ISSN 2515-8260 Volume 09, Issue 01, 2022

ORIGINAL RESEARCH

To study the normal values of citrate in urine: A population based study

[1]Dr. Shiv Shankar Sharma, [2]Dr. Nachiket Vyas, [3]Dr. Shivam Priyadarshi, [4]Dr. Anwar Ali

[1,4]MCh(Urology), [2]ProfessorDepartment of Urology, SMS Medical College, Jaipur, Rajasthan, [3]HOD, Department of Urology, SMS Medical College, Jaipur, Rajasthan, India

Corresponding Author
Dr. Anwar Ali,
MCh, Department of Urology, SMS Medical College, Jaipur
Email: dranwarali9986@gmail.com

INTRODUCTION

Citrate is a tricarboxylic acid, synthesized in mitochondria from oxaloacatate and acetyl Co-A by the enzyme citrate synthase.[1, 2] Citrate is thought to be freely filterable at the glomerulurs, in humans, 65 to 90% of the filtered citrate is reabsorbed and 10 to 35% is excreted in the urine as a byproduct of oxidative pathways in the body.[3, 4] It is known to inhibit precipitation of calcium oxalate and phosphate and growth of their crystals[5].

In 1990 Pak has defined normal 24 hour urinary citrates as more than 320 mg for both genders[6]. Hypocitraturia is defined as urinary citrate excretion lower than 1.67 mmol (320mg) per day. However, there are some reports of low urinary citrate output in stone formers (SF) and renal failure as compared with healthy subjects[7-9], while other studies found no differences[10,11].

Prevalence of hypocitraturia varies widely from 8% to 68.3% in patients with renal stones.[6] Furthermore; there are some differences in the range of 24-hour urinary citrate excretion in normal subjects.[10,12]

Urinary pH is also an important factor in stone risk, with higher values favoring calcium phosphate stones and lower ones uric acid stones[13]. Although final urine pH is associated with acid load, it is also influenced by ammonium excretion and the ability of the distal tubule to acidify the collecting duct. Overall factors that influence urine pH and citrate are similar, but not identical.

Various studies have evaluated the citrate levels and have conflicted results. Most of the studies have been done in stone former patients and very limited studies have been done in normal Indian population. In this study we intend to find out the normal range of citrate excretion in normal subjects and its relation with various factors.

MATERIAL AND METHODS

This was a prospective study conducted from Jan 2019 to July 2019 in the Department of Urology & Renal Transplant at SMS Hospital, Jaipur. A total of 100 cases were enrolled for present study.Detailed history was taken and subjects were selected after applying strict inclusion and exclusion criteria. They were instructed to remain on normal diet. Twenty four hour urine was collected and was sent for citrate estimation in proper cold chain. Citrate level was ascertained by enzymatic method.Twenty-four hour urinary concentration of citrate, urine pH and other determinants of supersaturation were measured in the Biochemistry Laboratory. Serum creatinine was assessed using a standardized enzymatic assay.

INCLUSION CRITERIA

Patients admitted in urology wards ranging from 18 years to 80 years.

EXCLUSION CRITERIA

Patients suffering from renal calculi taking drugs like citrate supplement (potassium citrate) Acetazolamide and Thiazide which alter citrate metabolism.

STATISTICAL ANALYSIS

Statistical analyses were done using computer software (SPSS Trial version 23 and primer). The qualitative data were expressed in proportion and percentages and the quantitative data expressed as mean and standard deviations. The difference in proportion was analyzed by using chi square test and the difference in means among the groups was analyzed using the student T Test. Correlation between quantitative outcomes was assessed using Pearson correlation coefficient. Significance level for tests was determined as 95% ($P< 0.05$).

RESULTS

A total of 100 cases were enrolled for present study. Among that the most common age group was 26-35 years (23%) followed by 46 to 55 years (21%). The mean ± SD of the study population age was 46±14.60 years. Sixty seven males and thirty three females were enrolled in this study.

The demographic characteristics are summarized in Table 1. There were no significant differences in these parameters.

Correlation between Citrate level (m.mol/24hr) and other variables is shownin Table 2.Association of the age with other variables is summarized in table 3.The Association of the BMI with other variablesis shown in Table 4. There was no significant difference in citrate excretion between men and women.

Table 1: Descriptive statistics of the quantitative variables

Variables	Mean	Median	SD
Age (Year)	46.60	46.00	14.60
Height (Cm)	164.07	165.00	6.63
Weight (Kg)	69.62	70.00	11.62
BMI	25.98	25.68	4.78
Urine Volume	1678.49	1657.00	622.5
Serum Creatinine	1.06	1.05	0.43
Urine pH	6.45	6.00	1.55
Citrate level m.mol/24hr	2.32	2.36	1.14

Table 2: Correlation between Citrate level m.mo1/24hr and other variables

Variables	Citrate level m.mo1/24hr	
	Pearson Correlation	Sig. (2- tailed)
Age	.318	.241
Height (cm)	.060	.555
Weight (kg)	.103	.306
BMI	.065	.518
Urine Volume	.037	.712
Serum Creatinine	-.147	.143

Urine pH	-.204	.304

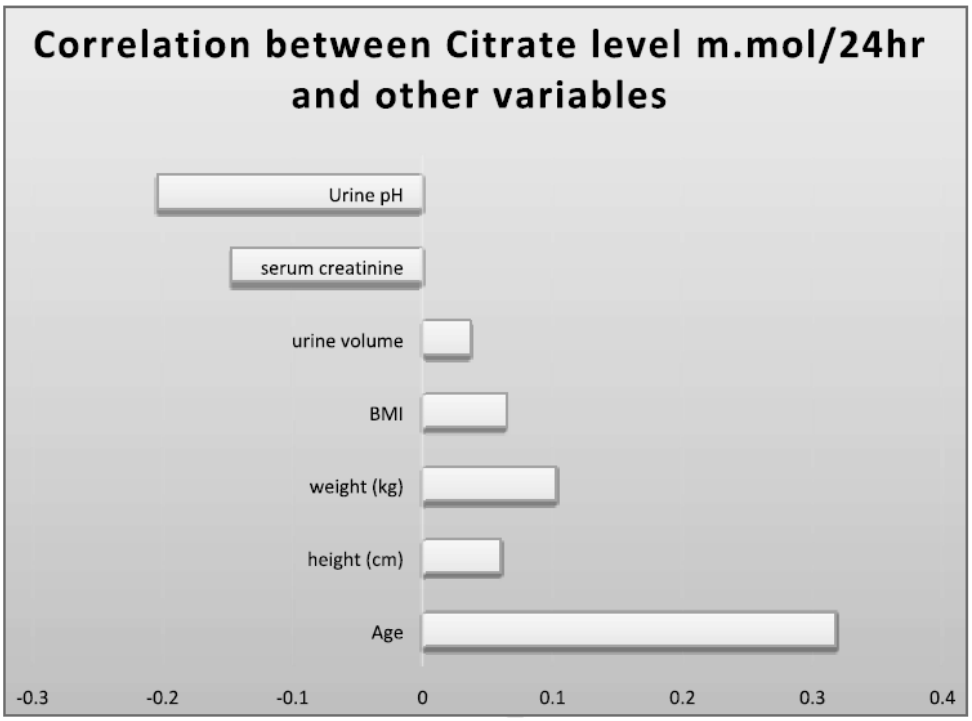
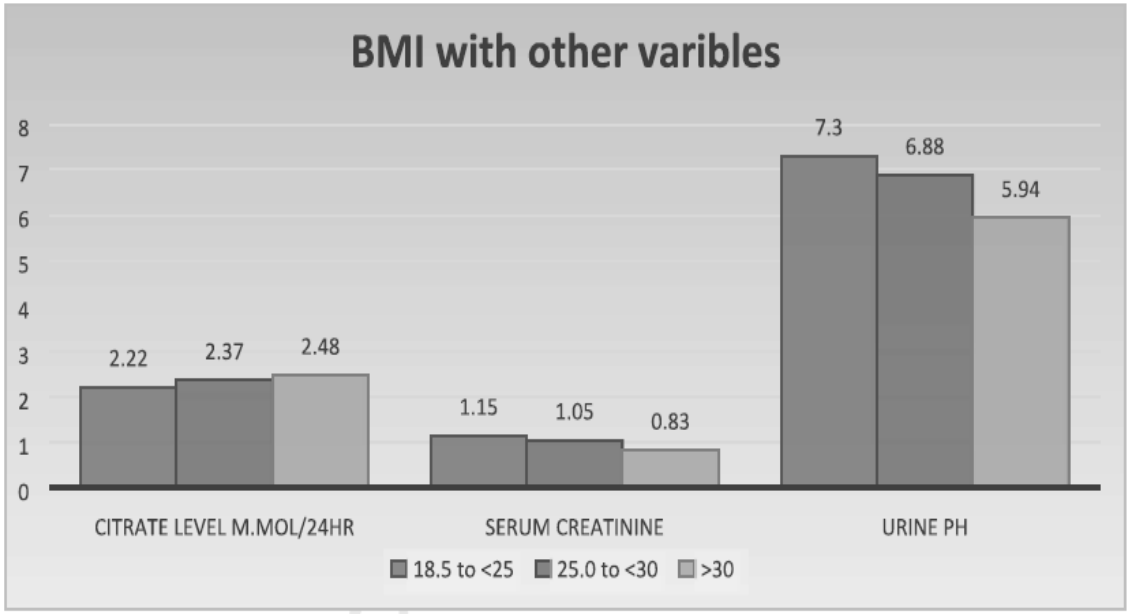


Table 3 Association of the age with other variables

Age in years		Citrate level	Urine volume	Serum creatinine	Urine pH
<25	N	6	6	6	6
	Mean	2.16	1569.00	1.13	6.52
	Std.	1.53	623.64	0.39	0.52
26 to 35	N	23	23	23	23
	Mean	2.77	1745.78	1.03	6.32
	SD	1.05	611.90	0.45	.55
36 to 45	N	19	19	19	19
	Mean	3.10	1585.16	1.11	5.89
	SD	1.22	571.57	0.42	0.73
46 to 55	N	21	21	21	21
	Mean	3.54	1607.62	1.06	5.79
	Std.	1.24	650.48	0.37	0.59
56 to 65	N	19	19	19	19
	Mean	3.97	1815.47	0.92	5.76
	SD	1.06	663.72	0.40	0.75
>65	N	12	12	12	12
	Mean	4.25	1659.17	1.04	5.66
	SD	1.08	679.71	0.51	0.47

Table 4 Association of the BMI with other variables

BMI		Citrate Level	Urine Volume	Serum Creatinine	Urine pH
18.5 to <25	N	45	45	45	45
	Mean	2.22	1716.84	1.15	7.30
	SD	1.09	596.52	0.45	0.58
25.0 to <30	N	41	41	41	41
	Mean	2.37	1671.24	1.05	6.88
	SD	1.16	634.74	0.42	0.76
>30	N	14	14	14	14
	Mean	2.48	1576.43	0.83	5.94
	SD	1.32	699.33	0.34	.71
P Value		.715	.715	.051	.038



DISCUSSION

Urinary citrate is a major inhibitor of kidney stone formation due to binding of calcium in urine. Low urine citrate levels are considered a risk for kidney stone formation[15]. Several metabolic disorders are associated with low urine citrate. Any condition that lowers renal tubular pH or intracellular pH may decrease citrate (eg, metabolic acidosis, increased acid ingestion, hypokalemia, or hypomagnesemia). Low urinary citrate promotes kidney stone formation and growth, and is subject to therapy by correcting acidosis, hypokalemia, or hypomagnesemia by altering diet or using drugs such as citrate and potassium[16].In this study we sought to determine the age and sex dependence of urinary citrate excretion in healthy individuals.

The distinction in urinary citrate excretion between the sexes can also be partially explained by ascertained differences in urinary pH. In our study, median urinary pH values decreased with increasing age and additionally were lower in male than in female participants—these

changes were in similar directions to those observed for citrate when calculated in relation to weight orCreatinine excretion. We can speculate that the fall in urinary pH with age is due to changes in dietary habits and exertion.

In this study we found the mean citrate excretion in normal healthy individual was 2.32± 1.14 mmol/24hour which was in accordance with various studies[11, 17]

In this study we also found that the as the age increases the urinary citrate excretion also increases with age. The mean urinary citrate excretion was 2.16± 1.53 at the age of less than 25 years while at more than 65 years the mean urinary citrate excretion was 4.25± 1.08. Our results are consistent with Simmi K Ratan et a1[18] who also reported an increase in citrate excretion with increasing age.

In our study, the median of urinary citrate/creatinine ratio was higher in female than in male and showed a significant trend to decrease with increasing age in both our results are concordant with the study conducted by Srivastava et a1[19] who also reported, the median of urinary citrate/creatinine ratio trend to decrease with increasing age in both sexes.

In this study we found that urinary pH has been decreased as BMI increases. The mean urinary pH was 7.3 at BMI 18 - <25 while at the BMI > 30 the urinary pH was 5.94. Our results are concordance with Maalouf et a1[20] who also reported lower urinary pH those with a higher BMI. Similarly higher body weight was also associated with greater urinary citrate excretion (Table 2). Powell and colleagues studied 5942 stone formers of which 414 were obese (>120 kg in males >100 kg in females) and also found the obese group to have a higher 24-hour urinary citrate excretion[21]. However, Mandel and colleagues found having high BMI was associated with a lower urinary citrate.[22] Since we found an effect of weight more than BMI on urinary citrate in themain effects model, it suggests that body habitus is important.

Urine volume is also a risk factor in urinary stone disease. In fact a high fluid intake and raised urine volume reduces urinary super saturation, thereby reducing the driving force for crystallization and stone formation[23]. In this study we found the mean urinary volume of normal healthy individual was 1678.49±622.35 ml/24 hour which is statistically not significant. Our results are in accordance with Shoaib Mithani et al[10] who reported the mean urinary volume of normal healthy individual was 1568 ± 1044 m1/24 hour.

Overall we found that there is a positive correlation between urinary citrate excretion and age, height, weight, urine volume while there is a negative correlation between urinary citrate excretion and serum creatinine and urine pH.

Some authors have pointed that different method of citrate analysis may be the cause of conflicting results[24]. So there is a wide range of values of for the urinary levels of citrate have been obtained for normal healthy individuals as there is number of variables which affect urinary citrate excertion[25].

CONCLUSION

Urinary citrate excretion is depends upon the age, height, weight, urinary volume and urine pH. Our results, based on a large representative population of healthy individual, may provide useful normative data to screen for urinary citrate, particularly in individuals at risk of urolithiasis and/or nephrocalcinosis.

REFERENCES

1. Krebs H A, Johnson W A. the role of citric acid in intermediate metabolism in animal tissues. FEBS Left. 1980; 117(suppl): K 1 -K10.
2. Krebs HA, Salvin E, Johnson WA. The formation of citric and alphaketoglutaric acids in the mammalian body. Biochem J 1983; 32:113-7.

3. Simpson DP: Citrate excretion: a window on renal metabolism. Am J Physio11983; 244:223-34.
4. Mmtiso LS, Rossi W, Pacitti MT, Scarnecchia L, Bigi F, Carnevale V, M.zzuoi GT. Studies on citrate metabolism in normal subjects and kidney stone patients. Miner ElectrolMetab 1989; 15:303-8.
5. DP Simpson. Citrate excretion: a window on renal metabolism. Am J Physio11983; 244:223-34.
6. Pak CV. Hypercalciuric calcium nephrolithiasis: In Resnick MI, Pak CV (eds): Urolithiasis: A medical and Surgical Reference. Philadelphia. WB Saunders. 1990; 7888.
7. Silora P, Bienias B, Majewski M, Borzecka H, wawrzyszuk M. Urinary citrate excretion in children with calcium urolithiasis. Przeq Lek2006; 63:134-6.
8. Hassani MA, Hennequin C, Lacour B, Daudon M. Influence of urinary citrate levels on spontaneous calcium oxalate dehydrates crystalluria. ProgUro12005; 15: 650-5.
9. Osther PJ, Ugeskr Laeger. Citrate and kidney stones 1993;22:3835-9
10. Mithani S, Zaidi Z. Comparison of 24hours urinary citrate levels in urolithiasis patients and healthy controls. J Pak Med Assoc 2005; 55: 371-373.
11. Mohammad Taghi Goodarzi, FarzadForouzanfar, Amir HosseinMoaddab. Comparison of 24-Hour Urinary citrate Excretion in Stone Formers and Healthy Volunteers Saudi J Kidney Dis Transpl 2012; 23:1227-31.
12. Rizvi SA, Naqvi SA, Hussain Z, et al. The management of stone disease. BJU Int 2002; 89:62-8.
13. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. J. Urol. 2014; 192:316-24.
14. Frasetto L, Ingrid K. Treatment and prevention of kidney stones: Am Fam Physicians 2011 ;84(11):1234-42
15. Curhan GC, Taylor EN. 24-h uric acid excretion and the risk of kidney stones. Kidney Int. 2008;73:489-496
16. Hosking DH, Wilson JW, Liedtke RR, et al: The urinary excretion of citrate in normal persons and patients with idiopathic calcium urolithiasis (abstract). Urol Res 1984;12:26
17. Kirejczyk JK, Porowski T, Konstantynowicz J, et al. Urinary citrate excretion in healthy children depends on age and gender. Pediatr Nephrol 2014;29:1575-82
18. Ratan SK, Bhatnagar V, Mitra DK,Basu N, Malhotra LK. Urinary citrate excretion in idiopathic nephrolithiasis. Indian Paediatrics 2002; 39: 819-25.
19. Srivastava T, Winston MJ, Auron A, Alon US. Urine calcium/ citrate ratio in children with hypercalciuric stones. Pediatr Res 2009;66:85-90
20. Maalouf NM, Sakhaee K, Parks JH, et al. Association of urinary pH with body weight in nephrolithiasis. Kidney Int. 2004; 65:1422-5.
21. Powell CR, Stoller ML, Schwartz BF, et al. Impact of body weight on urinary electrolytes in urinary stone formers. Urology 2000; 55:825-30.
22. Mandel EI, Taylor EN, Curhan GC. Dietary and lifestyle factors and medical conditions associated with urinary citrate excretion. Clin. J. Am. Soc. Nephrol. 2013;8:901-8.
23. Teotia M, Teotia SPS. Nutrition and Urolithiasis. In nutitional and metabolic bone and stone disease. An Asian Perspective. Pt ed. CBS Publishers and Distributors, New Delhi.2008 p 777
24. Schwille PO, Scholz D, Paulus M, Citrate in daily and fasting urine. Results of control patient with recurrent idiopathic calcium urolithiasis and primary hyperparathyroidism. Invest Urol 1979;16:457-62

25. Scott WW, Huggins C, Selman BC. Metabolism of Citric acid in urolithiasis. J Urol 1943; 50:202-09.