range 6 to 168). Of the patients 40% were on 1 additional medication that affects urinary metabolic profiles, while 7% were on 2 additional medications. In 37% and 10% of cases these medications were thiazide and allopurinol, respectively.

Citrate therapy had a significant alkalinizing effect (table 2). Urinary pH increased significantly from 5.89 ± 0.49 to 6.46 ± 0.55 ($p < 0.0001$, table 2). Urinary citrate also increased significantly from 470 ± 329 to 700 ± 380 mg per day ($p < 0.0001$, table 2). As expected, urinary potassium was also significantly increased after the initiation of KCit therapy (52 ± 23 to 84 ± 34 mEq per day, $p < 0.0001$). This change was also durable during the course of KCit therapy. A positive association between the change in urinary pH and change in urinary citrate was noted ($r = 0.24636$, $p < 0.001$, fig. 2). An increase in urinary pH after the initiation of KCit was seen in 82% of patients, whereas 16% had a decrease and 2% had no change in urinary pH. When patients were subdivided by the duration of KCit therapy, urinary pH and urinary citrate became and remained significantly increased for all of the various treatment durations (fig. 3).

KCit therapy resulted in a significant decrease in the stone formation rate from 1.89 to 0.46 stones per year ($p < 0.0001$). Complete remission of stone formation, defined as no stone activity (new stones or stone growth) during followup, occurred in 68% of this subset of patients. There was a decrease in the

Table 2. *Urinary metabolic parameters before and after KCit therapy*

	Before KCit	After KCit	p Value
Total vol (ml)	1,766	2,189	<0.0001
pH	5.89	6.46	<0.0001
Calcium (mg/day)	207	180	<0.0001
Magnesium (mg/day)	97	97	0.57
Phosphorus (mg/day)	948	997	0.045
Sodium (mg/day)	167	198	<0.0001
Potassium (mg/day)	52	84	<0.0001
Creatinine (mg/day)	1,525	1,554	0.17
Uric acid (mg/day)	534	587	<0.0001
Oxalate (mg/day)	32	38	<0.0001
Citrate (mg/day)	470	700	<0.0001

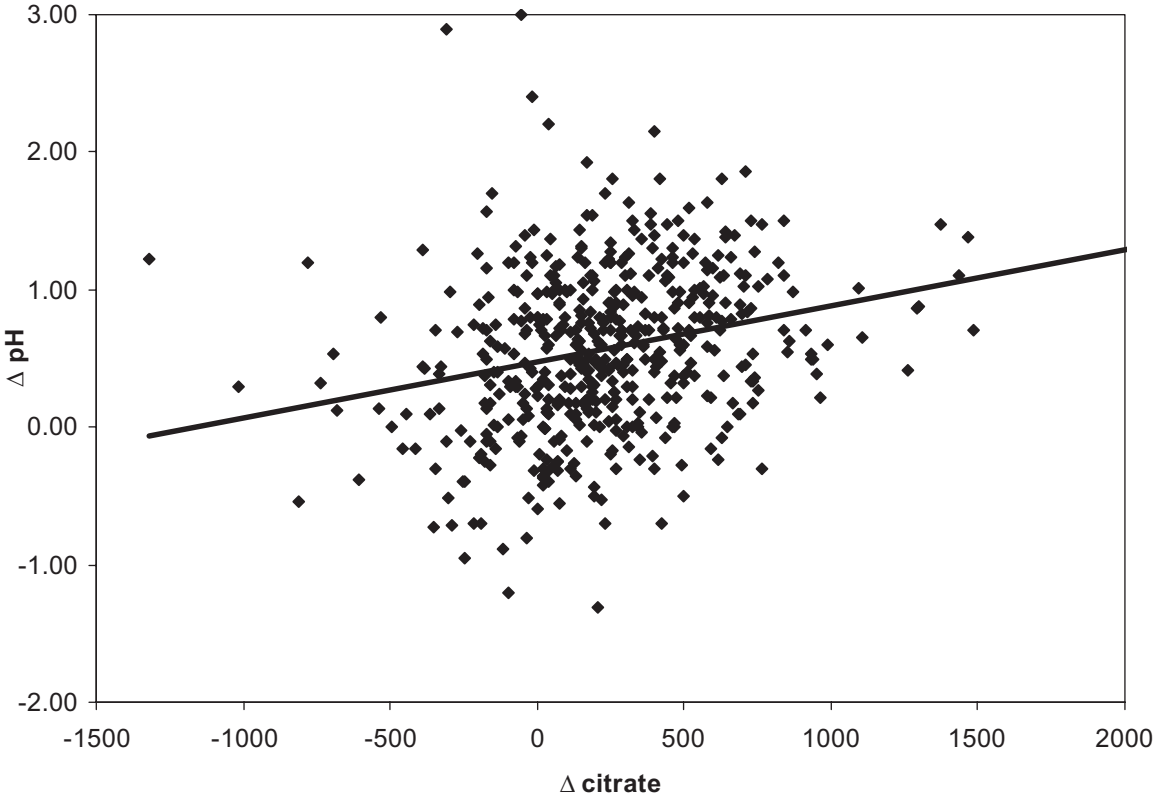

Figure 2. Change in urinary citrate vs change in urinary pH

stone formation rate in 93% of this patient population, while only 2% had no change in the stone formation rate. Table 3 lists metabolic abnormalities in patients with a complete response to KCit, defined as the complete remission of stone formation, and patients who did not have a complete response to KCit, defined as continued stone formation.

Patients who were placed on KCit as the only medication for urinary stone disease were analyzed as a separate subgroup to determine whether KCit alone without the potential additive effects of other medication could still have a long-term durable effect on the urinary metabolic profile. This group comprised 264 patients and baseline demographics were the same as in the original group except for fewer metabolic abnormalities per patient (table 1). Urinary metabolic profiles and stone formation rates mirrored those in the overall study population with statistically significant increases in urinary pH, urinary citrate and urinary potassium, and a similar decrease in the stone formation rate (tables 4 and 5).

DISCUSSION

KCit has been a mainstay of medical stone management for more than 25 years. The primary mechanisms of action are to increase the solubility of stone forming salts and increase inhibitor activity against calcium oxalate and calcium phosphate stones. It is well-known that this medication causes an increase in urinary pH and urinary citrate.[1] It has also been shown to result in a decreased stone formation rate.[2,3] However, the question has been raised as to whether this effect is truly durable in the long term or whether there is a potential decrease in effectiveness of this therapy with time, as has been seen for thiazide diuretics.[4]

We noted a durable response up to 14 years after the initiation of KCit therapy for urinary lithiasis. There was no degradation of the effect of KCit, as has been seen with thiazides, which can be associated with a certain degree of tolerance with prolonged treatment.[4] There was a statistically significant correlation between the increases in urinary citrate and urinary pH in the entire study population and in the subgroup in which KCit was the only medication for medical stone management. Previously groups have reported a similar mean followup but in significantly smaller study populations.[3,5,6] As urinary pH increases, there is enhanced renal citrate production and increased tubular reabsorption of citrate, thereby increasing the inhibitor activity of citrate to decrease calcium based and uric acid calculi.

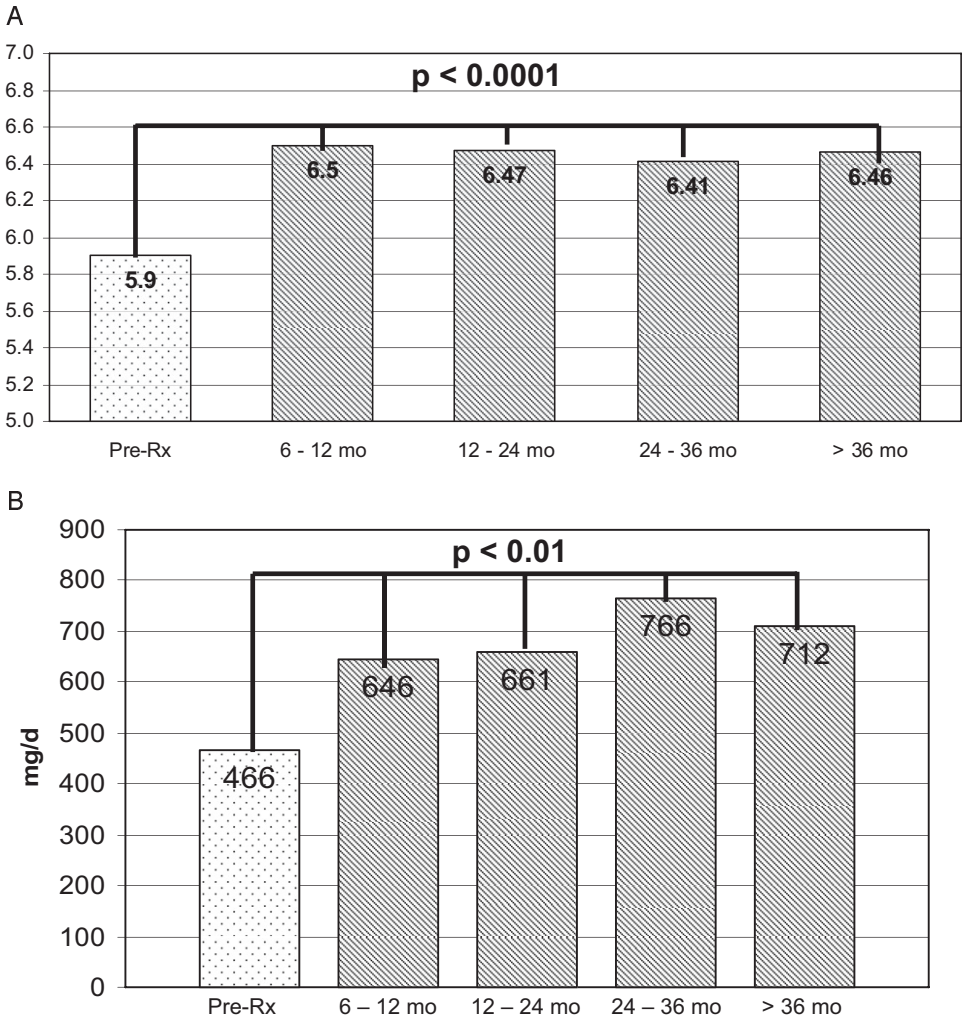

Figure 3. Change according to KCit therapy (*Rx*) duration. *A*, urinary pH. *B*, urinary citrate

The current study also confirms previous investigations demonstrating that many recurrent stone formers have more than 1 metabolic abnormality.[7] Therefore, a multimodality approach to stone disease with multiple medications, lifestyle changes and dietary changes may be required. Our results support the conclusion that even in patients with multiple etiologies of stone disease the initiation of KCit therapy can effectively decrease the stone formation rate when used with other medications and diet/lifestyle modifications.

Baseline and posttreatment stone formation rates are slightly higher than in other reported studies.[2,3,5] This finding may reflect the fact that many patients seen at our center are referred specifically

Table 3. *Metabolic diagnoses in patients in vs not in complete stone remission*

	No. Remission (%)	
	Complete	None
Gouty diathesis	84 (49)	28 (36)
Hypercalciuria	77 (45)	36 (47)
Hypocitraturia	123 (72)	61 (79)
Low urinary vol	103 (60)	56 (72)
Hyperuricosuria	19 (11)	13 (17)

Table 4. *Urinary metabolic profile in 269 patients only on KCit*

	Before KCit	After KCit	p Value
Total vol (ml)	1,707	2,132	<0.0001
pH	5.93	6.40	<0.0001
Calcium (mg/day)	173	171	0.84
Magnesium (mg/day)	91	90	0.53
Phosphorus (mg/day)	886	924	0.11
Sodium (mg/day)	159	179	<0.001
Potassium (mg/day)	50	79	<0.0001
Creatinine (mg/day)	1,496	1,531	0.26
Uric acid (mg/day)	520	582	<0.001
Oxalate (mg/day)	31	36	<0.0001
Citrate (mg/day)	435	711	<0.0001

Table 5. *Stone formation in 134 patients only on KCit*

	Before KCit	After KCit
Stone formation rate change	1.22	0.19*
% Remission		72
% Decrease		94
% No change		2
% Increase		4

* Vs before KCit $p < 0.0001$.

because of difficult medical management of recurrent urinary stone disease. As a result, patients with more significant metabolic abnormalities may be over represented in this patient population. Moreover, since 73% of patients had preexisting stones on imaging at the initiation of medical therapy, it was occasionally difficult to discern whether any stone activity represented the passage of preexisting or newly formed renal calculi. Thus, many stones that were spontaneously passed may have been fragments of the initial stone for which the patients had received intervention. Therefore, the true remission rate may actually be higher than our reported value of 68%.

Our study has several limitations. Most patients entering the study were not stone-free at the initial assessment, which makes the accurate determination of new stone formation or stone growth challenging. Furthermore, during the study course stone protocol CT technology for stone surveillance became more widely used at our institution. The increased sensitivity of stone protocol CT for detecting small stones compared to that of traditional excretory urography or plain x-ray of the kidneys, ureters and bladder, and tomography, may have biased the current results to higher stone recurrence. Small renal calculi that may not have been visible on plain x-ray of the kidneys, ureters and bladder could be easily identified on CT.

The retrospective nature of this study may have introduced a selection bias whereby patients who had recurrent stones may not have returned for further evaluation, thereby biasing in favor of those who had a favorable response to treatment. However, the durable increase in urinary potassium suggests continued compliance with medication, although patients who continued to attend the metabolic clinic were likely those who were most compliant.

Despite these limitations our results are buttressed by several factors, including a long followup and a large patient population. However, it is clear that KCit therapy is a durable and reliable therapy for correcting many metabolic abnormalities that contribute to stone formation. With time and in a large cohort of patients the complete response rate remained high and the stone formation rate remained low.

CONCLUSIONS

KCit therapy provides a significant and durable long-term alkali and citraturic response. Improvements in 24-hour urinary profiles are sustained for as long as 14 years of treatment. No degradation with time in the effect of KCit was found, as has been seen with thiazide diuretics. Moreover, long-term KCit therapy contributes to a significant decrease in the stone formation rate. KCit therapy appears to be an effective option for long-term treatment in many patients with recurrent calcium nephrolithiasis.

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