Familial Relations and Recurrence Pattern in Nephrolithiasis

New Words About Old Subjects

Abbas Basiri[1], Nasser Shakhssalim,[1] Ali Reza Khoshdel,[2] Ahmad Javaherforooshzadeh,[3] Hossein Basiri,[4] Mohammad Hadi Radfar,[3] Negar Dorraj[4]

Purpose: While medical and surgical approaches to urolithiasis are different for single and recurrent stone former (RSF), the RSF definition itself is commonly overlooked. Moreover, despite consensus on association between family history (FH) and urolithiasis, more epidemiologic evidence is required to clarify the nature of this relationship. Our purpose was to propose a more precise definition of RSF, and also to investigate how family history may affect urolithiasis.

Materials and Methods: Using a multistage stratified sampling in 4 seasonal phases, 6127 subjects with imaging-proven urolithiasis were detected in 12 Iranian regions. The FH of urolithiasis and the average interval between episodes (cycles) were determined by an informed interview.

Results: Of 6127 patients with the mean age of 41.8 ± 15.1 years, 42% had FH, and 22.2% were RSF of whom 61% were men. The patients with FH had a greater chance of recurrence (OR = 1.2, 95% Confidence Interval (CI), 1.1 to 1.4). Furthermore, patients with positive FH had more episodes (P = .0001), comparable cycles and younger ages at the onset (P = .02) than those patients without a FH. In the RSF group, the 90th percentiles of the cycle were 60 months and the estimated mean stone cycle for the population was 25.34 months (99% CI, 23.0 to 27.7).

Conclusion: Family history seems very common in Iranian population and is a risk factor for recurrence. Moreover, RSF could be identified by the estimated average cycle in the population (25.3 months) or by the percentiles.

Keywords: epidemiology, genetics, recurrence, urolithiasis

Urol J. 2010;7:81-6.
www.uj.unrc.ir

[1]*Urology and Nephrology Research Center, Shahid Labbafinejad Medical Center, Shahid Beheshti University, MC, Tehran, Iran*
[2]*AJA University of Medical Sciences, Tehran, Iran*
[3]*Urology and Nephrology Research Center, Shahid Labbafinejad Medical Center, Tehran, Iran*
[4]*Urology and Nephrology Research Center, Tehran, Iran*

Corresponding Author:
Nasser Shakhssalim, MD
No.103, 9th Boustan St., Pasdaran Ave., Tehran, Iran
Tel: +98 21 2256 7222
Fax: +98 21 2256 7282
E-mail: slim456@yahoo.com

Received May 2009
Accepted February 2010

INTRODUCTION

Urolithiasis is a common worldwide disease and its lifetime incidence is approximately 10% to 15% .[1-4] Furthermore, 20% to 75% of the patients experience the recurrence of the disease within ten years of the first episode.[4-6] Consequently, urolithiasis causes a burden on the society and significantly influences patients' life quality. Therefore, various approaches, including several metabolic workup protocols have been suggested in order to reduce the recurrence rate of the disease.[2,4,7,8] Due to economic considerations and limited resources, however, metabolic evaluation of the disease is not usually recommended for the first-timers or occasional recurrent stone formers (RSFs);[8] thus, medical treatment is considered cost-effective only in RSFs.[9,10]

Nevertheless, the definition of RSF is still vague and mainly based on arbitrary cut-points, personal opinions, or even economic and insurance standards, whereas epidemiologic evidence has rarely been referred to classify the patients. Although there is consensus on the association of family history (FH) and the urolithiasis, more epidemiologic information regarding the nature and the impact of FH are required to enable us to recognize the high risk groups for community interventions.

This population-based study aimed to identify the magnitude of the stone episode interval as a marker of RSF definition in Iranian population, particularly in patients with FH of the disease. Such definition not only could help in the related risk assessments in those patients, but also provides the health system with the opportunity to have a forecast for the related services.

MATERIALS AND METHODS

This study was conducted as part of a nationwide epidemiologic research in 787 imaging centers in 12 ecologic regions (composed of 30 provinces) across Iran. A stratified "*epsem scheme*" (equal probability selection method) sampling method was used and radiologically documented 6 127 positive subjects for urinary stone were determined out of 117 956 referrals (for various causes) to the imaging centers.

Based on a detailed interview, the history of stone disease in close family members, including father, mother, siblings, and the descendants was asked from the patients as well as the history of the disease in their spouses, and the relative frequency of each was recorded. In addition, the number of the family members with the disease was considered as a separate variable. To minimize any potential confounding effect of the gender on the results, the familial profile was also evaluated in genders, separately.

The relationships between the familial profile (either as a dichotomous or as a string variable) and the other variables such as the number of stone episodes, age of onset, and recurrence intervals were evaluated by non-parametric spearman correlation and chi-square, and the difference in subgroups was analyzed by Kruskal-Wallis and Median tests.

Patients with one or more previous episodes of the stone disease were recognized as RSF. The duration of the disease from the time of the diagnosis to the date of the interview was recorded, and patients with duration of less than 240 months were selected for study purposes, since data beyond this point were scant and unreliable. Thereafter, the stone episode interval (cycle) was obtained for each patient that was the duration divided by the episode number. Subsequently, the mean and the standard error (SE) for the point estimate were calculated and 99% confidence interval (CI) of the episode cycle was determined using the following formula:

$$99\%\ \text{confidence interval} = \text{Mean} \pm (2.58 \times \text{SE})$$

The demographic reports for the population were tabulated, and the "cycle" and the mean episode number were compared in different sexes by Mann-Whitney *U* test, and multivariate analysis was applied using the SPSS (Statistical Package for the Social Science, version 12.0, SPSS Inc, Chicago, Illinois, USA) software. A *P* value less than .05 was considered statistically significant.

RESULTS

General characteristics: Forty-two percent of the stone positive subjects had FH of urinary stone disease in their close families and 22.2% had at least one episode of recurrence (labeled as RSF). Around 61% of the samples were men and more than 75% were from urban areas. The mean age was 41.8 ± 15.1 years and 82.5% were married. In the studied population, there were 13.7% smokers, and 22.2% uneducated participants.

Approximately, 34% had received some forms of medications in their lifetime for urolithiasis, 31% experienced extracorporeal shock wave lithotripsy, and 17.4% had a history of a surgical intervention for urinary stones (either endoscopic, or open). Reducing the salt consumption, dairy products, and protein were considered by 49%, 39%, and 35% of the patients, whereas increasing water intake was taken seriously in about 70% of the patients.

Familial Pattern: Of 6127 subjects, over 22% had a parental history of the disease, while 1.7% had a dual parental history (both parents). The FH in the siblings and descendents was 27.9% and 9.8%, respectively, ie, 14.2% in sisters and 20.7% in brothers. When gender was separately analyzed, 40.8% of men and 46% of women had a positive FH of the urinary stone disease ($P = .0001$). Women were dominant with respect to the FH in their sisters and children ($P = .001$ and $P = .0001$, respectively). However, men and women groups were comparable regarding the frequency of the disease in their parents and their brothers ($P = .88$ and $P = .67$, respectively). In other words, the FH in brothers was the most frequent relationship in both genders. Interestingly, the frequency of the stone disease history in the spouse was 54% in women, whereas it was 46% in men ($P < .0001$); ie, the concurrence of the disease in spouse is more likely in women. Nonetheless, this might be due to the male predominance in the disease.

Family history in the younger group (≤ 40 Y, n = 3056) was more frequent than the older group (> 40 Y, n = 2946) (44.5% vs. 41.5%, $P = .03$). Mann-Whitney U test demonstrated that the number of stone episodes was significantly higher in the group with a positive first degree FH ($P = 00.1$) (Figure 1). Nevertheless, the cycle was not significantly different between the groups ($P > .05$) (Figure 2). Instead, the age of onset of

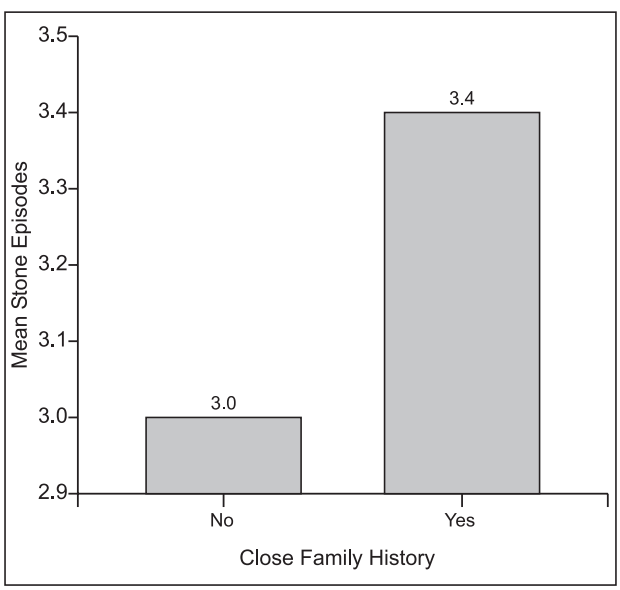

Figure 1. Mean episodes for urolithiasis in patients with and without first degree family history of the disease ($P = .001$).

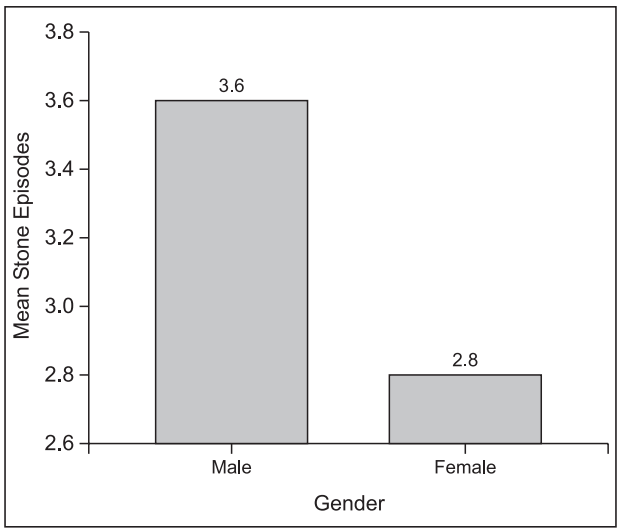

Figure 2. Mean stone episodes in urolithiasis patients, males and females ($P = .001$).

the disease was younger in patients with a FH [Medians: 34 interquartile range (IQR) = 19) vs. 36 (IQR = 22), $P = .02$].

As a categorical scale, the stone episodes raised with increase in number of family members with urolithiasis (Pearson $Chi^2 = 28.3$, $P = .03$). Consequently, when both variables were considered as dichotomous variables, patients with a positive FH had 1.2 times more chance of recurrence (Fisher exact test, $P = .002$, OR = 1.2, 95% CI, 1.1 to 1.4).

To compare the median age at the onset based on the number of the affected family members, since only 28 and 1 patients remained with 4 or 5 positive FH, respectively, they were discarded for the next analysis. Kruskal-Wallis test demonstrated a trend of younger age at onset for stronger FH ($P = .02$)
(Figure 3), which was also confirmed by the median test (median = 35.3, $P = .004$).

There was a weak but significant positive relationship between the number of family members with the stone disease and the number of stone episodes (Spearman's Rho = 5%, $P = .001$). In contrast, there was a weak but significant inverse correlation between the number of the affected family members and the age of the onset of the disease (Spearman's Rho = 6%, $P = .006$).

Recurrence pattern: The mean duration of the disease was 53.3 months (SD = 58.0, SE = 1.6),

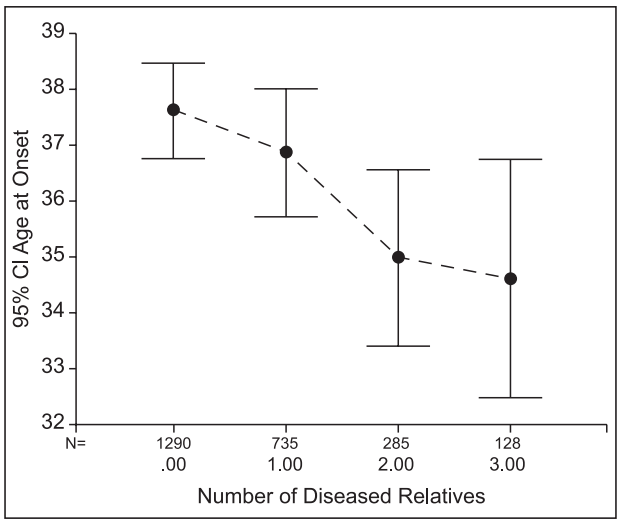

Figure 3. Non-parametric comparison of the age of onset according to the number of the affected individuals in the close family members.

and over 41% had 3 or more episodes (mean = 3.3, SD = 5.3, SE = 0.1) of the disease. The median cycle was 12 months, and 75th and 90th percentiles were 32.4 and 60 months in our sample, respectively. More importantly, the estimated mean stone episode interval (cycle) was 25.34 months (SE = 0.91) (99% CI, 23.0 to 27.7) for the population.

While men and women in this group had a comparable mean age ($P > .05$), men had more stone episodes than women on average ($P = .001$). Nevertheless, the cycle was not significantly different in men if compared to women ($P > .05$). The age of onset was significantly younger in men than the women (Mann Whitney *U* test, mean difference = 1.4 y, $P = .01$).

The age of the disease onset was inversely (though weakly) associated with the number of episodes (Spearman's Rho = -0.1, $P = .001$). Multivariate analysis demonstrated that in a model containing potential influential factors on the cycle (episode interval), some factors such as night-time sleeping, smoking, and family history were associated with shorter cycles, and some others, including medical treatment, increasing fluid intake, and reducing salt intake were correlated with longer interval between episodes ($P = .001$ for model). However, among these factors, only age remained significantly correlated after the adjustments ($P = .001$).

DISCUSSION

Several studies have examined the impact of FH on the incidence and prevalence of nephrolithiasis. [11-13] Comparing these studies demonstrates a large variation in different geographic regions and various types of stones. Polito and colleagues reported the probability of positive FH to be 69% in patients with hypercalciuia, 75% in patients with hyperuricusuria, 78% in patients with both of the diseases, and 22% in the control group.[14] The positive FH of stone has been reported in 16% to 37% of patients with the kidney stone compared with 4% to 22% in healthy control subjects.[11] The prevalence of FH in our study was 42%. This high rate might be due to intra-familial marriage in Iranian culture. Safarinejad reported a 2-fold increase in urolithiasis prevalence in the first degree relatives of the patients compared to the general Iranian population.[15] In agreement with the previous reports,[11,16] our study showed that FH also increases recurrence by 20% compared to 25% in the study by Indridason and associates [17] and 15% in the study by Stamatiou and coworkers. [18] Also men experienced more recurrence in our study. Moreover, the results showed that the more family members with urinary stone are, the more the chances for recurrence. However, the episode interval (cycle) was relatively constant. Instead, the disease started earlier in RSFs than those patients without recurrence. To our best knowledge, this is the first study reporting that despite the relationship between the number of the affected family members and the male gender with the disease incidence at a younger age, recurrence intervals (cycles) are not related with the family history.

Recurrence is now a well-known characteristic of urolithiasis with a great impact on the community as well as the patients' quality of lives.[1,5,8,19] However, there is a marked variety of the recurrence rate in different parts of the world and the treatment approach is considerably influenced by the burden of disease, economic condition, access to the medical services, and patients' attitude and compliance. While identifying RSF has a pivotal role in the selection of the appropriate treatment protocol, epidemiologic

studies about RSF definition and recurrence cycle (episode interval) is sparse. In this study, we evaluated the urinary stone recurrence according to a population-based study and the presented epidemiologic evidence to facilitate RSF definition in our population.

The reported recurrence rate of urolithiasis widely varied from 20% to 75% in different studies due to the diversities in the populations, sampling, study settings, designs, follow-up periods, response rates, etc. [1,3,5,6,8,19,20] While retrospective studies are prone to cause bias and usually overestimates the rate because of using the referral clinic data, prospective researches may be influenced by extrapolation limitations, follow-up completions, loss, and symptomless episodes when no radiologic screening is used for recurrence determination. In our population-based study, 22% of the patients with a current imaging-proven stone had at least one previous episode of the disease. However, we may underestimate the recurrence rate in the community in this cross-sectional study and miss some asymptomatic RFSs who did not attend the imaging centers at the time of study.

A major focus of this study was on the interval between the episodes (cycle) in order to facilitate RSF definition because of its important impact on the treatment approach. In a recent review article, Chandhoke noted that metabolic work-up and medical therapy are not recommended for the first-time or occasional RSF who forms new stones less frequently than once every 5 years.[8] In a study, Strohmaier reviewed 31 references, and reported 30% to 40% recurrence rates, and 0.10 to 0.15 stone per year (equivalent to 79.2 to 120 months as interval) and that the first 4 years was claimed to have the highest recurrence probability.[3] However, the study was neither systematic nor homogenous with respect to the included studies. Chandhoke evaluated the frequency of the stone recurrence in 10 academic centers and concluded that a recurrent calcium stone former should have a recurrence at least once in 2 years in the USA for medical prophylaxis to be cost-effective,[9] but the cost of suffering and time lost from work was unaccounted for. Daudon and colleagues labeled their patients from France as "non-recurrent" only if they had no evidence of new stone formation for at least 3 years.[21] Although they referred to the average interval recurrence reported in 2 other studies from the USA as the rationale for such a classification,[7,20] the original studies did not clearly describe their findings. Furthermore, geographic variations were overlooked in this extrapolation. All in all, although considering the average recurrence time as an index for RSF definition is justified, the spectrum of the reported recurrence time is very wide, ranging from 13[2] to 81 months,[1] and there could not be a model suitable for all. In other words, the recurrence time must be individually estimated in each population. More importantly, the evidence should be obtained from population-based studies, not the referrals to the tertiary clinics. We tried to overcome these potential biases by a representative sampling and precisely estimated that the mean cycle between the episodes was 25.34 months that could be from 23 to 27.7 months with 99% CI in our "general population". We also reported 75th and 90th percentiles of the samples (32.4 and 60 months) to facilitate proper classification of the patients based on the practical applications including clinical, laboratory, economic, legal, and social purposes. Defining RSF based on the above indexes, not only improves recurrence risk stratification of the patients, but also points to the patients with higher probability of co-existing diseases. Furthermore, it helps to select the metabolic evaluation of the candidates and improves disease prevention.

Male gender was associated with greater number stone episodes in our study; however, the cycle was comparable between various genders. In fact, it seems that the higher rate of episodes is mainly caused by an earlier onset of the disease in men. This finding is in parallel with the majority of the studies about urolithiasis recurrence demonstrating a higher tendency of men for recurrence and potential inhibitory role of female hormones on urolithiasis;[6,22,23] but it contradicts studies by Trinchieri and colleagues as well as Hess and associates, who reported similar recurrence rates and episodes in genders. [2,5] Nevertheless, the former reported a tertiary clinic

data, and the latter result may be influenced by greater response rate from women than men in their study.

CONCLUSION

In this large epidemiologic study, a high frequency of FH in imaging-proven urolithiasis was observed. While recurrence was more frequent among patients with FH and in men, cycle was relatively constant and in fact, more number of episodes was due to younger age at the first onset of the disease.

Since average cycle has been traditionally considered for RSF definition, we may define RSF as any patient with a recurrence of the urinary stone earlier than 23 months (lower limit of the estimated mean episode interval) in our population. Furthermore, the presented 75th and 90th percentiles could also been applied for the RSF risk classification, while including a certain proportion of the patients. This approach promises to improve patients' care and prevention strategies.

ACKNOWLEDGEMENTS

This study was supported by Iranian Ministry of Health.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Coe FL, Keck J, Norton ER. The natural history of calcium urolithiasis. Jama. 1977;238:1519-23.
2. Hess B, Hasler-Strub U, Ackermann D, Jaeger P. Metabolic evaluation of patients with recurrent idiopathic calcium nephrolithiasis. Nephrol Dial Transplant. 1997;12:1362-8.
3. Strohmaier WL. Course of calcium stone disease without treatment. What can we expect? Eur Urol. 2000;37:339-44.
4. Krepinsky J, Ingram AJ, Churchill DN. Metabolic investigation of recurrent nephrolithiasis: compliance with recommendations. Urology. 2000;56:915-20.
5. Trinchieri A, Ostini F, Nespoli R, Rovera F, Montanari E, Zanetti G. A prospective study of recurrence rate and risk factors for recurrence after a first renal stone. J Urol. 1999;162:27-30.
6. Unal D, Yeni E, Verit A, Karatas OF. Prognostic factors effecting on recurrence of urinary stone disease: a multivariate analysis of everyday patient parameters. Int Urol Nephrol. 2005;37:447-52.
7. Parks JH, Asplin JR, Coe FL. Patient adherence to long-term medical treatment of kidney stones. J Urol. 2001;166:2057-60.
8. Chandhoke PS. Evaluation of the recurrent stone former. Urol Clin North Am. 2007;34:315-22.
9. Chandhoke PS. When is medical prophylaxis cost-effective for recurrent calcium stones? J Urol. 2002;168:937-40.
10. Pak CY. Should patients with single renal stone occurrence undergo diagnostic evaluation? J Urol. 1982;127:855-8.
11. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. Family history and risk of kidney stones. J Am Soc Nephrol. 1997;8:1568-73.
12. Ahmadi Asr Badr Y, Hazhir S, Hasanzadeh K. Family history and age at the onset of upper urinary tract calculi. Urol J. 2007;4:142-5; discussion 5-6.
13. Amato M, Lusini ML, Nelli F. Epidemiology of nephrolithiasis today. Urol Int. 2004;72 Suppl 1:1-5.
14. Polito C, La Manna A, Nappi B, Villani J, Di Toro R. Idiopathic hypercalciuria and hyperuricosuria: family prevalence of nephrolithiasis. Pediatr Nephrol. 2000;14:1102-4.
15. Safarinejad MR. Adult urolithiasis in a population-based study in Iran: prevalence, incidence, and associated risk factors. Urol Res. 2007;35:73-82.
16. Ljunghall S, Hedstrand H. Epidemiology of renal stones in a middle-aged male population. Acta Med Scand. 1975;197:439-45.
17. Indridason OS, Birgisson S, Edvardsson VO, Sigvaldason H, Sigfusson N, Palsson R. Epidemiology of kidney stones in Iceland: a population-based study. Scand J Urol Nephrol. 2006;40:215-20.
18. Stamatiou KN, Karanasiou VI, Lacroix RE, et al. Prevalence of urolithiasis in rural Thebes, Greece. Rural Remote Health. 2006;6:610.
19. Sutherland JW, Parks JH, Coe FL. Recurrence after a single renal stone in a community practice. Miner Electrolyte Metab. 1985;11:267-9.
20. Ulmann A, Clavel J, Destree D, Dubois C, Mombet A, Brisset JM. [Natural history of renal calcium lithiasis. Data obtained from a cohort of 667 patients]. Presse Med. 1991;20:499-502.
21. Daudon M, Hennequin C, Boujelben G, Lacour B, Jungers P. Serial crystalluria determination and the risk of recurrence in calcium stone formers. Kidney Int. 2005;67:1934-43.
22. Iguchi M, Takamura C, Umekawa T, Kurita T, Kohri K. Inhibitory effects of female sex hormones on urinary stone formation in rats. Kidney Int. 1999;56:479-85.
23. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. Kidney Int. 2001;59:2290-8.