

Study of Urine Composition of Patients With Recurrent Nephrolithiasis in Lorestan, Iran

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Introduction. Nephrolithiasis is one of the most common urinary tract diseases. After the first episode of urinary calculus, the risk of recurrence is nearly 40% to 50% at 5 years. Nephrolithiasis is a systemic disease that is associated with some metabolic disorders. This study aimed to provide a picture of the frequency of metabolic abnormalities in patients with nephrolithiasis from west part of Iran.

Materials and Methods. Patients with recurrent urinary tract calculi referred to the Nephrology-Urology Clinics in Khorramabad city were recruited. After collection of demographic data of all the patients, 24-hour urine and blood samples were taken to measure biochemical factors.

Results. Of the 232 participants, 125 were males and 107 were females. Hyperoxaluria was seen in 93 (40.1%) of the participants, hypercalciuria in 55 (23.7%), hypocitraturia in 58 (25%), and hyperuricosuria in 33 (14.9%). Hyperoxaluria in the males was significantly more frequent than in the female patients. There were no significant differences between the two groups in other urinary metabolic disorders.

Conclusions. Patients with nephrolithiasis from Lorestan province may have metabolic characteristics varying from those of regions; ethnicity may be a possible reason. Variation of dietary regimens, such as the amount of meat or vegetable in the diet that can change oxalate, calcium, or citrate of urine, might have influenced the results. Time of sampling is another factor. Population-specific studies are helpful to health care providers for preventive planning for nephrolithiasis.

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INTRODUCTION

Office management of urinary calculus disease is an important component of a nephrologist's practice. Nephrolithiasis results in frequent referral of patients to hospital. It is one of the most important causes of acute and chronic kidney diseases. Up to 16% of men and 8% of women will have at least 1 symptomatic calculus by the age of 70 years.¹ A more recent National Health and Nutrition Examination Survey study, from 2007 to 2010, demonstrated a marked increase

in the prevalence at 8.8%, compared to the 1994 survey showing the prevalence of urinary calculi to be 5.2%. One study showed that nephrolithiasis prevalence rate in Iran is 5.7%, and the incidence is 145 per 100000 population.^{1,2} Studies of the natural history of urinary calculus disease have shown that in a patient who has passed a first calcium calculus, the likelihood of forming a second one is approximately 15% at 1 year, 35% to 40% at 5 years, and 50% at 10 years, with men being more likely to have recurrence than women.^{3,4}

Nephrolithiasis is a systemic disease that is associated with some metabolic disorders. Aside from sex, race, age, ethnicity, and socioeconomic class, conditions associated with metabolic syndrome were shown to be predictive of kidney calculus disease.² In addition to the potential of uncovering treatable underlying diagnosis, the pathophysiologic definition of kidney calculi can also guide selection and help monitor therapy. Nephrolithiasis is a costly malady to society. Estimates in the 1970s exceeded \$5 billion annually in the United States.⁵

Biochemical and physical disturbances that contribute to the formation of calcium calculi are quite varied. Several disturbances have the potential to create the environment conducive to calculus formation. Several investigators utilize the presence of such disturbances as the basis for diagnostic categorization of nephrolithiasis. Earlier studies based on ambulatory evaluations of patients with nephrolithiasis reported 10 metabolic etiologies composing 4 types of hypercalciuria, hyperuricosuria, hyperoxaluria, renal tubular acidosis, uric acid calculi, and infectious calculi, and an 11% incidence of finding no metabolic abnormalities.⁶

Usually, patients with recurrent calculi, a family history of calculi, and multiple calculi with a history of calculus passage per urethra are the candidates for metabolic evaluation. This evaluation is useful for calculus prevention and to identify patients with kidney calculi who might have other significant diseases. The 24-hour urine collection is an important test for metabolic evaluation in nephrolithiasis that postpones at least 6 to 8 weeks after calculus passage.

There is not significant data about frequency of metabolic abnormalities in patients with nephrolithiasis from west parts of Iran. The aim of this study was to evaluate 24-hour urine and blood biochemistry elements related to kidney calculus for determining types of common metabolic disorders in recurrent nephrolithiasis in Lorestan province.

MATERIALS AND METHODS

This cross-sectional study was conducted on all the patients with recurrent urinary tract calculi referred to the Nephrology-Urology Clinics of Lorestan University of Medical Sciences in Khorramabad city, from January 2016 to September

2016, using the convenience sampling method. The inclusion criteria were age at the onset of 14 years and greater and having maintained the usual typical diet. Patients with a recent hospitalization, a history of calculus passage during the recent 8 weeks, medical or dietary treatment for nephrolithiasis, and use of calcium, vitamin D supplement, diuretics, allopurinol, glucocorticoids, triamterene, indinavir, and sulfadiazine were excluded from study. Informed consent was obtained from the eligible participants. The majority of the participants were from the Lore ethnicity. Lorestan is a province in the west of Iran in the Zagros Mountains. The climate is generally sub-humid and continental with winter precipitation.

There are different approaches for timing of urinary collection. Some authors believe in 1-time collection and others believe in 2-time collection.⁷⁻⁹ The 24-hour urine collection in our patients was made only 1 time (during routine work day and routine diet).

We defined recurrent calculus formers as those with a history of at least 2 unique calculi separated by at least 6 months. We excluded first calculus former patients from the study. Diagnosis of nephrolithiasis was done by ultrasonography. Suspicious cases of nephrolithiasis were referred for helical abdominal-pelvic computed tomography scan (without contrast) for confirmation of the results.

Demographic data of all the patients, 24-hour urine, and blood samples were taken to measure biochemical factors. Demographic data of the patient included age and sex. Blood level of calcium, phosphate, and uric acid were measured after an 8-hour night fasting. Urine samples were collected over 24 hours. Citrate and oxalate were measured by photometry method (Biorexfars). Calcium was measured by photometry (Arsenazo), and uric acid by the enzymatic colorimetric method (Toos). Urine pH was measured by a dipstick test on a freshly voided urine (spot urine). To control the accuracy of 24-hour urine collection by the patients, 24-hour urine creatinine was measured, with a concentration expected to be about 20 mg/kg to 25 mg/kg in men and 15 mg/kg to 20 mg/kg in women. All the investigations were conducted under supervision of one experienced specialist in the laboratory.

The following definitions were considered,

as generally accepted in population studies: hypercalciuria, urine calcium excretion greater than 300 mg/d in men and greater than 250 mg/d in women; hyperoxaluria, urine oxalate excretion greater than 45 mg/d; hypocitraturia, urine citrate excretion less than 320 mg/d; and hyperuricosuria, urine uric acid excretion greater than 800 mg/d in men and greater than 750 mg/d in women.¹⁰

Statistical analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, IL, USA), and variables were compared using the independent Student *t* test. Statistical significance was set at a *P* value less than .05.

RESULTS

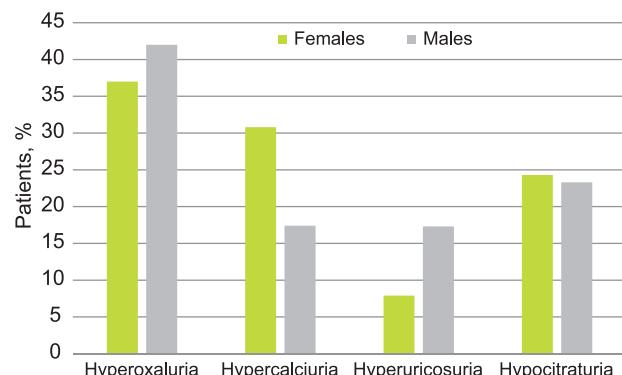
Of the 232 participants, 125 (53.9%) were males and 107 (46.3%) were females. The mean age of the study participants was 46.10 years, 45 years in the males and 48 years in the female group. All the urine and blood biochemical data are showed in the Table.

Hyperoxaluria was seen in 93 (40.1%) of the participants, hypercalciuria in 55 (23.7%), hypocitraturia in 58 (25%), and hyperuricosuria in 33 (14.9%). Only hyperoxaluria in the males was significantly more frequent than in the female patients. There was no significant difference between the two groups in other urinary metabolic disorders (Figure).

The mean 24-hour urine volume was 1564 ± 724 mL (1437.23 ± 756.41 mL in the females and 1640.04 ± 684.08 mL in the male group). The mean sodium level in 24-hour urine was 158.47 ± 113.14

Summary of Demographic and Laboratory Data of Patients With Nephrolithiasis

Parameter	Number of Patients	Mean Value
Age, y	232	46.10 ± 14.39
Urine oxalate, mg/24 h	210	39.19 ± 23.04
Urine sodium, mg/24 h	191	157.86 ± 89.54
Urine calcium, mg/24 h	232	175.69 ± 148.69
Urine citrate, mg/24 h	205	451.96 ± 244.76
Urine uric acid, mg/24 h	222	518.42 ± 258.82
Urine volume, mL	231	1546.09 ± 724.03
Urine pH	232	5.14 ± 0.38
Urine specific gravity	232	1019.70 ± 5.45
Blood calcium, mg/dL	228	9.38 ± 0.53
Blood phosphorus, mg/dL	227	3.76 ± 1.54
Blood uric acid, mg/dL	220	6.59 ± 4.64



Metabolic disorders in male and female patients with nephrolithiasis.

mg/L in the females and 157.34 ± 63.38 mg/L in the males. There was no significant difference between the two groups.

The mean serum calcium level was 9.37 ± 0.59 mg/dL and 9.38 ± 0.48 mg/dL in the male and female groups, respectively. The mean serum uric acid level was 6.52 ± 5.41 mg/dL in the females and 6.66 ± 3.89 mg/dL in the males. Although the levels of these elements in the male group were higher, there were no significant differences. The mean urine pH was 5.15 ± 0.40 in the female and 5.13 ± 0.36 in the male group. There was no significant difference between the two groups.

DISCUSSION

Studies show that the prevalence of kidney calculi is increasing during recent decades. There are many factors responsible for recurrent calculus disease. Nephrologists' motto in treatment of these patients is "I leave no calculi untreated." Prevention significantly reduces recurrence rates, so metabolic evaluation of urine is of utmost importance for better diagnosis and management of kidney calculus disease.

There are various approaches for metabolic evaluation. Some groups believe in metabolic evaluation of high-risk patients or recurrent calculus makers, and others believe in the evaluation of even first-time calculus makers. Sex and age of patients are important in predisposition to kidney calculus forming. In our study, the prevalence of disease in the males was higher than that in the females. Male sex is a risk factor for kidney calculus disease. This result was similar to Naeem and colleagues' study in which male-female ratio was 1.89, and Healy and colleagues' study in which 52% of patients

were male.^{11,12} One Study in Iran showed that the prevalence of nephrolithiasis was 6.1% in men and 5.3% in women, and another study reported 65% of 200 patients with nephrolithiasis were men.^{2,13} In our study, the mean age of the patients was 46 ± 14 years, but in other studies it was 29.72 ± 5.8 years and 53.2 years.^{11,12} In another study from Iran, the mean age was 40.5 ± 15.1 years.¹⁴

In our study, 23.7% of the patients had hypercalciuria, while other studies have reported greater prevalence rate; in Naeem and colleagues' study,¹¹ the rate was 48.6%, Park and coworkers reported a rate of 35% to 65%, and in Eisner and colleagues' study, 43.3% had hypercalciuria.^{15,16} Hyperoxaluria was seen in 40.1% of our patients, while other studies have reported rates varying from 22.9% to 77%.^{11,16,17} In our study, hyperuricosuria was seen in 14.9% of the patients, compared to 17.2% in Naeem and colleagues' study.¹¹ Hypocitarturia was seen in 28% of the patients, compared to 31.4% in Naeem and colleagues' study and 45% in Eisner and colleagues' study.^{11,16} These results are different from Emami-Naini and coworkers' study that showed that hypocitraturia was the most (40.5%) and hypercalciuria the least common metabolic causes (9.2%).¹⁸ Finally, hyperoxaluria was the most common abnormality, which is different from other studies.¹⁹

Dehydration and reduced urinary volume are well-known risk factors for kidney calculus formation.^{20,21} In this study, we observed low urinary volume in approximately 50% of the cases, which was different than the values reported from 2 other regions of Iran (58.2% and 76%), where climate is warmer.^{22,23} The mean of urine volume in our patients was about 1.5 L to 2 L, which is a risk factor for nephrolithiasis. Multiple studies recommend that for prevention of nephrolithiasis, urine volume must be more than 2 L/d.²⁴⁻²⁸

There was a relationship between 24-hour urine level of uric acid and male sex of the patients. It may be due to influence of sex hormone or diet or body size on the metabolism of uric acid. Only 1% of our patients had hypercalcemia and finally in 3 patients hyperparathyroidism was documented. In Nouri-Majalan and colleagues' study and Park and colleagues' study, 5.6% and 4.2% of the patients had hypercalcemia.^{23,29}

Urine PH is a risk factor for specific types of kidney calculus. In people who are not vegetarians, the pH

of urine tends to be acidic. In our study, more urine samples had acidic pH. Urine pH in Naeem and colleagues' study was near acidic (5.31 to 6.010),¹¹ and it was 5.5 in Nouri-Majalan and colleagues' study (in majority of patients).²³ We suppose that variation of dietary regimen results in changing of urine acidity. Regardless of diagnosis, evaluation of urine pH in treatment of patients is important.^{23,30}

We noticed differences between our results and some other studies. We suppose that variation of regions and ethnicities may be a possible reason for it. Variation of dietary regimen of people (for example, meat- or vegetable-containing diet can change oxalate and calcium or citrate of urine) may influence results of studies. Time of sampling (warm or cold seasons) is another factor. Another explanation for discrepancy of our results (especially about hypercalciuria) may be the prevalence of vitamin D deficiency that affects the urine calcium and nephrolithiasis. There is no significant data about vitamin D deficiency in Lorestan province.³¹

CONCLUSIONS

Our hypothesis was that the rate of urine metabolic abnormality in recurrent nephrolithiasis might be more than first calculus makers (most of previous studies were done on the nonrecurrent calculus makers), but our results were not significantly different. An important question is whether it is time for change of metabolic evaluation method or even better markers for study of metabolic disorders in kidney calculus makers. In the majority of studies, the cost and burden on the patients for collection of 24-hour urine is a limiting factor that must be considered (including our study).³²

We acknowledge limitations of our study, most of all no measurement of serum creatinine and glomerular filtration rate and other important electrolytes (sodium and potassium). In addition, the kidney calculus types were not evaluated in our study, since we were unable to extract the data of calculus analysis in majority of cases. We recommend larger studies to determine urine saturation of risk factors instead of absolute values. Population-specific studies are helpful to health care providers for preventive planning for nephrolithiasis.

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CONFLICT OF INTEREST

None declared.

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