Original Article

Urine and serum fetuin-A levels in patients with urolithiasis

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ABSTRACT

Introduction: Fetuin-A is a glycoprotein secreted by liver and has been shown to inhibit extraosseous mineralization. Urolithiasis may be a manifestation in the urinary tract due to fetuin deficiency in urine. The objective of this study was to compare the 24-h urine and serum fetuin-A levels of patients with and without urolithiasis.

Methods: Serum and 24-h urine fetuin-A levels were measured in 41 patients with bilateral, multiple, or recurrent urinary tract calculi (Group A) and 41 matched controls with no calculi (Group B). Fetuin levels were measured by enzyme linked immunosorbent assay. Serum and urine fetuin-A levels in the two groups were compared.

Results: The median (range) 24-h urine fetuin-A value in Group A was 11.9 (1.12–221) mg/day and in Group B was 37.7 (1.28–125) mg/day. This difference was statistically significant (Mann–Whitney test, $P = 0.0169$). The median (range) serum fetuin-A in Group A was 0.67 (0.05–2.68) g/L and in Group B was 0.99 (0.01–5.5) g/L. The difference between serum values in the two arms was not statistically significant (Mann–Whitney test, $P = 0.1817$). However, the serum creatinine-adjusted mean log serum fetuin and urine fetuin were significantly different in the two arms ($P = 0.003$). The mean ± standard deviation (range) serum creatinine in Group A was 0.98 ± 0.25 (0.56–1.58) mg% and in Group B was 0.83 ± 0.16 (0.58–1.18) mg% (two sample t-test, $P = 0.0031$).

Conclusions: Patients with urolithiasis have lower urine fetuin-A and creatinine-adjusted serum fetuin-A levels.

INTRODUCTION

Urinary tract calculus formation is a multistep process. Identifying molecules and metabolic disturbances that affect this process provides opportunity to intervene for preventing stone formation. Fetuin-A (α-Heremans Schmid glycoprotein), a 59kd glycoprotein secreted by liver,[1] has been identified to inhibit extraosseous mineralization[2-4] and its role in urolithiasis is under investigation. Significantly, decreased urine and serum levels in stone formers have been identified by a few investigators, but others have failed to reproduce similar results.[5-9] As the findings have been conflicting, further study is required. The present study aims to compare 24-h urine and serum fetuin-A levels of patients with and without urolithiasis.

METHODS

This was a case–control study conducted from April 2014 to March 2016. Ethics committee approval was obtained and informed written consent was taken. The patients who visited for treatment of recurrent, bilateral, or multiple upper urinary tract calculi formed the study group (Group A). Only patients with calcium oxalate calculi or radiopaque calculi were included in the study. The control group consisted of individuals with no documented calculus disease on an ultrasound or an X-ray kidney, ureter, and bladder (KUB) (Group B). The controls were selected by

Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/iju.IJU_340_16

Received: 17.10.2016, **Accepted:** 16.05.2017

Financial support and sponsorship: Christian Medical College, Vellore, Tamil Nadu, India.

Conflicts of interest: There are no conflicts of interest.

screening patients visiting urology outpatient department for complaints unrelated to urolithiasis.

The individuals with urinary tract infection, urinary tract obstruction, or metabolic abnormalities on complete metabolic workup for stone disease were excluded from the study. In addition, those with anatomic abnormalities on an ultrasound or a computerized tomography scan were also excluded. Individuals in the control group did not undergo further evaluation for anatomic abnormalities if no calculus was detected on X-ray KUB.

The study groups were matched at the time of selection with respect to age, gender, and body mass index [Table 1].

Twenty-four-hour urine and serum fetuin-A levels were measured in both study groups using enzyme linked immunosorbent assay (ELISA) kit KAPEPKT800 (DIAsource Immunoassays SA, Belgium). The ninety-five percentile normal range for the kit was 5–270 ng/ml. The intra-assay variations were evaluated by measuring two samples in 20 replicates (intra-assay coefficient of variation <6%) and inter-assay variations were evaluated by measuring two samples in duplicate in 12 individual assays (inter-assay coefficient of variation <7%), limit of detection 5 ng/mL). The cost of each ELISA measurement was approximately US$ 23.

In addition, all the individuals underwent complete metabolic evaluation for urolithiasis. The serum and urine calcium, phosphorus, uric acid, creatinine, albumin, and glucose were analyzed colorimetrically, serum sodium and potassium via ion selective electrode, and urine oxalate and citrate spectrophotometrically on an automated chemistry analyzer from Roche and parathormone by immunoassay. Calculi analysis was done using chemical methods. Serum and urine samples were collected in Group A before surgical treatment of calculus disease.

Table 1: Baseline characteristics of the patients

Characteristic	Group A (*n*=41)	Group B (*n*=41)
Age (years), mean±SD (range)	41.34±11.54 (18–68)	41.09±11.23 (18–66)
BMI (kg/m^2), mean±SD (range)	24.56±3.91 (18–31.4)	24.49±3.57 (16.6–32.4)
Males/females (%)	33 (80.5)/8 (19.5)	33 (80.5)/8 (19.5)

BMI=Body mass index, SD=Standard deviation

Statistical methods

A sample of size 86 (43 in urolithiasis and 43 without urolithiasis) was calculated to detect a mean difference of 0.10 g/L in fetuin-A concentration between the groups with 80% power and 5% level of significance. We assumed that the mean and standard deviation (SD) of serum fetuin-A concentration was 0.71 (0.16) g/L in cases and 0.81 (0.17) g/L in controls.[5]

Data were collected and reported as counts and frequencies for categorical variables. Continuous variables were summarized as mean and SD or median and range for normally and nonnormally distributed variables, respectively. We compared the outcomes between cases and control groups using the two-sample *t*-test for the normally continuous outcome variables and Mann–Whitney test for nonnormally distributed continuous variables. All statistical analyses were done using statistical software STATA version 13.0, StataCorp LLC, USA. All *P* values are two-sided and significance was set at 5%.

RESULTS

Forty-one individuals were enrolled in the study in each group. The median (range) 24-h urine fetuin value in Group A was 11.9 (1.12–221) mg/day and in Group B was 37.7 (1.28–125) mg/day. This was significantly lower ($P = 0.0169$) in individuals with stones [Table 2].

The median (range) serum fetuin value Group A was 0.67 (0.05–2.68) g/L and in Group B was 0.99 (0.01–5.5) g/L. The difference between values in the two arms was not statistically significant ($P = 0.1817$) [Table 2]. However, serum creatinine-adjusted mean log serum fetuin was significantly lower in individuals with urolithiasis ($P = 0.003$).

Eighteen patients had sufficient volume of stones available for complete chemical analysis and they had calcium stones.

DISCUSSION

The 24-h urine fetuin in patients with urolithiasis was significantly lower ($P = 0.0169$) than in matched controls. This is consistent with a similar finding in two earlier studies,[8,9] while in one[6] there was no significant difference. This suggests that low urine fetuin excretion may be an important risk factor for urolithiasis. Low urinary excretion of fetuin appears to be an important intrinsic defect in the

Table 2: Results

Variable	Group A (*n*=41)	Group B (*n*=41)	*P*
24-h urine fetuin (mg/day), median (range)	11.9 (1.12–221)	37.7 (1.28–125)	0.0169
Serum fetuin (g/L), median (range)	0.67 (0.05–2.68)	0.99 (0.01–5.5)	0.1817
24-h urine volume (mL), median (range)	2860 (820–5600)	3340 (800–4730)	0.2351
Serum creatinine (mg%), mean±SD (range)	0.98±0.25 (0.56–1.58)	0.83±0.16 (0.58–1.18)	0.0031

SD=Standard deviation

excretion of fetuin via kidney. A calculus once formed may have fetuin in matrix, but it is unlikely to continuously consume fetuin in significant amounts leading to low levels in urine. Therefore, low urine fetuin level appears to be a cause rather than effect.

The serum fetuin in patients with stone disease was lower than in individuals without stones, but this difference did not reach statistical significance (P = 0.1817). Serum creatinine-adjusted mean log serum fetuin was significantly lower in the study group than in controls (P = 0.003). There is only one report[5] showing lower levels of serum fetuin in patients with urolithiasis, but this was not consistent with four others.[6-9]

Only the high-risk group of patients with bilateral, multiple, and recurrent calculi was included in our study as in one other.[8] The other previous studies[5-7,9] had patients with documented urolithiasis or a history of urolithiasis. The difference in inclusion criteria, especially stone burden, genetics, and other environmental factors, may be important factors leading to discrepant results among the studies done so far.

Fetuin is also an important marker of renal damage and higher serum fetuin values have been found in end-stage renal failure in various prior publications.[10,11] In our study, the mean ± SD (range) serum creatinine in patients with stone disease was 0.98 ± 0.25 (0.56–1.58) mg%, which was significantly higher (P = 0.0031) than the mean ± SD (range) serum creatinine in controls. Despite higher serum creatinine values, serum fetuin value in patients with urolithiasis was lower than the control group; serum creatinine-adjusted mean log serum fetuin and urine fetuin were significantly different in cases and controls (P = 0.003).

Fetuin may have a preventive role in predisposed individuals. Once the causative role is established, prevention via stem cell therapy or replacement via oral or parenteral route may be attempted in future.

Our study is not without limitations. Stone formation is a multifactorial process. The study groups were not matched for all the potential stone causative factors, and ideally, genetic matching should be done. The serum creatinine was also not matched between the two groups. Multicentric studies with a larger sample size may yield definitive results.

CONCLUSIONS

The patients with bilateral, multiple, and recurrent renal calculi had significantly lower 24-h urine fetuin and serum fetuin adjusted to serum creatinine values compared with individuals without stones. Serum and urine fetuin evaluation may be included in the metabolic profile of stone formers with a high risk of recurrence.

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How to cite this article: Arora R, Abrol N, Antonisamy B, Vanitha S, Chandrasingh J, Kumar S, *et al.* Urine and serum fetuin-A levels in patients with urolithiasis. Indian J Urol 2017;33:291-3.