ORIGINAL ARTICLE

CHEMICAL COMPOSITION OF STONES IN PAEDIATRIC UROLITHIASIS

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Background: Chemical composition of stones is one of the important diagnostic criteria for aetiology of stone formation and treatment to prevent recurrence. This paper reports composition of stones in children at a tertiary hospital by Fourier Transformation Infrared Spectroscopy (FTIR). **Methods:** Between January–June 2015, 412 urinary stones from children were analysed by FTIR. Chi-square tests were used for the comparison of categorical measurements between groups. All reported values were 2-sided and statistical significance was considered at *p*-value ≤0.05. **Results:** Of the 412 stones, 263 (63.8%) were renal, 101(24.5%) bladder and 48 (11.7%) ureteric. The mean age of children was 7.15±4.13 years with a M:F ratio 2.4:1. Of the 412 stones, 144(34.9%) were pure stones composed of one compound and 268(65.1%) were mixtures. Frequency of compound in stones was Ammonium Acid Urate (AAU) (65%), Calcium Oxalate (CaOx) (76.9%), Uric Acid (5%), Calcium Phosphate Apatite (7%), Whitlockite (8.4%), Struvite (4%), Cystine (0.72%) and Xanthine (2.11%). Frequency of compounds analysed in three ages groups 0-5, 6–10 and 11–15 years showed high frequency of AAU (73%) in 0-5 years as compared to (60%) in 11–15 years ($p<0.018$). CaOx (90%) in 11–15 as compared to (62.5%) in 0–5 years ($p<0.001$). Bladder stones were more prevalent in children 0–5 years (32%) vs 19% in 11–15 years ($p<0.004$) while renal were 75% in 11–15 years and 54% in 0–5 years ($p<0.04$). **Conclusion:** AAU stones known to be associated with malnutrition and chronic diarrhoea are highly prevalent in paediatric stones formers in our population in the kidney, bladder and ureter.

Keywords: Paediatric; Urolithiasis; Chemical composition

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INTRODUCTION

Paediatric urolithiasis remains endemic in the developing countries with high prevalence rates of 1–15% when compared with 1–5% reported from the developed world.[1,2] Evaluation of stone chemical composition is one of the important diagnostic criteria for determining the aetiology and pathophysiologic mechanisms that are involved in the formation of stones. Furthermore, in combination with urinary risk factors it helps to develop strategies for medical management and prevention of recurrence.[3,4] In fact according to the European Association of urology and American urological association guidelines, analysis of 24-hour urine and stone composition are recommended as the first line of investigation in the prevention of recurrence.[5,6]

In this paper, we report chemical composition of stones in children from a developing country using the technique of Fourier Transformation Infrared Spectroscopy (FTIR).

MATERIAL AND METHODS

Between 1st January to 30th June 2015, 412 urinary stones were surgically removed from 397 children of age <1–15 years. Chemical composition was analysed by FTIR. Two milligrams of grinded stone was mixed with 200 milligram of potassium bromide powder and made into a pellet under hydraulic pressure of 8 ton (Shimadzu). The pellet was scanned by FTIR machine (Perkin-Elmer). Spectral patterns were interpreted using standard algorithm and matched to spectral data of known reference[7] and built in library of the FTIR machine software. Constituents of mixed stones were reported in percentage of compound.

The categorical measurements were summarized as numbers and percentages, whereas the numerical measurements were summarized as means and standard deviations. Chi-square tests were used for the comparison of categorical measurements between groups. All reported values were 2-sided and statistical significance was considered at *p*-value ≤0.05. All statistical calculations were done using SPSS-19.

RESULTS

The mean age of the children from whom stones were removed was 7.15±4.13 years with a M:F ratio of 2.4:1. Of the 412 stones, 263 (63.8%) were renal, 101 (24.5%) bladder and 48 (11.7%) ureteric stones. Of the 412 stones, 31 (7.5%) were removed by open surgery and 381(92.5%) by minimally invasive techniques. These were percutaneous nephrolithotomy(PCNL) 245, Ureterorenoscopy (URS) 38, Cystolithotomy 5, Perurethral cystolithotomy(PUCL) 83 and Percutaneous cystolithotripsy (PCCL) 10. Chemical composition of stones showed that 144 (34.9%) were pure composed of a single compound and 268 (65.1%) were mixtures (Figure 1). Of the 263 renal 83 (31.5%) were pure and 180 (68.4%) mixed. Of the 101 bladders 37 (36.6%) were pure and of the 48 ureteric stones 16 (33.3%) were pure and the rest were mixed stones. The overall frequency of compounds in renal, bladder and ureteric stones is given in table-1. The main constitutions were AAU in 65.04% and CaOx in 76.9% of the stones. AHU were highest in renal stones, CaOx in renal and ureteric stones, CAP in bladder and ureteric and Whitlockite in ureteric. The frequency of compound in stones removed from male and female children is given in table-2. The frequency of compound was similar in both groups of children. The location of stones removed from children in 3 age groups, 0–5, 6–10 and 11–15 years is given in (Figure-2). Bladder stones were highest in children 0–5 years and renal in children 11–15, years.

The overall frequency of compound in stones removed from children in age group 0–5, 6–10 and 11–15 years is given in table-3. AAU had the highest frequency in stones removed from children 0–5 years while CaOx had the highest frequency in children 11–15 years. The rest of the compounds were equally distributed. The frequency of compounds in 144 pure stones from kidney, bladder and ureter are given in table-4. The frequency were similar except xanthine stones were more prevalent in bladder and ureter. The frequency of pure AAU and CaOx stones in kidney, bladder and ureter in different age groups are given in figure-3 (A, B). AAU had the highest frequency in all locations in the age group 0–5 years, while CaOx in age group 11–15 years.

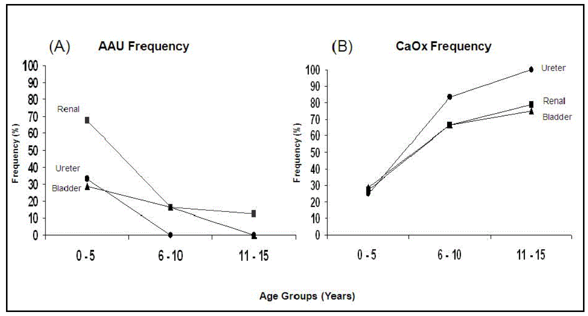

Figure-1: Chemical composition of stones

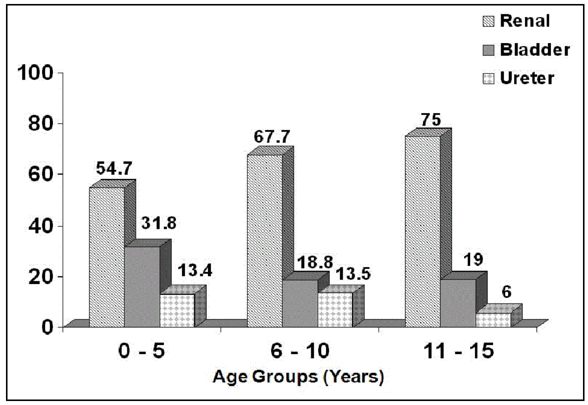

Figure-2: Stone location in different age group

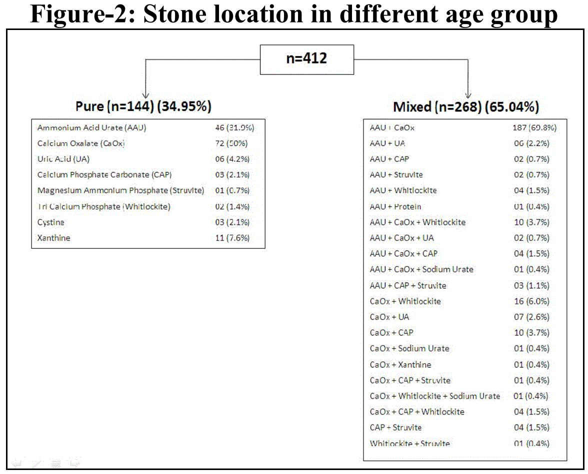

Figure-3: Frequency of Pure AAU and CaOx Stones in different age groups.

Table-1: Frequency of compound in stones removed from different locations

Stone Composition	Overall (n=412)	Renal (n=263)	Bladder (n=101)	Ureter (n=48)	*p*-Value
AAU (n, %)	268 (65.04)	197 (75)	53 (52)	18 (37.5)	0.001
CaOx (n, %)	317 (76.9)	212 (80.6)	69 (68)	36 (75)	0.042
UA (n, %)	21 (5)	8 (3)	11 (8.02)	2 (4.1)	0.009
CaPO4 Apatite (CAP) (n, %)	29 (7)	7 (2.6)	16 (15.8)	7 (14.5)	0.001
Whitlockite (n, %)	35 (8.4)	13 (4.9)	10 (9)	12 (25)	0.001
Struvite (n, %)	16 (3.8)	6 (2.2)	10 (9.9)	0 (0)	0.001
Sodium Urate (n, %)	3 (0.72)	3 (1.1)	0 (0)	0 (0)	0.425
Cystine (n, %)	3 (0.72)	1 (0.38)	0 (0)	2 (4.1)	0.011
Xanthine (n, %)	12 (2.11)	3 (1.1)	6 (5.9)	3 (6.25)	0.018
Protein (n, %)	1 (0.2)	1 (0.38)	-	-	0.753

Table-2: Frequency of compound in stones removed from male and female children

Stone Composition	Stone from Male (n=292)	Stone from Female (n=120)	*p*-Value
AAU (n, %)	186 (63.6)	82 (68.3)	0.426
CaOx (n, %)	220 (75.3)	97 (80.8)	0.249
UA (n, %)	16 (5.5)	6 (5)	1.000
CAP (n, %)	25 (8.9)	5 (4.1)	0.146
Whitlockite (n, %)	24 (8.2)	11 (9.1)	0.846
Struvite (n, %)	12 (4.1)	4 (3.33)	1.000
Sodium Urate (n, %)	1 (0.3)	2 (1.6)	0.204
Cystine (n, %)	3 (1)	0 (0)	0.559
Xanthine (n, %)	10 (3.4)	2 (1.6)	0.522
Protein (n, %)	1 (0.3)	-	0.084

Table-3: Frequency of compound in stones removed from children in different age groups.

Stone Composition	Age Group (1-5 years) n =179	Age Group (6–10 years) n=133	Age Group (11–15 years) n=100	*p*-Value
AAU (n, %)	130 (72.6)	78 (58.6)	60 (60)	0.018
CaOx (n, %)	112 (62.5)	114 (85.7)	90 (90)	0.001
UA (n, %)	12 (6.7)	7 (5.2)	2 (2)	0.229
CAP (n, %)	11 (6.1)	10 (7.5)	9 (9)	0.673
Whitlockite (n, %)	8 (4.4)	20 (15)	5 (5)	0.001
Struvite (n, %)	7 (3.9)	6 (4.5)	3 (3)	0.840
Sodium Urate (n, %)	0 (0)	0 (0)	2 (2)	0.043
Cystine (n, %)	2 (1.1)	0 (0)	1 (1)	0.484
Xanthine (n, %)	8 (4.4)	4 (3)	0 (0)	0.103
Protein (n, %)	0 (0)	1 (0.7)	0 (0)	0.349

Table-4: Frequency of compounds in pure stone at different location. (n=144)

Stone Composition	Overall (n=144)	Renal (n=87)	Bladder (n=38)	Ureter (n=19)	*p*-Value
AAU (n, %)	46 (31.9)	34 (39.1)	8 (21.1)	4 (21.1)	0.062
CaOx (n, %)	71 (49.3)	46 (52.9)	17 (44.7)	9 (47.4)	0.684
UA (n, %)	6 (4.2)	2 (2.3)	3 (7.9)	1 (5.3)	0.323
CAP (n, %)	3 (2.1)	2 (2.3)	1 (2.6)	0 (0)	0.033
Whitelockite (n, %)	2 (1.4)	0 (0)	2 (5.3)	0 (0)	0.059
Struvite (n, %)	1 (0.7)	0 (0)	1 (2.6)	0 (0)	0.245
Cystine (n, %)	3 (2.1)	1 (1.1)	0 (0)	2 (10.5)	0.077
Xanthine (n, %)	11 (7.6)	2 (2.3)	6 (15.7)	3 (15.8)	0.012

DISCUSSION

Our study has shown that AAU is a major component of urinary tract calculi of all the stones analysed located in kidney, bladder and ureter in this region. AAU was present in 65% and CaOx in 77%. Uric acid was found in 5%, struvite in 4% and calcium phosphate apatite in 7%. Metabolic stones cystine or xanthine were found in 3%. Pure stones composed of a single compound constituted 35% of all the stones, analysed where 50% were CaOx and 32% AAU. We did not observe differences in stone composition between genders. However, children in age group 0-5 years had AAU in 73% of the stones while CaOx was more frequent in children in age group 6–10 and 11–15 years, 80% and 90% respectively. The highest frequency of bladder stones was found in children 0–5 years and kidney stones in age group 11–15 years.

The aetiology and composition of stones varies in different populations influenced by several factors including economics, diet, climate and genetic factors.[8,9] An important finding in our study is the high frequency of AAU in stones in kidney (75%), bladder 52% and ureter 37%. Similar observations in recent years have been reported from other developing countries. In Egypt AAU was found in 26% of the upper tract and 27% of the lower tract stones.[10] In Tunisia 14% of the stones had AAU[11] while another study from Tunisia reported AAU in 47% of the stones.[12] A study from the North of Pakistan reported AAU in 45% of the stones.[13] A study from our centre a decade and a half ago reported AAU in renal, bladder and ureteric stones and this pattern remains in the present series.[2] In contrast AAU containing stones are rare in children in developed world. A study from USA on 5245 stones reported AAU in 2.8% of stone[14] while studies from Canada, Poland and China did not report AAU in their series[15–17]

Nutritional deficiencies in the developing world[18] combined with low protein and high carbohydrate diet has been considered an important factor in lithogenic process[2]. Hot climate, dehydration, uric acid saturation and conversion of glutamine to ammonia cause precipitation of ammonium acid urate and also increase calcium excretion leading calcium oxalate excretion.[19] This is perhaps the reason that majority of the stone are composed of mixture of AAU and CaOx in our series. Malnutrition, dehydration, legume rich diet and dietary deficiencies contribute to AAU stone formation.[19] The overall frequency of cystine was 2.1% and xanthine 7.1% in our series. This is comparative to cystine stones reported from USA 2.3%[14] while another reported 8%[20], Canada, cystine 5%[15], China, cystine < 1%[17] Poland, cystine < 1%[16] and Tunisia, cystine 6%[11]. There were no reports identifying xanthine stones. The frequency of infection stones, struvite was 0.7% and calcium phosphate apatite (CaP) 2.1%. These are lower than other countries in the region, Egypt struvite 8.7% CaP 10.7%[10], Tunisia, struvite 10%, CaP 6%[11]. Poland, struvite 24%.[16] China, struvite 4%[17], USA, struvite 4.1%[14] comparable is a report for northern Pakistan, struvite 1.4%[13]. Urinary tract infection and anatomical abnormalities have been associated with infection stones.[14]

Our study did not show any differences in composition of stones between genders however there was male predominance as reported by several reports.[10,11,13,21,22] Studies from USA showed higher percentage of CaOx and Struvite stones in females and uric acid stones in males.[14] Urinary tract infections have been implicated for higher struvite stones in females.[11,14] In our series frequency of struvite stones was 4.1% in male and 3.3% in female (*p*-Value 1.000).

We observed differences in stone composition in different age groups. AAU stones were more prevalent in children 0–5 years (73%) as compared to children 11–15 years (60%). CaOx stones were more prevalent in children 11–15 years (90%) as compared to children 0–5 years (62%). Similar were the findings in pure stones with AAU in children 0–5 years and CaOx in older children. In a study from USA, similar to our findings CaOx stones were more prevalent in children 11–16 (48%) as compared to children 0–5 years (38%).[20] Smaller children 0-5 years had more of struvite 26% as compared to older children 13% and half of the children 0–6 years had urinary tract infection.[20] Similar to finding in USA, pre-school children 0–6 years in Korea had more infection stones.[4] In contrast in our series struvite constituted less than 5% in all age groups. In the study from USA the findings were similar to our study where CaOx had the highest frequency in age group 14–18 years (88%) vs 58% in 1–5 years and AAU 8.8% in age group 1–5 years vs 1.3% in age group 14–18 years.[14] They also reported struvite stones 12% in age 1–5% vs 2.4% in age 14–18%.[14] All these observations suggest a global pattern AAU and infection stones in younger children due to malnutrition inflammatory bowel disease and UTI while CaOx in older children mainly related to dietary factors. The differences are only in the frequencies of these compounds. The strength of our study is a large cohort of stone from children and the use of FT-IR spectroscopy for stone analysis which is now considered the gold standard for stone analysis.[23,24] It allows analysis of small amounts of samples whereby several portions of the stones can be analysed and the method is standardized.[23,24] This has allowed us to accurately report pure and mixed stones specially urate containing stones helping in the management and prevention of recurrence. There are several limitations of our study. Firstly, we were not able to accurately identify the nucleus or core of calculus as majority of the stones were removed by minimally invasive techniques where the laboratory received multiple fragments rather the whole stones. Secondly our data does not include demographic, dietary medical or historical information except gender and age. We are therefore not in a position to adequately discuss the reported difference in stone composition.

CONCLUSION

We have presented data on urinary stone composition in children where we found significant differences based on location of the stones in the urinary tract and age of the patients. We have confirmed that AAU stones are still prevalent in high numbers most likely due to malnutrition, diarrhoea and chronic dehydration. Further studies are required to investigate metabolic risk factor to allow for better diagnosis and prevention of recurrence.

Conflict of Interest: None to declare.

AUTHORS' CONTRIBUTION

KI & MNZ: Literature search, study design, concept, data collection, data analysis, drafting. NF: Data collection, analysis, concept, drafting. UO, SS, SAHR: Data collection, analysis, study design, concept, final approval.

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