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SYMPOSIUM PAPER

Female stone disease: the changing trend

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Abstract This paper has attempted to assess the changes noted in the trends in the incidence and biochemical pattern of female urolithiasis patients during the period 1971–2008. A prospective descriptive clinical study was done on 8,590 stone patients belonging to both sexes treated at the urinary stone clinic. The incidence of stone disease among the two sexes was plotted. The various metabolic parameters including 24-h urine volume, urine calcium, phosphorus, uric acid, oxalate, magnesium, creatinine and citrate, serum creatinine, calcium, phosphorus, uric acid and magnesium and calculated parameter calcium:magnesium ratio were studied. The possible causes for the change in incidence of stone disease in the female sex were elucidated. Of the patients studied, 12.7% (1,091) were females. There was a definite increase in the incidence of female urolithiasis over the past 37 years ($P < 0.001$). There were significant variations in urine biochemical parameters. There was a definite increase in the excretion of urinary calcium over the years ($P < 0.001$). The excretion rate of oxalate in urine of females also increased steadily over the years ($P < 0.001$). The magnesium in urine of females reduced over the years ($P < 0.001$). Urinary citric acid has however shown an increase over the years ($P < 0.001$). Urinary excretion of phosphorus ($P < 0.001$) and urinary uric acid ($P < 0.001$) showed a decreasing trend. There was a considerable increase in the percentage of females with high calcium:magnesium ratio over the years ($P < 0.001$). There was a definite decrease in female patients with hypercalcemia over the years. Serum phosphorus and magnesium also increased significantly with the passage of time. Serum uric acid did not vary significantly through the years. The decrease in the excretion rate of magnesium which is inhibitory to stone genesis, together with the increased excretion of calcium and oxalate may have contributed to the increasing incidence of stone disease in females. This might be due to changes in living standards and dietary habits.

Keywords Urinary stone · Incidence · Female · Urine calcium · Oxalate · Magnesium · Citric acid · Phosphorus

Introduction

Nephrolithiasis is a cosmopolitan disease occurring in both industrialized and developing countries. In the recent times, the prevalence of stone disease has been relentlessly increasing in parallel with profound changes in living standards and dietary habits [1]. It has also been reported that there is an appreciable decrease in the male predominance of nephrolithiasis [2]. However, studies evaluating the changes in the various biochemical parameters over the years in males and females, which may relate to the changing gender prevalence of stone disease are scarce. In this paper, the changing trends in the biochemical parameters over the years in males and females have been assessed during the period 1971–2008.

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Methods

A descriptive clinical prospective study was done on 8,590 stone patients belonging to both sexes treated at the urinary stone clinic from 1971 to March 2008. The various metabolic parameters including 24-h urine volume, urine calcium, phosphorus, uric acid, oxalate, magnesium, creatinine and citrate, serum creatinine, calcium, phosphorus, uric acid and magnesium and calculated parameter calcium:magnesium ratio were compared and analysed over the years in females. The incidence of stone disease among females was plotted. The biochemical values were compared between various years 1971–2008. The recorded data were transformed into nonparametric form and frequencies and cross tabs were obtained. To elucidate the associations and comparisons between different parameters, Chi square (χ^2) test was used as nonparametric test. Multivariate logistic regression analysis was performed to assess the risk factors (odds ratio) of different factors for each group. The possible causes for the change in incidence of stone disease in the two sexes were elucidated.

Results

Of the 8,590 stone patients studied, 12.7% (1,091) were females. The percentage of females ranged from 6.62 to 17.04% with an odds ratio of 6.87:1.0 (Table 1). The highest incidence of females was noted in the recent years. A significant increase in the percentage of female stone patients over the past 37 years was made out as evidenced in Fig. 1 ($P < 0.001$).

The various values of the different biochemical parameters during the different year groups from 1971 to 2008 are depicted in Table 2. There was no significant change in the 24-h urine volume of females over the years ranging between 1,568 and 2,102 cc, with a mean of 1,741 cc. There were significant variations in other urine biochemical parameters. There was a definite

Table 1 Sex-wise incidence among Urolithiasis patients from 1971 to 2008

Year	Total urinary stone patients	Male no.	Male (%)	Female no.	Female (%)
1971–1975	741	682	92.04	59	7.96
1981–1985	1,315	1,228	93.38	87	6.62
1991–1995	1,665	1,479	88.83	186	11.17
1998–2002	2,081	1,797	86.35	284	13.65
2003–2008	2,788	2,313	82.96	475	17.04
Total	8,590	7,499	87.3	1,091	12.7

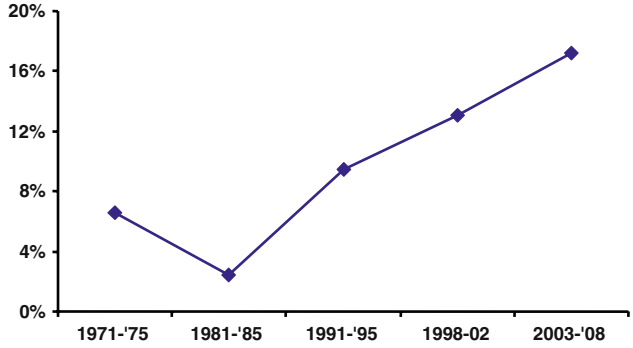

Fig. 1 Pattern of incidence of female stone patients from 1971 to 2008

increase in the excretion of urinary calcium over the years ($P < 0.001$). It was lowest at 146 mg/day in early 1970s and increased to 230 mg/day in 2003–2008 with a mean of 195 mg/day. The mean value of urinary oxalate was 73.8 mg/day with the excretion rate increasing steadily over the years from 46 mg/day to 80s in the later years and the variation was statistically highly significant ($P < 0.001$) as noted in the regression graph (Fig. 2). The magnesium in urine of females has decreased over the years from 7.3 to 4.3 mEq/day with a mean of 5.9 mEq/day with highly significant statistical significance ($P < 0.001$) as shown in Fig. 3. Urinary citric acid however showed an increase over the years from 267 to 564 mg/day with very high statistical significance ($P < 0.001$). The man value was 361 mg/day, which was above the basic required limit. Urinary excretion of phosphorus showed significant reduction ($P < 0.001$) ranging from 1,356 to 987 mg/day, with a mean of 1,172 mg/day. Urinary uric acid also showed very highly significant statistical variation ($P < 0.001$) ranging from 601 to 432 showing a decreasing trend. The mean values were mostly below the upper limit of normal with a mean of 501 mg/day. There was a considerable increase in the percentage of females with high calcium:magnesium ratio over the years ($P < 0.001$), the ratios ranging from 24.1 to 54.76 with a mean of 37.7, ultimately crossing the normal limit of 50 in the latest years. Like urine, the serum parameters calcium, phosphorus and magnesium showed significant changes in females over the years as compared to uric acid that failed to show any significant variation. There was a definite decrease in female patients with hypercalcemia over the years. The mean serum calcium ranged from 8.1 to 9.0 mg% with a mean of 8.6 mg% with significant variation ($P < 0.05$). The serum phosphorus gradually increased from 2.7 to 4.2 mg% with a mean of 3.34 mg% with significant variation ($P < 0.05$). Serum magnesium values increased from 1.6 to 2.4 mg% over the years with a mean of 1.96 mg%. Serum uric acid stayed fairly constant with a mean of 4.66 mg%.

Table 2 Variations in different values among female stone patients from 1971 to 2008

No.	Parameter	1971–1975	1981–1985	1991–1995	1998–2002	2004–2008	*P* value
1	Incidence (%)	7.96	6.62	11.17	13.65	17.04	$P < 0.001$
2	Urine volume (cc)	1,682	1,732	1,568	2,102	1,620	NS
3	Urine calcium (mg/day)	146	176	210	214	230	$P < 0.001$
4	Urine oxalate (mg/day)	46	63	89	87	84	$P < 0.001$
5	Urine magnesium (mEq/day)	NA	7.3	5.9	6.1	4.2	$P < 0.001$
6.	Urine creatinine (g/day)	1.2	1.7	1.6	2.1	2.1	$P < 0.001$
7	Urine citric acid (mg/day)	NA	267	289	325	564	$P < 0.001$
8	Urine phosphorus (mg/day)	1,267	1,356	1,178	1,098	987	$P < 0.001$
9	Urine uric acid (mg/day)	532	601	475	432	465	$P < 0.001$
10	Serum calcium (mg%)	8.9	9.0	8.7	8.3	8.1	$P < 0.05$
11	Serum phosphorus (mg%)	2.7	3.2	2.9	3.7	4.2	$P < 0.05$
12	Serum magnesium (mg%)	1.6	1.9	1.8	2.1	2.4	$P < 0.01$
13	Serum uric acid (mg%)	4.5	3.9	5.2	4.6	5.1	NS
14	Calcium:magnesium ratio	NA	24.1	35.6	35.0	54.76	$P < 0.001$

NA Data not available (as magnesium and citrate were not estimated during that period, *NS* not significant

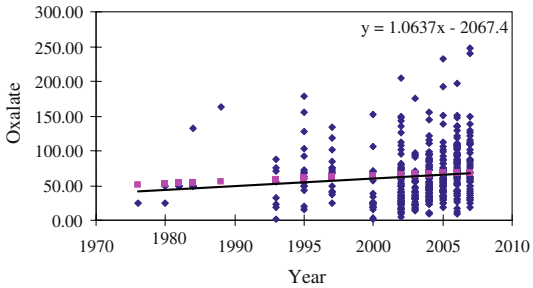

Fig. 2 Regression between urinary oxalate and years in female

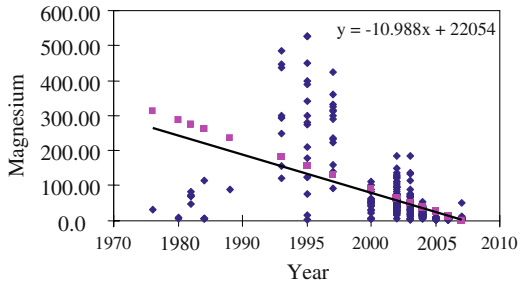

Fig. 3 Regression between urinary magnesium and years in female

Discussion

The incidence of stones in females has been reported differently in different studies. Unal et al. [3] in a gender study of 173 urinary stones found the male to female ratio to be 88:85. In America, a hospital incidence study showed a high occurrence of stones in women with 21.0% for renal calculi and 19.2% for ureteral calculi [4]. In another US study, the overall male:female ratio decreased from 3.1 to 1.3 between 1970 and 2000 [5]. In Iran, urolithiasis was slightly more frequent and persisted in males (6.1%) than females (5.3%) giving a male-to-female ratio of 1.15:1 [6]. A study from Italy reported 117 boys and 18 girls with a male: female ratio of 6.5:1 [7]. A report from Argentina shows a slightly higher incidence in men (4.35%) than in women (3.62%), with a male to female ratio of 1.19:1 [8]. The present study shows the female incidence to be fairly lower with odds ratio of 6.87:1.

A study over the years for the change in stone composition showed that phosphate stones were on average heavier and relatively more common in women, had an earlier age peak frequency in women than oxalate stones and became less frequent over time [9]. Our study also evidenced an increase in the percentage of hyperphosphatemic female stone patients over the years. There was a considerable increase in the percentage of females with a high calcium:magnesium ratio over the years ($P < 0.001$).

This study has brought out the increasing incidence of stone disease over the past 37 years and proved a change in the gender prevalence of this disease, whereby the male predominance of the nephrolithiasis is definitely on the decline. Studies have linked low serum and/or lymphocyte magnesium to an increased tendency to form calcium stones [10]. There is also evidence that supports increased calcium excretion in urine to precipitate urinary stone formation [11]. The decrease in the excretion rate of magnesium which is inhibitory to stone genesis, together with the increased excretion of calcium and oxalate may have contributed to the increasing incidence of stone disease in females. The results of this study thus show the importance of studying the metabolic status of female stone patients

from a biochemical point of view since this is the only way to achieve a diagnosis of the metabolic abnormality and to initiate a specific therapy to bring down the female incidence of renal stone disease.

Conclusion

The decrease in the excretion rate of magnesium which is inhibitory to stone genesis, together with the increased excretion of calcium and oxalate may have contributed to the increasing incidence of stone disease in females. This might be due to changes in living standards and dietary habits.

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