Urinary Citrate Level In Urinary Stone Formers Versus Controls

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ABSTRACT

Objective — *To determine the urinary citrate (UC) level in stone formers (SF) versus controls.*

Study design — *Case control study.*

Place & Duration of study — *Department of Pediatric Nephrology, National Institute of Child Health (NICH), Karachi from January- July 2008.*

Methodology — *Eighty six children of 1-13 years, 43 in each group, stone former (SF) and controls were studied. In both groups, 24-hours UC was measured by citrate lyase method. Hypocitraturia was defined as 24- hours UC-level < 5mg/kg for children under 9 years and <7mg/kg for 9 years and above. Data including age, sex, weight, 24-hours urine volume (UV) and UC-level were analyzed using descriptive statistics on SPSS version 15.*

Results — *Of the 86 children, 59 (68.6%) were males and 27 (31.4%) females. Overall mean age was 5.65 + 3.05 years, while that of SF and controls was 5.61+ 3.1 and 5.70 + 3.04 years respectively. Mean 24-hours UV and UC-level in total of 86 samples was 385.10+130 ml and 88.10 + 62.11mg respectively. Mean + SD 24-hours UC-level (mg) in SF and controls was 69.4 + 53.55 (95%CI 53.39-85.41) and 106.8 + 65 (95%CI 87.37-126.23) respectively. Overall hypocitraturia was found in 42(48.8%) children. Frequency of hypocitraturia was high in SF (n 30, 69.8%) compared to controls (n 12, 27.9%) with a significant difference between the two groups (p<0.001).*

Conclusions — *Overall hypocitraturia was found in 48.8% of cases. Though hypocitraturia was prevalent in both groups, but was significantly high (69.8%) in SF compared to controls (27.9%). Hypocitraturia may be an important metabolic risk factor and urinary citrate level should be included in the metabolic evaluation in all stone formers.*

Key words — *Urinary calculi, Hypocitraturia, Metabolic risk factors.*

INTRODUCTION:

A high incidence of urolithiasis has been reported from India, Pakistan, Turkey and Middle East countries.[1-3] It accounts for 40-50% of pediatric urological work load and 12-14% of renal diseases at general pediatric hospitals.[4, 5] Pediatric urolithiasis is associated with significant morbidity in developing countries and responsible for acute kidney injury (AKI 21.4%) and chronic kidney disease (CKD 20-22%) requiring renal replacement therapy.[6-8] Determination of etiology of stone disease requires clinical assessment, stone analysis, metabolic work up, detection of congenital anomalies of kidney and urinary tract (CAKUT) and urinary tract infection (UTI).[8-10]

In the vast majority of pediatric urolithiasis, the stones are composed of calcium oxalate (CaOx 60-90%) and calcium phosphate (CaP 10-20%) where as 5-10% are made up of uric acid, struvite and cystine.[1] Major variations in etiological factors in different regions of the World and within Pakistan have been reported.[1-3, 7-9] In a recently published large series on pediatric urolithiasis, hypocitraturia was reported

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as the most common metabolic risk factor (87%) followed by hyperoxaluria (43%) and hyperuricosuria (26%).[8]

Dietary and environmental factors like hot climate (low urine output, scant water intake) particularly in rural area are important contributing factors for increased predisposition for urolithiasis in our country. Common diet consumed in our society is low in citrate and potassium (negligible intake of citrus fruits), rich in oxalate, sodium but low in calcium. Furthermore, chronic diarrhea and malabsorption in children may also contribute to hyperoxaluria.[8]

Citrate is a most potent naturally occurring urinary stone inhibitor and its concentration depends upon the tubular absorption capacity which depends upon blood pH. Thus, a delicate balance is maintained at physiological range of pH of body fluids. An alkalosis increases and acidosis decreases the urinary citrate level. Most therapeutic agents that modify citrate excretion in stone disease usually work by changing pH of tubular fluid. Citrate forms soluble complexes with Ca and decreases urinary Ca thus inhibits crystallization and growth of CaOx and CaP stones.[11,12]

There is no universal consensus on the normal range for urinary citrate in pediatric population. Arbitrary but different values have been used in western and local studies to define the lower normal limits in both adults and children.[7, 8,10-13] In adults, hypocitraturia has been defined in various local and international studies as 24 hour UC level < 200-320 mg whereas in children most commonly used reference value is 24 hour UC level < 180 mg/gm of creatinine.[1,11,13-15] Other reference values quoted are urinary citrate level < 2mg/kg/24 hour irrespective of age; another one as < 5mg/kg/24 hour in under 9 years and < 7 mg/kg in children of 9 years and above.[8,16]

This study aimed to determine the urinary citrate level in children with urinary stone formers and to compare it with that of normal children.

METHODOLOGY:

This case control study was carried out from January to July 2008. A total of 86 children (43 SF, 43 controls) of either sex and 1-13 years age were studied. Keeping in mind the frequency of hypocitraturia as 50-70% in children with urolithiasis and 30% in normal children, sample size was calculated as 86 with similar age and sex with case-control ratio of 1:1.

All children with urolithiasis and normal serum creatinine were taken as stone former group where as controls were those children who did not have urinary stone disease and presumed to have normal urinary citrate level. Children with renal insufficiency, renal tubular acidosis (RTA), nephrocalcinosis, malabsorption states. UTIs, on diuretic or potassium citrate therapy and with CAKUT were excluded. In all cases and controls 24-hours UC- level was estimated by enzymatic citrate lyase method in a standard urine sample collected in a special jar containing thymol as preservative.

Verbal and written instructions about 24 hours urine collection method were given to parents. Young children were catheterized at night and urine collection started from 8.00 am to next morning 8.00 am and urine then was transformed into the same container as used for older children. A urine sample equal to or more than 20 ml/kg/24 hours was taken as adequate for quantitative estimation. The cutoff values for hypocitraturia and arbitrary 24 hour UC less than 5.0 mg/kg in children below 9 years and less than 7.0 mg/kg in 9 years and above, was taken as hypocitraturia in this study.[8]

The data was computed and analyzed using descriptive statistics on SPSS version 15.00. Categorical variables like gender was represented in frequencies and percentages where as numerical variables like 24 hour UC level, were represented by mean + standard deviation (SD). Chi-square test was applied to compare hypocitraturia between SF and control groups. Odd ratio was also computed with 95% CI and a $p<0.05$ considered as significant.

RESULTS:

Among 86 patients studied, 59 (68.6%) were males and 27 (31.4%) females. There were 43 in stone former group (SF) and 43 in controls (table I). Overall mean age was 5.65 + 3.05 years, while that of SF and controls was 5.6+13.1 and 5.73+04 years respectively. 24 hour urine volume (UV) and UC level in overall, SF and control group are shown in table II. Overall mean UV and UC was 385.10+130 ml (95% CI 357.6-412.6) and 88.1+62.11mg (95%CI 74.97-101.23) respectively. Overall hypocitraturia was found in 42 (48.8%) children, whereas UC was normal in 44(51.2%). In SF, the hypocitraturia was observed in 30 (69.8%) patients as compared to 12 (27.9%) in controls ($p <0.001$). Chi-square test shows significant differences in 24 hours UC level between SF and controls ($p<0.005$) but there was no significant difference in urine volume (p 0.333).

Thirty (34.88%) males and 12 (13.95%) females had hypocitraturia in this study. Comparison of

Table I: Demographic Characteristics

Variables		Overall (n 86)	Stone Formers (n 43)	Control (n 43)	P value
Gender	Male	59 (68.6%)	31 (72.1%)	28 (65.1%)	0.486
	Female	27 (31.4%)	12 (27.9%)	15 (34.9%)	
Age (years)	Min – Max	1.07 – 13	1.07 – 13	1.10 – 13	0.904
	Mean + SD	5.65 + 3.05	5.61 + 3.1	5.70 + 3.04	
	95% CI	5 – 6.3	4.68 – 6.54	4.8 – 6.6	
Age Groups	1 – 5 years	44 (51.16%)	22 (51.16%)	22 (51.16%)	0.999
	> 5 – 10 years	36 (41.8%)	18 (41.8%)	18 (41.8%)	
	> 10 yrs	6 (7%)	3 (7%)	3 (7%)	
Weight (kg)	Min – Max	5.9 – 35	5.9 – 31	9.0 – 35	0.397
	Mean + SD	16.34 + 6.14	15.80 + 6	16.91 + 6.3	
	95% CI	15.04 – 17.64	14 – 17.6	5.01 – 18.81	

SD= Standard deviation, CI=Confidential interval

Table II: Comparative 24 Hours Urinary Volume and Citrate Level in Stone Formers Vs Control

Variables		Overall (n 86)	Stone Formers (n 43)	Control (n 43)	P value
24 hour Urine Volume (ml)	Min – Max	130 – 780	130 – 720	220 – 780	0.333
	Mean + SD	385.10 + 130	371.44 + 129.6	398.72 + 130.45	
	95% CI	357.6 – 412.6	332.71 – 410.17	359.72 – 437.72	
24 hour Urinary Citrate level (mg)	Min – Max	5.8 – 300	5.8 – 212	12 – 300	0.005
	Mean + SD	88.1 + 62.11	69.4 + 53.55	106.8 + 65	
	95% CI	74.97 – 101.23	53.39 – 85.41	87.37 – 126.23	
Normal Urinary Citrate	n (%)	44 (51.2%)	13 (30.2%)	31 (72.1%)	< 0.001
Hypocitraturia	n (%)	42 (48.8%)	30 (69.8%)	12 (27.9%)	

Table III: Comparative Frequency of Hypocitraturia in Male and Female Stone Formers and Controls N=42

Hypocitraturia	Stone Formers n (%)	Controls n (%)	Total N (%)
Male	21 (70)	09 (75)	30 (71.42)
Female	09 (30)	03 (25)	12 (28.57)
Total	30 (71.42)	12 (28.57)	42 (100)

hypocitraturia according to gender in SF and controls is shown in Table III. Among the 42 hypocitraturic children, it was more common in males in both SF (70%) and control group (75%).

DISCUSSION:

Hypocitraturia is a common metabolic abnormality in patients with urolithiasis particularly in those with calcium oxalate stone disease. In this study, overall

hypocitraturia was found in 48.8% and 69.8% among stone formers. This is consistent with 46% and 57.74% of hypocitraturia observed in studies from Turkey.[17, 18] The results are also consistent with a study from India in which 43% of children had hypocitraturia.[19] In our study, majority of the SF (69.8%) had hypocitraturia. The overall finding of the hypocitraturia in the absence of UTI, CAKUT and RTA suggest that hypocitraturia is an important metabolic risk factor for stone disease in this country.

In a recent study, DeFoor WR et al have shown that both hypercalciuria and hypocitraturia were the most important independent risk factors for stone recurrence.[20] Another study by Francisco S et al showed that either hypercalciuria alone or in combination with hypocitraturia were the two most frequent risk factors found in 40% and 37% of patients respectively.[21] Our findings are in contrast with the findings of Mortazavi et al and Naseri M et al from Iran, who either did not find hypocitraturia at all or a very low frequency (2.1%) in their studies.[22, 23] This could be due to use of different cut off value from our study, low 24 hour urine volume(<20 ml /kg/day), geographical variation or site of stones as bladder calculi may not have hypocitraturia . However, our findings are consistent with a more recent study from same country (Iran) showing hypocitraturia as the most common metabolic cause (68%) in stone formers.[24] Also, a low figure (7%) for hypocitraturia has been found in 69 patients in a recent report from Canada.[25] This may be explained on the basis of number of factors which may affect urinary citrate level like consumption of large volume of water (dilute urine and beverages containing sucrose may decrease citrate level), consumption of more citrus fruits and low salt in diet and cool climate in Canada compared to Pakistan.

In a study of pediatric patients by Tekin and colleagues, urinary citrate excretion was significantly lower in stone formers in comparison to healthy children.[26] Our observation is similar to Tekin A et al with a significant difference (P<0.001) in citrate excretion between stone formers and controls. A wide range of values for the urinary levels of citrate have been used by researchers. It is known that a number of variables affect citrate excretion like age (lower in infants than in adults), weight (increases with increase in weight), urinary pH (decreases in acidic pH), diet (increases after a high sucrose diet), metabolic acidosis (decreases level), urinary tract infections (decreases the citrate level) and method of citrate analysis (colorimetric or enzymatic citrate lyase). All these factors were not looked into and needs consideration. In this study we found a low urinary citrate level for males in both SF and controls as compared to females. However such difference has not been observed by others.[3, 8,19]

CONCLUSIONS:

Overall hypocitraturia was observed in 48% of study population. There was a significant difference in urinary citrate level in stone formers versus controls suggesting that hypocitraturia may be an important metabolic risk factor for stone formation in this region.

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