Original Article

24 Hours Urinary Citrate Deficiency (Hypocitraturia) in Recurrent Renal Stone Formers

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ABSTRACT

Objective: Nephrolithiasis is a common disorder and a significant number of recurrent renal stone formers have urinary citrate deficiency (hypocitraturia), which is a known risk factor for nephrolithiasis. The objective of present study was to determine the frequency of urinary citrate deficiency (hypocitraturia) in recurrent stone formers, so this knowledge can help to formulate stone preventive strategies.

Study Design: Retrospective study

Place and Duration of Study: This study was conducted at the Multan Institute of Kidney Diseases (MIKD) from 1st August, 2016 to May, 2019.

Materials and Methods: The study included 112 suitable adult patients of both genders. Those patients who had recurrent renal stones (at least two times) within last two years were included in the study. The patients' demographics, family history, history of stone passage and type of intervention for stones, stone composition and 24-hour urine volume were recorded. The 24 hour urinary citrates estimated and the differences in the citrate levels between genders, age groups, positive family history of nephrolithiasis, were analyzed.

Results: There were 96 male and 16 female patients. Family history of renal stones was present in 37(33%) patients. The mean 24 hours urinary volume was 1617.49 ±822ml and 92 (82.14%) patients had a lower 24-hour urine volume (i.e. less than 2 liters). The mean 24 hours urinary citrate was 277.26 ±173.37 mg and it ranged from 68mg to 1152mg. The female patients had lower mean urinary citrates than male patients [222.93±150.62 mg vs 286.32±175.94 mg: p=0.177) and there was no significant difference of age on citrate levels. The patients with family history of renal stones had lower 24 hour urinary citrates and were of relatively younger age.

Conclusion: The present study revealed a high frequency of hypocitraturia in recurrent renal stone formers. However, no statistically significant differences in the frequency of hypocitraturia were observed in both genders and age groups. Patients with positive family history of nephrolithiasis had lower urinary citrate levels. This knowledge of high frequency of hypocitraturia can help in formulating stone preventive strategies.

Key Words: Nephrolithiasis, Hypocitraturia, Renal stones, Citrate, Calcium

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INTRODUCTION

The prevalence of kidney stones has been rising throughout developed and underdeveloped countries[1]. Recurrence of renal stones continues to remain a significant clinical problem, because of its associated acute and chronic morbidity.

The stone formers are more likely to have urinary metabolic abnormalities than healthy population[2] . The patients need a thorough metabolic evaluation in order to identify possible risk factors responsible for or contributing towards stone formation. The patient may have either an individual abnormality or it may be present in conjunction of other abnormalities. Both EAU guidelines[3] and American Urological Association's guidelines[4] recommend metabolic evaluation in high risk individuals to identify altered urinary factors that could be corrected with specific treatment. Following these guidelines, an increasing trend in the frequency of 24-hour urine collection for urine chemistry is being observed.

Urinary citrates are considered potent inhibitors of calcium oxalate and phosphate stones. In renal stone formers, citrate deficiency (hypocitraturia) is common. Citrates inhibit the nucleation of calcium oxalates (Ca Ox), crystal aggregation and growth[5]. In addition, it increases the stone inhibiting activity of other urine macromolecules (e.g. Tamm-Horsfall protein). Urinary citrate levels vary with respect to gender and age. Despite noting gender differences, Resnick and Pak[6] defined normal 24 hour urinary citrate as greater than 320mg for both genders. Urinary citrate value less than

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100mg per day is called severe hypocitraturia and patients with urinary citrates between 100 to 320mg per day are considered to have mild to moderate hypocitraturia.

The review of literature clearly indicates differences in the reported frequency of hypocitraturia in stone formers in different countries. There is limited data on the frequency of hypocitraturia in recurrent stone formers from the stone prevalent region of Pakistan. The objective of present study was to determine the frequency of urinary citrate deficiency (hypocitraturia) in recurrent stone formers, and this knowledge can help to formulate stone preventive strategies.

MATERIALS AND METHODS

This retrospective study was carried out at the Multan Institute of Kidney Diseases (MIKD) from 1st August, 2016 to May, 2019. The adult patients of both genders, aged 18 years to 60 years were included in the study if they had recurrent (at least two times) renal stones passed per urethra, or had undergone open or minimally invasive surgery or shockwave lithotripsy within the last 2 years. Patients with chronic kidney disease, diabetes mellitus, hypertension, those on medication with potential effect on urine chemistry or having urinary tract infection or renal tract abnormality were excluded. The permission for study was granted by the Institution's Head of Campus to use the ethically collected data for retrospective study. Well informed consent of all study patients had already been obtained by the Institute where the Institute was allowed to the use of clinical data for research and presentation. So, no repeat informed consent of study patients was deemed necessary. One hundred twelve patients were found suitable to be included in the study.

The patients demographics, family history, stone location (unilateral or bilateral), history of stone passage and type of intervention for stones, stone composition and 24-hour urine volume was recorded. All patients had 24 hour urinary citrates estimated from the same laboratory, which used the same method for citrate estimation as described by Mollering et al[19] and reported a normal reference value of 24 hour urine citrate >320mg.

The statistical analysis of data was performed by using SPSS software (Statistical Package for Social Sciences, version 20, SPSS Inc, Chicago, IL, USA). Frequency tables were generated to depict differences in gender, hypocitraturia, side and family history of renal stones. The descriptive statistics were applied to calculate mean age, urinary volume and urinary citrates along with their standard deviation. By applying independent sample *t* test, differences in urinary citrate levels between genders, positive family history of renal stones and unilateral or bilateral renal stones were calculated. The patients were divided in to different age groups (*i.e.* 18 to 30 years, 31-40 years, 41 to 50 years and more than 50 years) and the effect of age on urinary citrate excretion at different age groups was calculated by applying ANOVA test at 95 % confidence interval. Hypocitraturia was distributed with regards to gender, family history of renal stones and side of stone after applying chi-square test and *p* value equal/less than 0.005 was taken as statistically significant.

RESULTS

One hundred and twelve patients with recurrent renal stones were included in the study. There were 96 (86.7%) male and 16 (14.2%) female patients. The age range of study patients was 18 to 60 years. The mean age of male and female patients was 33.46 (± 10.30) and 29.63 (±12.64) years respectively. Family history of renal stones was present in 37 (33%) patients. Most patients (67.8%) had bilateral renal stones.

The mean 24 hours urinary volume was 1617.49±822ml and ranged between 400ml to 5200ml and 92 (82.14%) of patients had a lower 24-hour urine volume (*i.e.* less than 2 liters).

The mean 24 hours urinary citrate was 277.26 ±173.37 mg and it ranged from 68mg to 1152mg.

Hypocitraturia was noted in 78 (69.64%) patients and its distribution is given in Table (1).

Table No.1: Distribution of hypocirtaturia with regards to different study variables.

Study variable		Hypocitraturia		P value
		Yes	No	
Gender	Male (n=96)	64	32	0.141
	Female (n=16)	14	02	
Family History	Yes (n = 37)	29	08	0.193
	No (n = 75)	49	26	

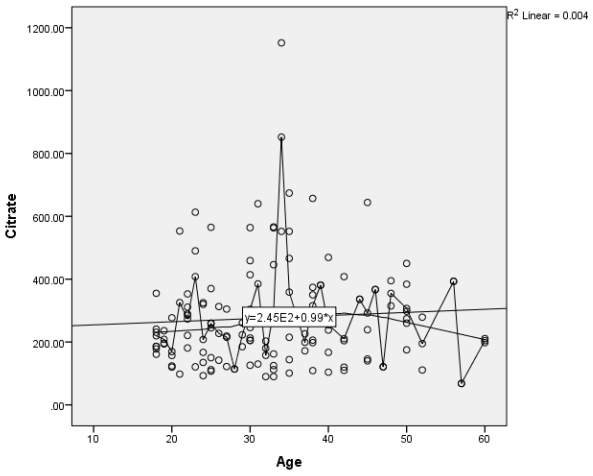

Figure No. 1: The relationship of 24 hours urinary citrate with age.

By applying *t* test, the differences in the urinary citrate levels in male and female patients were calculated. The female patients had lower mean urinary citrates than male patients (222.93 ±150.62 mg vs 286.32 ±175.94 mg respectively, *p*=0.177).

The relationship of 24 hour urinary citrate levels with age is depicted in (Fig.1). The analysis of the effect of age on 24 hour urinary citrates levels revealed no significant difference among 4 different age groups (Table 2). The relationships of age and gender on urinary citrate showed decreased urinary citrate levels in female patients with increasing age (Fig 2)

The patients with family history of renal stones had lower 24 hour urinary citrates than those patients with no positive family history for renal stones [241.37 ±124.4 mg vs 294.97 ±191mg, *p*=0.124]. In addition, the patients with family history of stones were relatively of younger age (Fig. 3).

Result of renal stone composition was available in 37 patients. Stone analysis in each case was performed by infrared spectroscopy. The stone consisted of calcium oxalate plus uric acid (18), calcium oxalate (15), calcium phosphate (2), and calcium oxalate plus calcium phosphate (1). In 24 (64.8%) of these patients hypocitraturia was present. In 68 (60%) patients there was history of passage of stones per urethra, 8 (7 %) patients received shockwave (SWL) and others had undergone open or minimally invasive surgery.

Table No.2: ANOVA for 24 hours urinary citrate levels with regards to age

Age Groups	N	Mean Citrate levels (mg)	Std. Deviation	Minimum	Maximum	P value
Up to 30	53	250.92	130.9786	93.00	613.00	
31 - 40	34	326.7353	238.56062	90.00	1152.00	
41 - 50	19	283.4737	139.46340	110.00	644.00	0.178
More than 50	6	210.000	116.92733	68.00	393.00	
Total	112	277.2679	173.37331	68.00	1152.00	

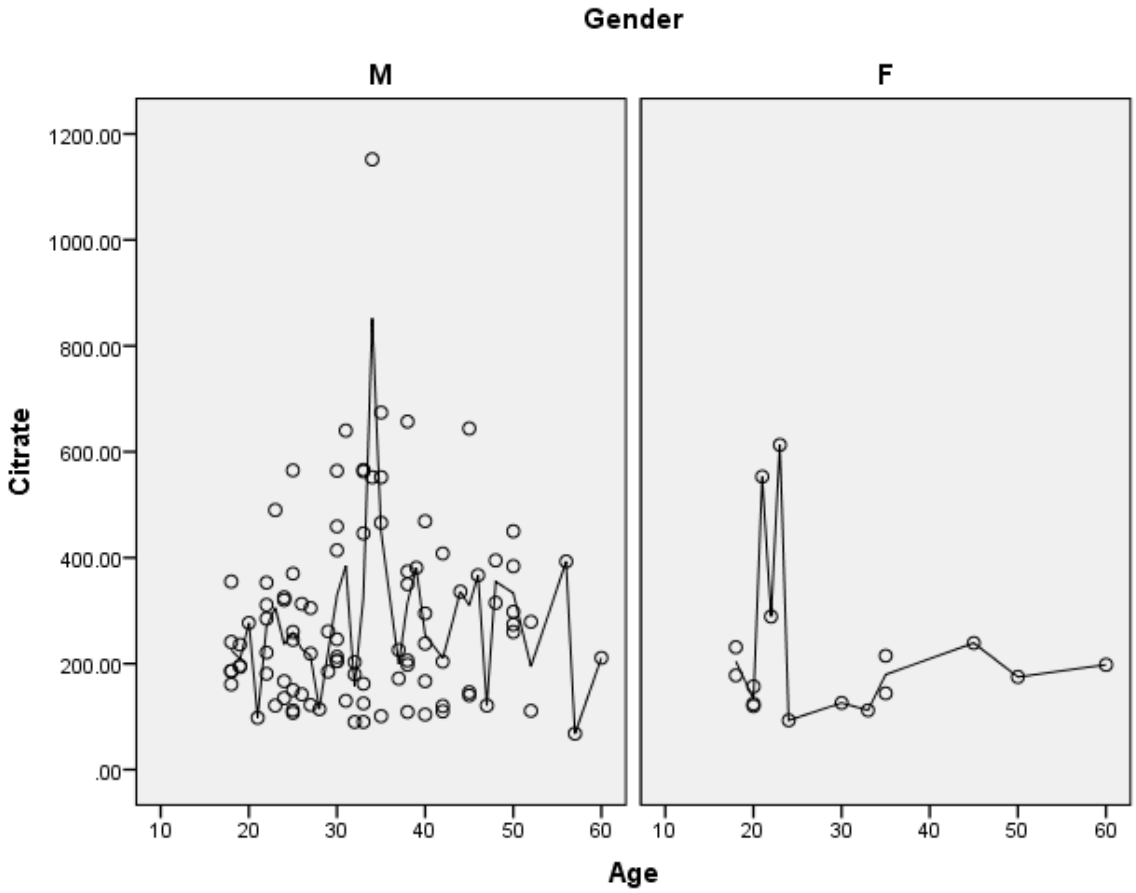

Figure No. 2: The relationship of urinary citrate levels with gender and age

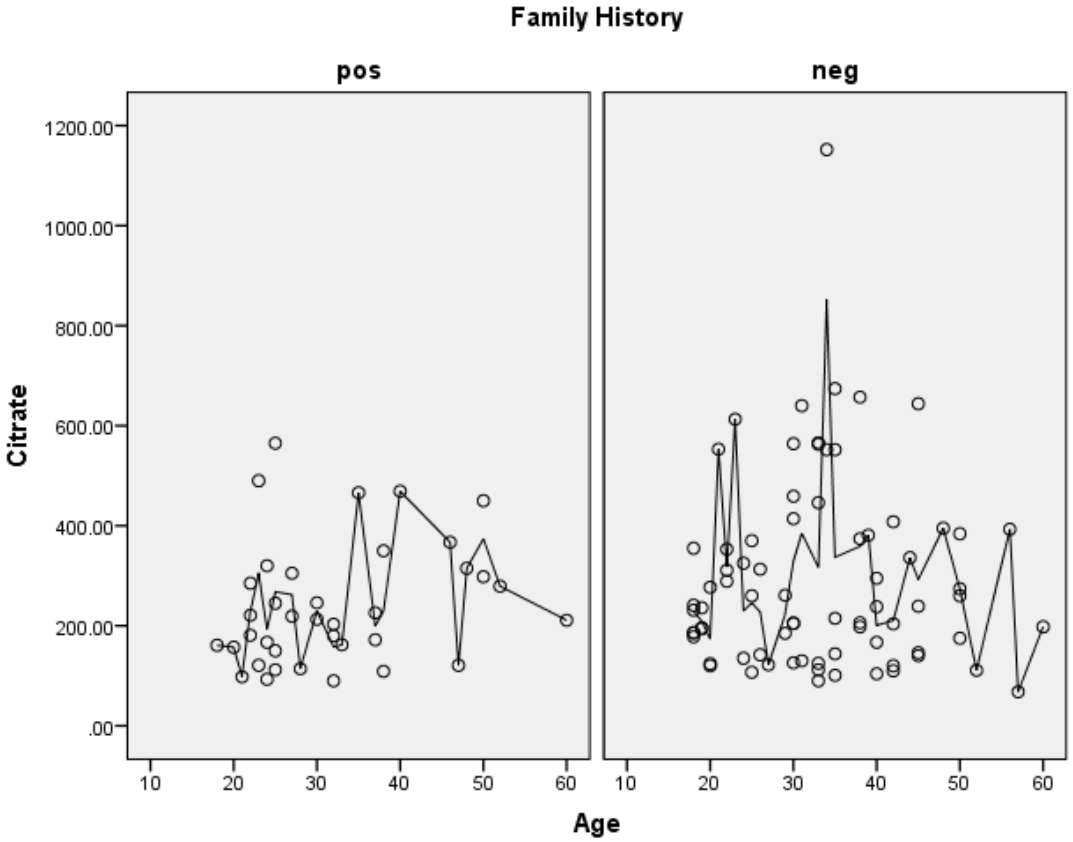

Figure No. 3: The relationship of 24 hour urinary citrate with age and family history of renal stones.

DISCUSSION

Published studies which had taken normal urinary citrate as 320mg/24 hours as a reference report different frequencies of citrate deficiency ranging from 22% to 78% of patients. In one Japanese study, Usui et al[7] estimated the frequency of hypocitraturia and its causes in the absence of obvious acid-base balance. The researchers selected 310 renal stone patients who had 24 hours urine chemistry on regular diet on 2 or more occasions during follow-up. Hypocitraturia was present in 38.4% of the patients. They noted significant differences in the average urinary citrate excretion in males and females [450±284.4mg/day vs 536.5 ±305.9mg (p<0.0001)]. In a small case controlled study from Iran, Goodarzi et al[8] aimed to compare the 24 hours urinary citrate excretion in stone formers and healthy volunteers. Their study included 28 stone formers and 27 age-matched healthy volunteers. Both group patients had similar living environment and diet. They reported significantly lower mean urinary citrate in stone formers than healthy controls (p<0.001). By applying the 320mg/24 hours citrate cut off value, the researchers reported 43% stone formers were hypocitraturia while none of healthy controls had hypocitraturia. Santos et al[9] in a retrospective study from Brazil, evaluated the prevalence of metabolic disorders with nephrolithiasis in 1737 female patients. The study patients had two or more 24-hour urine samples for evaluation. The authors reported hypocitraturia in 22.4% of the patients. Kanchan et al[10] from India investigated metabolic abnormalities in adult male renal stone patients and healthy controls. The mean urinary citrate level in stone formers and control was 287.2±36.8 and 550 ± 180.2 mg respectively and hypocitraturia was present in 73.33% of renal stone patients.

A small study from Pakistan included 40 age matched patients and compared the difference in citrate excretion between stone formers and healthy control[11]. Hypocitraturia was present in 70% of the stone formers and 72% of the controls. In the present study, the author used 320mg urinary citrate/24 hours as normal reference. The mean 24 hours urinary citrate was 277.26±173 mg (range 68mg to 1152mg). The analysis revealed that a significant number of patients had hypocitraturia (69.64%).

Women excrete more citrate[12] and have lower incidence of stone formation than men. In the present study, the author compared gender differences in citrate excretion in stone formers. The female patients were found to have lower mean urinary citrates than male patients [222.93 ±150.62 mg vs 286.32 ± 175.94: p=0.177). The relationship of age and gender on urinary

citrate showed decreased urinary citrate levels in female patients with increasing age. So, present study findings differ from other studies.

Various studies[2, 13] report that the type and degree of metabolic abnormality may change with age. In the present study the author did not find significant differences in 24 hours urinary citrate levels at difference age groups.

Positive family history has been reported to be present in 17–37% of patients with stone disease when compared with 4–22% of normal healthy control subjects[14]. Also, such patients are affected by renal stone disease at relatively younger age [15,16]. In the literature there is little information whether increased familial risk is attributable to genetic, environmental factors or combination. In present study, positive family history was present in 33% patients and such patients were relatively of younger age. In the present study, the patients with family history of renal stones had lower 24 hour urinary citrates than those patients with no positive family history for renal stones [241.37±124.4mg vs 294.97±191 mg: p=0.124].

A low 24 hour urinary volume (less than 1000 ml) has been implicated as a risk factor for nephrolithiasis and increased fluid intake may prevent stone formation[17] . Borghi et al[18] in a randomized control trial reported that urine volume was a real risk factor in nephrolithiasis and increasing urine volume to two liters per day resulted in lower stone recurrences in an idiopathic calcium stone disease. In author's study the mean urinary volume was 1617.49±822 ml, and 92 (82%) of patients had a lower 24-hour urine volume (*i.e.* less than 2 liters) and recommending an increased fluid intake in such patients may help prevent recurrence of stones.

Although the majority of patients have idiopathic hypocitraturia, there are a number of causes for this abnormality, including distal renal tubular acidosis, hypokalemia, bowel dysfunction, and a high-protein, low-alkali diet[19]. In the present retrospective study, the author was unable to ascertain the cause of hypocitraturia because of paucity of required information in the database.

Published literature reports that recurrence of renal stones in patients with hypocitraturia can be reduced by various dietary and lifestyle modifications and/or pharmacotherapy which help correct citrate deficiency. Hypocitraturia can be corrected by the administration of potassium citrate. A Cochrane review[20] reported that citrate salts significantly reduce stone size, prevent new stone formation, and stabilize stone size. In addition, patients on citrate treatment required significantly less retreatment for stone removal.

As it was a retrospective study, it reflects patients in a specific geographical region treated at a tertiary referral centre. The data on the race or ethnicity was not available so the results may not be applicable to all patient population. Because of lack of sufficient information, the author could not identify the clear cut cause of hypocitraturia in patients with urinary citrate deficiency. The present study was based on the findings from data of recurrent renal stone formers who had one 24 hour urine chemistry performed and may not be relevant to one time renal stone former or non-stone forming population. In order to elucidate the role of hypocitraturia in nephrolithiasis, there is need for large randomized controlled trials to compare the urinary citrate levels in healthy controls with no evidence of renal stones and recurrent renal stone formers.

CONCLUSION

The present study revealed high frequency of hypocitraturia in recurrent renal stone formers. However, no statistically significant differences in the frequency of hypocitraturia were observed in both genders and age groups. Patients with positive family history of nephrolithiasis had lower urinary citrate levels than those without family history of stone. Once identified, the patients with hypocitraturia can be offered dietary and life style modification and/or potassium citrate therapy can be prescribed to reduce the recurrence of renal stones.

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Author's Contribution:

Concept & Design of Study:	Shoaib Rafique
Drafting:	Shoaib Rafique
Data Analysis:	Shoaib Rafique
Revisiting Critically:	Shoaib Rafique
Final Approval of version:	Shoaib Rafique

Conflict of Interest: The study has no conflict of interest to declare by any author.

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