

24 Hours Urinary Citrate Levels and Frequency of Hypocitraturia among patients with Recurrent Nephrolithiasis

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ABSTRACT

Background: Nephrolithiasis is a common disorder with high rate of prevalence and recurrence without treatment. Urinary citrates, among others are important inhibitors of stone formation. The mean urinary citrate excretion is 640mg/d in healthy individuals. Hypocitraturia is a common metabolic abnormality detected in stone formers.

Aim: To determine frequency of hypocitraturia among patients with recurrent nephrolithiasis.

Methods: Two seventy eight (n=278) patients with renal stones admitted in Urology Ward Nishtar Hospital Multan who met the inclusion criteria were included in the study. Twenty four hour urine sample was collected and urinary citrate level was estimated using.

Results: Among the study group (n=278) Males were 158(56.8%) while females were 120(43.2%). Mean duration of disease was 3.66+1.88 years. Mean for 24 hour urinary citrate level was found out to be 290.21+74.96. Hypocitraturia was found to be present in 197(70.9%) of the patients with recurrent renal stones.

Conclusion: Low Urinary citrate levels are found frequently in our patients with recurrent nephrolithiasis. Twenty four hour urinary citrate level should be routinely checked in these patients. Therapies should be instituted to increase the urinary citrate levels as a preventive measure.

Key words: Nephrolithiasis, Hypocitraturia, Urinary citrate

INTRODUCTION

Nephrolithiasis is a common disorder with an estimated prevalence of up to 15% in lifetime¹. The recurrence rate without treatment for renal stones is 10% at 1 year, 35% at 5 years and 50% at 10 years². Known urinary inhibitors are citrates, magnesium, pyrophosphate, Tamm-Horsfall proteins, glycosaminoglycans, osteopontin (uropontin) and high urine flow³. Hypocitraturia, a low amount of citrate in the urine, is an important risk factor for kidney stone formation⁴. Citrate in the urine has long been recognized as an inhibitor of calcium salt crystallization. Citrate is the dissociated anion of citric acid, a weak acid that is ingested in the diet and produced endogenously in the tricarboxylic acid cycle. The mean urinary citrate excretion is 640 mg/d in healthy individuals. Hypocitraturia is a common metabolic abnormality detected in stone formers, occurring in 20% to 60%^{5,6}. However, there is no consensus about 24 hour urinary citrate level among patients with recurrent renal stones^{7,8}. Urine citrate excretion in normal women and men are 424mg/24 hours and 389mg/24 hours respectively⁹.

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Many authors have taken urinary citrate 320mg/24 hours as lower limit of normal and in both gender patients with urinary citrate level <320mg/24 hours will be considered to have hypocitraturia^{2,5}. Different authors have determined different 24 hours citrate levels and frequencies of hypocitraturia among different studies. Anjum et al⁸ described the mean 24 hours urinary citrate level in recurrent renal stone formers was 254±125 mg/24 hrs and the frequency of hypocitraturia in their study was 78%. Mithani et al²

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described a mean 24 hour urinary citrate level of 262 ± 197 mg/hrs and found that 70% patients were hypocitraturic. In a study by Deshmukh et al the mean 24 hours urinary citrate level found was 148.9 ± 5.035 mg/ 24 hrs¹². In a study by Usui et al, the mean 24 hours urinary level was as high as 453 ± 285 mg/24 hrs and the frequency of hypocitraturia was 38.4%¹³. In one study 350 consecutive stone formers were examined and the frequency of hypocitraturia was 23.71 %¹⁴.

MATERIAL AND METHODS

The descriptive cross sectional study was conducted in the Department of Urology, Nishtar Hospital, Multan from June 2014 to June 2016, consisting of 278 cases based on non probability purposive sampling. Patients both male and female with age range of 20-45 years with recurrent nephrolithiasis diagnosed on history, clinical examination and USG were included. Patients having documented urinary tract infection, impaired renal function (S. creatinine >1), using diuretics, receiving potassium citrate and those having co-morbid diseases were excluded from study. The study was conducted with the approval of Institutional Ethical Review Committee of Nishtar Hospital, Multan. All the collected data were analyzed and descriptive statistics was used to calculate mean and standard deviation for continuous variables like age, gender and duration of disease. Frequencies and percentages were calculated for categorical variables like hypocitraturia and gender. Effect modulators like age, duration of disease and gender were controlled by stratification. Chi-square test was applied to see the effect of these on outcome variables, taking $p \leq 0.05$ as significant.

RESULTS

The present study included 278 patients in total. Males were 158 (56.8%) while females were 120(43.2%) Mean duration of renal stone disease was 3.66 ± 1.88 years (range 1-10 years). Mean 24 hour urinary citrate level was found out to be 290.21 ± 74.96 . Hypocitraturia was found to be present in 197(70.9%) of the patients with recurrent renal stones (Table 1). Mean urinary citrate level was 284.80 ± 73.90 and 90/120 (75%) patients had hypocitraturia (Table-2). Hypocitraturia was found to be present in 53/72 (73.6%). p-value was found to be 0.651 (Table-3). Males were 43/85 (50.6%) while females were 42/85 (49.4%). Mean age of the patients was 33.86 ± 6.77 years. Mean 24 hour urinary

citrate level was 294.06 ± 75.14 and hypocitraturia was found to be present in 59/85 (69.4%) (Table 4). The p-value was found to be 0.775. Graph-1 shows the effect of age on the frequency of hypocitraturia in patients with recurrent nephrolithiasis Effect of duration of disease on frequency of hypocitraturia in patients with recurrent nephrolithiasis (Graph-2)

Table 1: Characteristics of the study population

Total number of patients	278
Males	158 (56.8%)
Females	120 (43.2%)
Mean for 24 hour urinary citrate level	290.21 ± 74.96
Mean duration of disease	3.66 ± 1.88
Hypocitraturia	197 (70.9%)

Table 2: Effect of gender on various study characteristics.

Characteristic	Males (n = 158)	Females (n= 120)
Mean age	33.77 ± 6.74	34.95 ± 6.68
Mean duration of disease	3.54 ± 1.82	3.81 ± 1.95
Mean 24 hour urinary citrate level	294.32 ± 75.73	284.80 ± 73.90
Frequency of hypocitraturia	107(67.72%)	90(75%)

P. value= 0.230

Table 3: Comparison of various characteristics of the study population in different age groups

	Age 20-29 (n=67)	Age 31-39 (n=139)	Age ≥ 40 (n=72)
Males	39(58.2%)	80(57.56%)	39(54.16%)
Females	28(41.8%)	59(42.5%)	33(45.9%)
Mean duration of disease	3.73 ± 1.79	3.61 ± 1.79	3.68 ± 2.13
Mean urinary citrate level	282.97 ± 71.29	292.91 ± 77.21	291.75 ± 74.47
Hypocitraturia	49(73.1%)	95(68.34%)	53(73.6%)

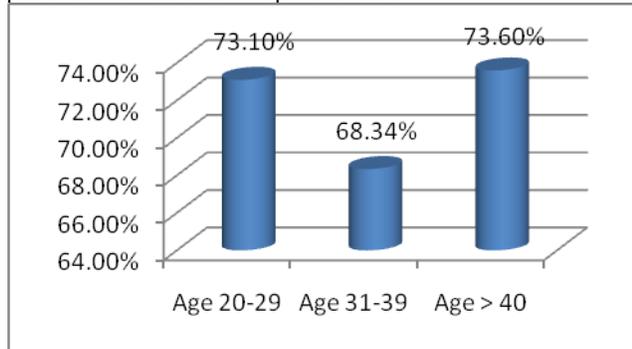
PP value = 0.651

Table 4: Effect of duration of disease on various characteristics of patients with recurrent nephrolithiasis

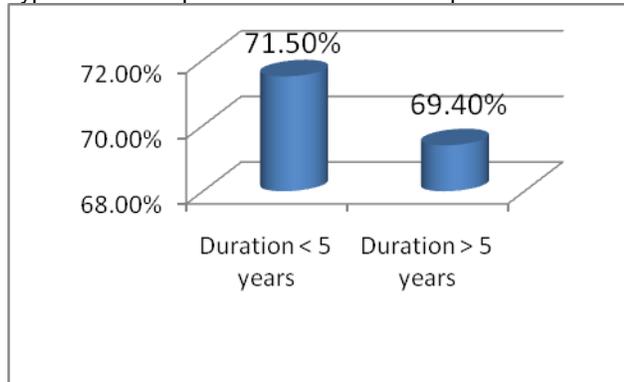
	Duration <5 yrs (n = 193)	Duration ≥5 years (n = 85)
Males	115/193 (59.6%)	43/85 (50.6%)
Females	78/115 (40.4%)	42/85 (49.4%)
Mean age	34.47 ± 6.72	33.86 ± 6.77
Mean urinary citrate level	288.52 ± 75.01	294.06 ± 75.14
Hypocitraturia	138/193 (71.5%)	59/85 (69.4%)

P. value = 0.775

Graph-1: Effect of age on the frequency of hypocitraturia in patients with recurrent nephrolithiasis



Graph-2: Effect of duration of disease on frequency of hypocitraturia in patients with recurrent nephrolithiasis



DISCUSSION

Despite advances in treatment methods, urinary stone disease remains a major source of morbidity. The understanding of pathophysiology of stone disease remains limited and stone recurrence continues to be a significant clinical problem and the reported rate of stone recurrence is 22.6-51% at a mean follow-up of 2-7.1 years¹⁵. Urolithiasis inflicts a huge burden on the health services in both developing and developed countries. So, the metabolic risk evaluation and appropriate recurrence prevention should be essential parts of care of patients with stone disease. It is only in this way that the future costs of stone treatment can be reduced and the quality of life of stone-forming patients improved¹⁶.

An understanding of the pathophysiology of stone formation is essential. This could allow a switch in focus from providing treatment for calculi that have already formed to the modulation of the underlying mechanisms leading to their development.

, the pathophysiology of the stone formation is complex. Many mechanisms have been shown to contribute to stone formation, but a unifying theory has yet to be demonstrated¹⁷. It is said that urine

contains both stone forming and stone inhibiting substances. There is a delicate balance between such substances which prevents the formation of renal stones. Known stone forming substances include calcium, oxalates, uric acid, and sodium while citrates, pyrophosphates, magnesium and polyanions of high molecular weight such as glyconaminglycans are considered stone inhibitors¹⁷. In addition, other inhibitory molecules include, uropontin, osteopontin, bikunin and Tamm-Horsfall proteins¹⁸.

Low urinary citrate excretion is a known risk factor for the development of kidney stones. Hypocitraturia, generally defined as urinary citrate level less than 320mg (1.6mmol) per day in adults, is a common metabolic abnormality, occurring in 20% to 60% of patients with renal stones^{4,19,20}. Citrate is a known inhibitor of renal stone formation, working through a variety of mechanisms. Citrate is a product of Krebs cycle and thus important in adenosine triphosphate generation. When excreted in to urine, in renal tubules it complexes with calcium, increasing its solubility and reducing the concentration of free calcium in urine. This citrate calcium complex limits calcium super saturation and prevents the nucleation of both calcium oxalates and calcium phosphates, at least partially through interaction with Tamm Hosfall proteins^{21,22}. Additionally citrate prevents crystal aggregation and growth through its ability to bind to the crystal's surface and may also prevent the adhesion of calcium oxalate to renal epithelial cells Citrate excretion is linked to urinary pH thus may influence the generation of a number of a type of stones.

A significant proportion of patients with nephrolithiasis have a low urinary citrate excretion in the absence of a known cause such as renal tubular acidosis, chronic bowel disease complicated by chronic diarrhea and intestinal alkali loss or hypokalemia inducing intracellular acidosis. The most important determinant of renal tubular reabsorption of citrate is acid-base balance. Systemic acidosis increases citrate reabsorption from the renal tubules because of an increased demand of the body (resulting in a lower urinary citrate excretion), and conversely, alkalosis or alkali-loading from the GI tract decreases citrate reabsorption (thus increasing urinary citrate excretion)^{23,24}.

Diet also has an impact on hypocitraturia. High meat intake increases the urinary excretion of calcium, oxalate, and uric acid and decreases urinary pH and citric excretion. The use of high-protein, low-carbohydrate diets for weight loss has led to concern about increased risk of stone formation, as these diets have been shown to be associated with decreased urinary citrate and pH levels and increased urine calcium and sodium levels in the

induction and maintenance phases²⁵. The prevalence of hypocitraturia has been reported variably in literature in various studies. Two studies from Pakistan reported that hypocitraturia was present in >70% of renal stone patients. Mithani et al from Karachi compared 24 hour urine citrate levels in patients with urolithiasis and healthy controls and reported that hypocitraturia was present in up to 72% of patients with renal stones². Anjum et al compared 24 hour urinary citrate in recurrent renal stone formers and healthy controls and reported that hypocitraturia was present in 78% of renal stone patients with mean urinary citrate 254±125mg per 24 hours⁸. Authors from other countries have reported variable frequency of hypocitraturia in patients with renal lithiasis. Usui et al from Japan reported that only 38.4% of their patients had hypocitraturia¹³ while Ratan et al from India reported a modest prevalence ie 43% of hypocitraturia in renal stone patients²⁶.

Strohmaier et al from Germany studied 350 consecutive renal stone patients and reported that 23.71% patients had hypocitraturia. They also studied the correlation between urinary citrate and urinary pH and observed that most patients with hypocitraturia had normal urinary pH potentially due to defects in the renal tubular citrate carriers, which is genetically determined¹⁴.

In our study, hypocitraturia was found to be present in 197(70.9%) of the patients with recurrent renal stones and mean 24 hour urine citrate level was 290.21±74.96. So our study is in line with other studies reported by various authors from Pakistan which reported >70% prevalence of hypocitraturia in patients with renal lithiasis. The reported lower prevalence of hypocitraturia in renal stone patients from European countries, Japan and India may be due to genetic or environmental reasons.

Urinary citrate levels are higher in premenopausal women than in men, contributing to the decreased incidence of renal stones in women²⁷. When comparing the prevalence of hypocitraturia in both genders, other authors^{13,14} reported a bit higher prevalence of hypocitraturia in males but in our study the prevalence of hypocitraturia was bit higher in females than in males (75% vs 67.72%) but it was statistically not significant ($p < 0.23$).

In the present study, we also explored the effect of age on the frequency of hypocitraturia and noted that there was no statistically significant difference among the three age groups. Other authors have reported similar results in their studies²⁸. In hypocitraturic patients, the risk of stone recurrence can be reduced by employing dietary modifications and/or drug therapy to correct hypocitraturia. In the majority of such patients dietary modifications are beneficial and should be employed first. These

include high fluid and citrus fruit intake, normal calcium consumption, and restriction of sodium, oxalates, animal protein^{29,30}.

In hypocitraturic stone formers increased consumption of fruit and vegetable has been demonstrated to significantly increase citrate excretion³¹. In addition, in such patients, the administration of citrates or alkali has been demonstrated to be beneficial^{32,33}. The citrate preparations increase urinary citrate by providing an alkali load and among the available citrate preparations, potassium citrate has emerged as the most tolerable and beneficial. Potassium citrate therapy in hypocitraturic patients may also prevent or correct hypokalemia, increase urine pH, which benefits uric acid and cystine stone formers³⁴.

One limitation of our study was that it was a cross-sectional study that included 278 patients. However, to prove the role of hypocitraturia in formation of renal stones, larger randomized controlled trials are necessary will compares the urinary citrate levels of patients with recurrent nephrolithiasis with those of the normal subjects without any evidence of renal stones.

CONCLUSION

Present study had revealed that there is high frequency of hypocitraturia in recurrent renal stone formers. There was no statistically significant difference in the frequency of hypocitraturia in both genders and different age groups. In patients diagnosed to have hypocitraturia, dietary modifications and/or drug therapy may be beneficial in preventing stone recurrence. Such an approach will help to reduce morbidity and improve quality of life renal stone patients. In addition, it will also lessen the burden on health care services.

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