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Urinary Biochemical Profile of Patients with Ureteric Calculi in Jodhpur Region (North Western India)

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Summary. Urine chemistry of 42 normal subjects (NS) and 59 ureteric stone formers (SF) from Jodhpur region of Rajasthan, India is presented. Twenty four hour urinary levels of calcium, oxalic acid and uromucoids were significantly higher and levels of magnesium, citric acid and inorganic phosphorus were significantly lower in SF as compared to NS. No significant difference was observed in the uric acid, sodium and potassium levels in the two groups. Significant correlation was observed between calcium and magnesium; calcium and oxalic acid; calcium and citric acid; magnesium and oxalic acid; and oxalic acid and citric acid in NS on the basis of mmol/l but not on the basis of mmol/24 h. Calcium and oxalic acid correlation was uninfluenced by magnesium and citric acid levels. The log of risk factor index (RI) was higher ($p < 0.001$) in SF (–1.652) as compared to NS (–2.103). The log of ion activity product (IAP) was also higher ($p < 0.001$) in SF (-3.192×10^{-3}) than in NS (-2.914×10^{-1}). Based on RI and IAP, a scale has been devised for the prediction of the risk of stone formation and recurrence.

Key words: Ureteric stone formers – Urine chemistry – Oxalates – Calcium – Risk index – Ion activity product

Introduction

A high prevalence of urolithiasis exists in Rajasthan [11, 18, 19] an economically backward state in the north-western part of India. We have already reported the incidence and etiological factors of this disease in the Udaipur region of Rajasthan [18, 20, 21, 29–32]. Our preliminary study of the incidence of Urolithiasis in Jodhpur revealed a much higher (more than 3 times) incidence [19] than at Udaipur. This prompted us to investigate the urinary profile of stone formers and normal subjects at Jodhpur, a district having an area of 22,850 km^2 and population of 1,667,791.

Material and Methods

Forty two adult healthy volunteers and fifty nine patients from M. G. Hospital, Jodhpur with radiologically proven ureteric calculi formed the control (NS) and experimental (SF) groups respectively. Subjects from both groups belonged to low socio-economic category. Both the groups were placed on comparable low-oxalate diet which was home cooked in the NS and was the standard hospital diet in the SF. This diet was given for 3 days. On the third day 24 h urine sample was collected in 2.5 l glass bottle containing concentrated H_2SO_4 as preservative.

From each 24 h urine sample a 100 ml aliquot was transported cold to the laboratory of the department of Biochemistry, Medical College, Udaipur. Each sample was analysed for calcium [5], citric acid [24], creatinine [15], inorganic phosphorus [15], magnesium [15], uromucoids [15], oxalic acid [9], potassium (Flame Photometer), Sodium (Flame Photometer) and uric acid [24].

Ionic activity product index (IAP) and calcium oxalate risk index (RI) of normal subjects (NS) and of stone formers (SF) were calculated by the formulae devised by Ahlstrand et al. [1].

Results

The urinary excretion of the parameters (mmol/24 h and mmol/l) investigated in NS and SF is given in Table 1. It showed significant differences in the urinary concentration (mmol/l) of oxalic acid, uromucoid, citric acid, sodium, inorganic phosphorus and creatinine between the two groups. The 24 h excretion showed a different pattern. Calcium and magnesium showed a significant difference whereas the difference in the sodium excretion was not significant.

Correlation coefficients (r) between some selected pairs of parameters were examined. The results are given in Table 2. In the NS a significant relationship was observed in all the pairs except between Ca and Na when calculated on a concentration basis. But when calculated on a mmol/24 h basis the relationship became nonsignificant in all the pairs. In the SF no consistent pattern was observed.

Table 1. Urine chemistry of normal subjects and ureteric stone formers

S. No.	Parameters	Normal subjects (42)		Stone formers (59)	
		mmol/l	mmol/24 h	mmol/l	mmol/24 h
1.	Calcium	3.01 ± 2.07	2.62 ± 1.17	3.76 ± 2.58	3.58 ± 1.87[a]
2.	Magnesium	3.20 ± 2.75	2.95 ± 1.16	4.06 ± 2.69	4.11 ± 3.07[a]
3.	Oxalic acid	00.38 ± 0.22	0.34 ± 0.12	0.59 ± 0.26[b]	0.56 ± 0.26[b]
4.	In. Phosphorus	33.89 ± 20.37	29.84 ± 11.75	16.76 ± 10.66[b]	16.78 ± 9.86[b]
5.	Uric acid	1.33 ± 0.90	1.28 ± 0.70	1.38 ± 1.11	1.21 ± 0.68
6.	Citric acid	2.54 ± 1.79	2.19 ± 0.98	1.37 ± 1.48[b]	1.12 ± 0.73[b]
7.	Creatinine	9.98 ± 4.74	9.32 ± 3.42	8.17 ± 3.65[a]	7.60 ± 3.40[a]
8.	Sodium	170.11 ± 89.75	193.75 ± 28.06	225.58 ± 92.87[c]	232.85 ± 135.88
9.	Potassium	31.85 ± 14.91	32.64 ± 16.50	27.27 ± 12.00	26.89 ± 15.03
10.	Uromucoid	6.69 ± 3.94 (mg/100 ml)	70.84 ± 32.07 (mg/24 h)	11.45 ± 10.40[b] (mg/100 ml)	127.06 ± 96.56[b] (mg/24 h)
11.	Volume		1,197 ± 762 ml		1,085 ± 567 ml

[a] $p < 0.05$, [b] $p < 0.001$, [c] $p < 0.02$

Table 2. Coefficient of linear correlation for some of the selected pairs of parameters

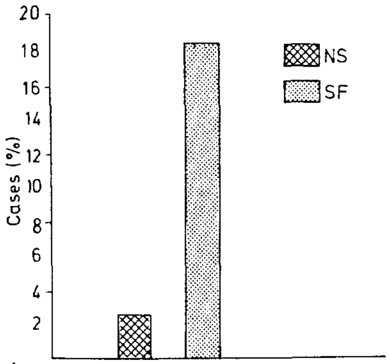
Pairs studied	Normal subjects		Stone formers	
	mmol/l	mmol/24 h	mmol/l	mmol/24 h
1. Ca vs Mg	0.3371[a]	−0.2602 NS	0.3136[b]	0.2763[a]
2. Ca vs Ox. A	0.6716[b]	0.2279 NS	0.1489 NS	0.2149 NS
3. Ca vs Na	0.0057 NS	−0.0985 NS	−0.0070 NS	0.2763[a]
4. Ca vs citric acid	0.4276[b]	−0.0757 NS	0.1087 NS	0.1661 NS
5. Mg vs Ox. A	0.3408[a]	0.1355 NS	0.1955 NS	0.1198 NS
6. Ox. A vs citric acid	0.5385[b]	0.1863 NS	0.1220 NS	0.0288 NS

[a] $P < 0.05$, [b] $P < 0.01$

Table 3. Equation of linear regression for the pairs of parameters where significant correlation has been observed

Subjects	x	y	Regression of y on x	Regression of x on y
NS (mmol/l)	Ca	Mg	$y = 4.5034 + 0.2711x$ [a]	$x = 8.8049 + 0.4193y$ [a]
	Ca	OxA	$y = 1.5094 + 0.1616x$ [b]	$x = 2.4132 + 2.7897y$ [b]
	Ca	Citric acid	$y = 29.9747 + 1.9405x$ [b]	$x = 7.0351 + 0.0942y$ [b]
	Mg	OxA	$y = 2.6394 + 0.1030x$ [a]	$x = 3.8736 + 1.1274y$ [a]
	OxA	Citric acid	$y = 18.2602 + 10.1533x$ [b]	$x = 1.9348 + 0.0286y$ [b]
SF	Ca (mmol/l)	Mg	$y = 7.4171 + 0.1852x$ [b]	$x = 16.759 + 0.5311y$ [b]
	Ca (mmol/24 h)	Mg	$y = 66.0202 + 0.2529x$ [a]	$x = 104.3949 + 0.3020y$ [a]
	Ca (mmol/24 h)	Na	$y = 3930.0175 + 10.5722x$ [a]	$x = 95.9608 + 0.0072y$ [a]

[a] $p < 0.05$, [b] $p < 0.01$



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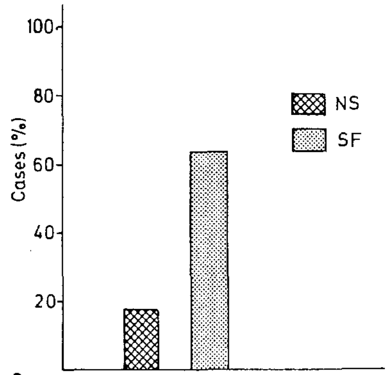

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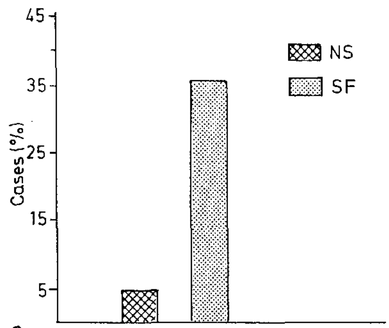

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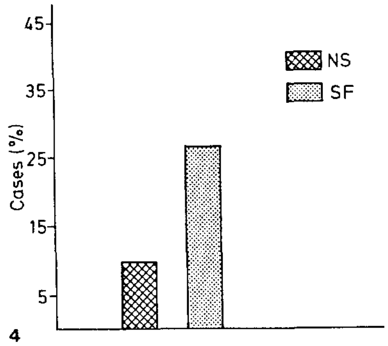

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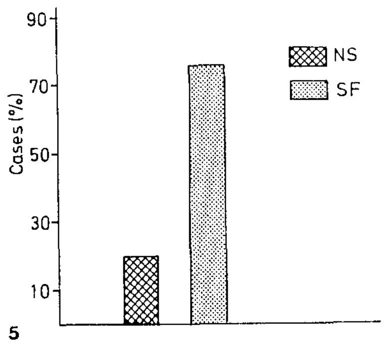

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Figs. 1–5. NS & SF excreting.
1 > 4.99 mmol calcium/24 h
2 > 0.44 mmol oxalic acid/24 h
3 > 159.4 mg uromucoid/24 h
4 < 1.68 mmol magnesium/24 h
5 < 1.42 mmol citric acid/24 h

Table 4. First order partial correlation coefficient for the pairs of parameters where significant correlation has been observed in case of normal subjects

Parameters considered (mmol/l)		Variable kept constant	Partial correlation Coefficient
Ca	Mg	Oxalic acid	0.1554 NS
Ca	Ox. A	Magnesium	0.6289[b]
Mg	Ox. A	Calcium	0.164 NS
Ox. A	Citric acid	Calcium	0.3752[a]
Ca	Ox. A	Citric acid	0.5794[b]
Ca	Citric acid	Oxalic acid	0.1056 NS

[a] $p < 0.05$, [b] $p < 0.01$

Table 5. Ion activity product index and calcium oxalate risk index in normal subjects and stone formers

Index	NS (mean ± SE)	SF (mean ± SE)
Ion activity product (IAP)	–0.2914 ± 0.0541	–0.0031 ± 0.0370[a]
Calcium oxalate risk (RI)	–2.1034 ± 0.0502	–1.6520 ± 0.0507[a]

[a] $p < 0.01$

Table 6. Number and percentage of normal subjects and stone formers with disturbed stone promoting and inhibiting substances

	NS	SF
Both promoters and inhibitors disturbed	Nil	Nil
Only inhibitors disturbed	1 (2.4%)	11 (18.6%)
Only promoters disturbed	Nil	3 (5.1%)

Promoters	Inhibitors
Oxalic acid > 0.44 mmol/24 h	Magnesium < 1.68 mmol/24 h
Calcium > 4.99 mmol/24 h	Citric acid < 1.42 mmol/24 h
Uromucoid > 159 mg/24 h	

Equations of linear regression for the pairs of parameters where significant correlation had been observed are given in Table 3. To ascertain any significant correlationship observed in the various pairs of parameters in NS, the first order partial correlation coefficient was worked out and the results are given in Table 4.

Percentage of SF and NS suffering from hypercalciuria, hyperoxaluria, raised uromucoid excretion, hypomagnesuria, hypocitraturia is given in Figs. 1–5.

Table 6 shows the distribution of the NS and SF having disturbed concentration of either promoters or inhibitors or both.

Ionic activity product index (IAP) and the calcium oxalate risk index (RI) were found to be significantly higher in

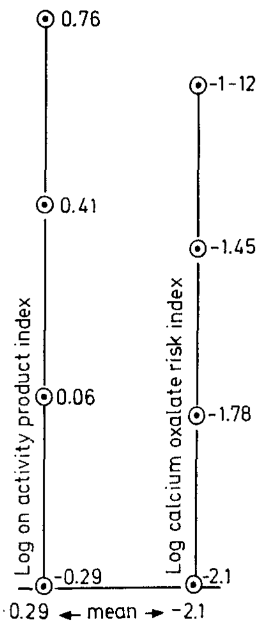

Fig. 6. Scale for predicting risk of stone formation from ionic activity product index and calcium oxalate risk factor index in the population under study

the SF as compared to NS (Table 5). Based on these observations we designed a scale (Fig. 6) to predict the risk of stone formation in an individual after observing his urinary profile.

Discussion

Several studies in India and abroad have implicated different etiological factors in different populations on the basis of the study of urine chemistry [16, 23, 28, 35]. Our studies [18, 20, 33] on urine chemistry in two different parts of India viz. Manipur (North-Eastern border state) and Udaipur (Western part) also have revealed that different etiologic factors are operating in these two areas. This study in Jodhpur region has also brought out interesting observations. Low urinary output has been reported to be one of the important etiologic factors in urolithiasis in some populations [4], but in this regard we did not observe any significant difference in NS and SF groups. However, 42.8% of the NS and 35.6% of SF had urinary out put of < 800 ml/day.

Urinary calcium has long been recognised as a major risk factor for urolithiasis [17, 25, 29]. In the present study significantly higher 24 h urinary calcium excretion was observed in the SF as compared to the NS. As all the subjects were taking < 9.98 mmol of calcium/day, an excretion of > 4.99 mmol of calcium per 24 h, was taken to indicate hypercalciuria. 18.6% of the SF and 2.3% of NS were hypercalciuric (Fig. 1).

Recent studies have indicated that hyperoxaluria is far more dangerous than hypercalciuria in the genesis of stone [2, 13, 26]. In the developing countries hyperoxaluria and oxalcrystalluria have been reported to be important features [18, 34, 38]. In Jodhpur region 16.67% and 62.72% of the NS and SF respectively were hyperoxaluric (excreting > 0.44 mmol/24 h, Fig. 2). As both NS and SF maintained a low oxalate diet (< 1.66 mmol/day), we feel that this hyperoxaluria was of endogenous origin and etiologically a very significant feature.

Uric acid has been indentified as a major risk factor in various populations [23]. In India hyperuricosuria has been shown to be a significant factor in the Manipur population [33]. However we have observed that uric acid excretion is fairly low in the Udaipur area of Rajasthan [29]. The results in this study show a similar pattern in the Jodhpur area.

The 24 h uromucoid excretion in the NS and the SF was 70.84 ± 32.07 mg and 120.06 ± 96.56 mg respectively. Even on the concentration basis its level was almost double in the latter as compared to the former (Table 1). These differences are statistically significant. Strikingly 33.8% of SF had 24 h excretion more than mean + 2 SD of NS (Fig. 3). We have observed higher uromucoid excretion in SF from the Udaipur region [32]. However, no other Indian epidemiological data are available for comparison. Uromucoids have been shown to be important in the initiation [6, 27] as well as in the promotion of calcium oxalate and calcium phosphate crystallization and in stone formation. It therefore, appears that uromucoids play a significant role in stone formation in the population under study.

The average 24 h urinary excretion of magnesium was within normal limits in the NS as well as in SF but notably it was significantly higher in the latter (Table 1). At a glance this finding appears to be paradoxical as most of the studies have reported hypomagnesiuria in SF [7, 18, 29]. Further analysis of the data however shows that 25.4% of the SF were actually hypomagnesuric (< 1.68 mmol/24 h) whereas only 9.5% of the NS were in this category (Fig. 4).

Citric acid has also repeatedly been shown to be an inhibitor of crystallization process in urine and several studies have reported low urinary citrate excretion in SF [14, 36], although few studies point to the contrary [10]. Our data show significantly lower excretion of citrate in the local SF as compared to the NS (Table 1) and Fig. 5 and thus support the former view.

The 24 h urinary excretion of inorganic phosphate was significantly lower in the SF as compared to the NS (Table 1). However its significance as an etiological factor in the local population can not be commented upon till further studies on various fractions of phosphates are taken up.

The urinary sodium and potassium excretion did not show any discernible trend in the study, nor seem to be associated with the etiology of the disease.

The relationship between urinary inhibitors and promotors of stone formation in the local population (Table 2) did not provide any conclusive information.

As the process of crystallization in any solution is influenced by the concentration of the solute, we felt that this relationship can better be examined by analysing the data on mmol/litre basis. When thus examined, interesting correlationships were observed between Ca and Mg, Ca and oxalic acid, Mg and oxalic acid, and Oxalic acid and citric acid in the NS. In the SF all these correlations were nonsignificant except for Ca and Mg. Positive correlation between urine sodium and calcium has been reported by several workers [12, 22], but our data do not lend support to this phenomenon.

The expected value of a dependent parameter for a given value of independent parameter can be worked out from the relationships given in Table 3. We feel that such data should be worked out in different population groups. Such data should also provide a basis for verifying the cause and effect relationship on a more comprehensive basis between various parameters.

The correlations between the selected parameters as observed in Table 2 may be independent of the influence of one or more urinary constituents. To examine this aspect we made the first order partial correlation coefficient (Table 4). Interestingly some of the significant correlations observed in Table 2 came out to be nonsignificant when one of the two variables was kept constant thereby indicating that these parameters did not have independent relationship. However, correlations between Ca and oxalic acid at a constant level of Mg; Oxalic acid and citric acid at a constant level of Ca and Ca and Oxalic acid at a constant level of citric acid were still significant.

Different indices have been suggested to predict the risk of stone formation/recurrence in a particular person. We have used RI and IAP [1] for this purpose. The index values for each person in both the groups were worked out and converted into their log values for valid comparison. Statistical comparison of the averages of the indices between the two groups revealed significantly higher ($p < 0.001$) risk values in the SF (Table 5).

The scale designed by us (Fig. 6) using IAP and RI, provides a convenient method of predicting the propensity of stone formation of any individual in the local population. Similar scales can be developed for individual population which can be used conveniently by the clinicians.

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