

Original Research Article

Evaluation of the role of serum and 24-hour urinary fetuin-A levels in patients with urolithiasis

Ritvij R. Patankar¹, Sreedhar Dayapule², Ankit Anand^{3*}, Sandeep Davalla⁴

¹Department of Urology, RG Urology and Laparoscopy Hospital, Porvorim, Goa, India

²Department of Urology, Government Medical College, Vijayawada, Andhra Pradesh, India

³Department of Urology, TS Mishra Superspecialty Hospital, Lucknow, Uttar Pradesh, India

⁴Department of Urology, ESIC Medical College, Hyderabad, Telangana, India

Received: 14 February 2026

Revised: 16 September 2026

Accepted: 02 October 2026

*Correspondence:

Dr. Ankit Anand,

E-mail: dr.ankitanand19@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Urolithiasis is a common urinary tract disorder with a substantial risk of recurrence. Fetuin-A (α 2-Heremans-Schmid glycoprotein) is a systemic inhibitor of ectopic calcification and may influence urinary crystal formation. This study compared serum and 24-hour urinary fetuin-A concentrations in patients with urolithiasis and controls and examined their relationship with stone radiopacity and composition.

Methods: This prospective case-control study included 40 patients with urolithiasis and 40 controls matched for age, sex, and weight. Serum and 24-hour urine fetuin-A concentrations were measured using an ELISA. Stone radiopacity and chemical composition were assessed. Continuous variables were compared using independent-samples t-tests, with $p < 0.05$ considered statistically significant.

Results: Mean serum fetuin-A concentrations were lower in patients with urolithiasis than in controls (35.06 ± 12.90 vs 41.31 ± 8.89 ng/mL; $p = 0.0137$). Mean 24-hour urinary fetuin-A concentrations were also lower (26.42 ± 10.15 vs 36.90 ± 18.31 ng/mL; $p = 0.0022$). Neither serum nor urinary fetuin-A differed significantly between patients with radiolucent and radio-opaque stones. Calcium oxalate, including mixed calcium oxalate-containing stones, was present in 31 of 40 cases (77.5%).

Conclusion: Patients with urolithiasis had lower serum and urinary fetuin-A concentrations than controls. These findings demonstrate an association but do not establish causality. Larger studies are needed to determine whether fetuin-A has a role in stone formation or recurrence.

Keywords: Urolithiasis, Fetuin-A, α 2-Heremans-Schmid glycoprotein, Urinary biomarker, Nephrolithiasis, Calcification inhibitor

INTRODUCTION

Urolithiasis is a common disease of the urinary tract and with significant risk of recurrence. It is a multifactorial disease influenced by dietary, metabolic, infectious, anatomical, and genetic factors.^{1,2}

In addition to reduced urinary supersaturation with lithogenic ions, endogenous inhibitors of mineralization

may influence crystal nucleation, growth, aggregation, and attachment to the renal epithelium.^{3,4}

Fetuin-A, also known as α 2-Heremans-Schmid glycoprotein, is predominantly synthesized in the liver and acts as a systemic inhibitor of ectopic calcification. It binds calcium and phosphate and contributes to the formation of soluble calciprotein complexes, thereby inhibiting uncontrolled mineral precipitation.⁵⁻¹⁰

Previous studies have suggested that patients with nephrolithiasis may have lower serum or urinary Fetuin-A concentrations than individuals without stone disease. However, the findings regarding serum Fetuin-A have been inconsistent, whereas reductions in urinary Fetuin-A have been reported more consistently.¹¹⁻¹⁷

The present study was therefore undertaken to compare serum and 24-hour urinary Fetuin-A concentrations between patients with urolithiasis and controls and to evaluate whether Fetuin-A concentrations differed according to stone radiological appearance and chemical composition.

METHODS

Study design and setting

This was a prospective case-control study conducted in the Department of Urology and Renal Transplantation, Dr. PSIMS & RF, Chinnaoutapalli, Krishna District, Andhra Pradesh. The study period was April 2018 to June 2019.

Study population

The study included 40 patients with documented urolithiasis and 40 controls without documented calculus disease. Cases and controls were matched for age, sex, and weight.

Inclusion criteria

Patients with symptomatic urolithiasis confirmed by radiological or sonographic examination were included. Both first-time and recurrent stone formers were included.

Exclusion criteria

Patients with acute urinary tract infection, genitourinary anatomical abnormalities, pregnancy, critical illness, chronic renal failure requiring dialysis, type 2 diabetes mellitus, and chronic calcium supplementation were excluded.

Laboratory assessment

Serum and 24-hour urine samples were collected from participants, and fetuin-A concentrations were measured using a commercial Human Fetuin-A ELISA kit. Stone analysis was performed to determine chemical composition.

Statistical analysis

Statistical analysis was carried out using SPSS version 16.0. Continuous variables were compared using an independent-samples t-test, with $p < 0.05$ considered statistically significant.

RESULTS

Serum Fetuin-A

The Mean serum Fetuin-A levels were lower in the case group than in the control group with values for Urolithiasis group being 35.06 ± 12.90 ng/ml and controls being 41.31 ± 8.89 ng/ml with a t value of -2.523 and $df=78$; $p=0.0137$. The difference was statistically significant.

Table 1: Serum Fetuin-A concentration in cases and controls.

Serum Fetuin-A	Controls, N (%)	Urolithiasis, N (%)	Total, N (%)
≤ 30 ng/ml	2 (5.0)	18 (45.0)	20 (25.0)
> 30 ng/ml	38 (95.0)	22 (55.0)	60 (75.0)
Total	40 (100)	40 (100)	80 (100)
Mean$\pm$SD, ng/ml	41.31 $\pm$ 8.89	35.06 $\pm$ 12.90	—
t statistic	—	-2.523	—
df	—	78	—
P value	—	0.0137	—

Twenty-four-hour urinary Fetuin-A

The Mean urinary Fetuin-A levels were significantly lower in the case group than in the control group, with values for Urolithiasis group being 26.42 ± 10.15 ng/ml and control group being 36.90 ± 18.31 ng/ml with t value of -3.166 ; $df=78$; $p=0.0022$.

Table 2: Twenty-four-hour urinary Fetuin-A concentration in cases and controls.

24-h urinary Fetuin-A	Controls, N (%)	Urolithiasis, N (%)	Total, N (%)
≤ 30 ng/ml	10 (25.0)	28 (70.0)	38 (47.5)
> 30 ng/ml	30 (75.0)	12 (30.0)	42 (52.5)
Total	40 (100)	40 (100)	80 (100)
Mean$\pm$SD, ng/ml	36.90 $\pm$ 18.31	26.42 $\pm$ 10.15	—
t statistic	—	-3.166	—
df	—	78	—
P value	—	0.0022	—

Serum Fetuin-A according to stone radiopacity

Among the 40 patients with urolithiasis, 11 had radiolucent and 29 had radio-opaque stones.

The Mean serum Fetuin-A levels were 35.23 ± 13.06 ng/ml in patients with radiolucent and 35.00 ± 13.11 ng/ml in patients with Radio-opaque. There was no statistically significant difference between the groups, t value was 0.050 ; $df=38$; $p=0.961$.

Table 3. Serum Fetuin-A according to stone radiopacity.

Serum Fetuin-A (ng/ml)	Radiolucent, N (%)	Radio-opaque, N (%)	Total, N (%)
15–30	5 (45.45)	13 (44.83)	18 (45.0)
30–45	2 (18.18)	6 (20.69)	8 (20.0)
45–60	4 (36.36)	10 (34.48)	14 (35.0)
Total	11 (100)	29 (100)	40 (100)
Mean±SD	35.23±13.06	35.00±13.11	—
t statistic	—	0.050	—
df	—	38	—
P value	—	0.961	—

Urinary Fetuin-A according to stone radiopacity

The Mean 24-hour urinary Fetuin-A levels were 27.18±11.26 ng/ml among patients with Radiolucent and 26.13±9.89 ng/ml in patients with Radio-opaque. The difference was not statistically significant between the groups with t value of 0.289; df=38; p=0.774.

Table 4: Serum Fetuin-A according to stone radiopacity.

24-h urinary Fetuin-A (ng/ml)	Radiolucent, N (%)	Radio-opaque, N (%)	Total, N (%)
10–25	6 (54.55)	13 (44.83)	19 (47.5)
25–40	3 (27.27)	6 (20.69)	9 (22.5)
40–55	2 (18.18)	10 (34.48)	12 (30.0)
Total	11 (100)	29 (100)	40 (100)
Mean±SD	27.18±11.26	26.13±9.89	—
t statistic	—	0.289	—
df	—	38	—
P value	—	0.774	—

Stone composition

Calcium oxalate was present in 31/40 stones (77.5%) when pure and mixed calcium oxalate-containing stones were considered together. The source manuscript reports that Fetuin-A levels appeared reduced across stone types but did not demonstrate a significant difference among individual stone compositions.

Table 5: Chemical composition of retrieved calculi.

Stone composition	N	%
Calcium oxalate	18	45.0
Calcium oxalate + uric acid	11	27.5
Uric acid	4	10.0
Uric acid + brushite	3	7.5
Calcium oxalate + ammonium urate	2	5.0
Brushite	2	5.0
Total	40	100

DISCUSSION

The principal finding of this study was that both serum and 24-hour urinary Fetuin-A levels concentrations were lower among patients with urolithiasis than among controls.

The serum results were generally consistent with the findings of Mehra et al, which reported a significant association between serum Fetuin-A and stone disease.¹⁶ However, Arora et al did not observe a statistically significant difference in unadjusted serum Fetuin-A concentrations between cases and controls.¹⁷ The original study authors suggested that differences in renal function could have contributed to this discrepancy.

The urinary findings are more consistent with previously published studies. The present study demonstrated significantly lower 24-hour urinary Fetuin-A among patients with urolithiasis, similar to findings reported by Stejskal et al., Mehra et al and Arora et al.^{13,16,17}

Fetuin-A has an established biological role in inhibiting ectopic mineralization. Experimental studies have demonstrated its ability to inhibit apatite formation and calcium-phosphate precipitation and to participate in the formation of calciprotein particles.^{5,6,8-10} The original study also did not find a significant difference in fetuin-A levels between patients with radiolucent and radio-opaque calculi. Similar to the overall results, the levels of fetuin-A were generally lower in patients with radio-opaque stones but not significantly so.

The most prevalent type of calculi was calcium oxalate, either in pure form or mixed with other substances. Calcium oxalate was present in 31 out of 40 stones (77.5%).

However, the findings of this study should be interpreted with caution due to the relatively small sample size and the single-centre design. Additionally, the number of patients in each group was also small, which limited the statistical power of the analysis, particularly in relation to individual stone composition. The original authors also acknowledged this limitation and suggested that larger multicentre studies were needed to confirm the findings. Furthermore, the original study did not report adjusting the urinary fetuin-A levels for creatinine or the volume of the urine sample.

Most importantly, the original study demonstrated an association but not a causal relationship. Therefore, the statements in the original manuscript about the reduced levels of urinary fetuin-A being an “intrinsic defect,” “cause rather than effect,” and requiring Fetuin-A replacement therapy should be tempered with caution,

CONCLUSION

The patients with urolithiasis had significantly lower serum and 24-hour urinary Fetuin-A levels than the

controls. The reduction in urinary Fetuin-A levels was statistically more pronounced than the reduction in serum Fetuin-A levels.

No significant difference was demonstrated in Fetuin-A levels according to stone radiopacity. The most prevalent type of calculi was calcium oxalate.

These findings suggest that reduced Fetuin-A levels, particularly urinary Fetuin-A levels, might be involved in pathogenesis of urolithiasis. However, larger multicentric studies are required to determine whether Fetuin-A has a role as a biomarker for stone formation or recurrence.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Sofia H, Nalini H, Manickavasakam K, Walter TM. Prevalence and risk factors of kidney stone. Glob J Res Anal. 2016;5:183-7.
2. Vijaya T, Kumar MS, Ramarao NV, Babu AN, Ramarao N. Urolithiasis and its causes: short review. J Phytopharmacol. 2013;2:1-6.
3. Schlieper G, Westenfeld R, Brandenburg V, Ketteler M. Vascular calcification in patients with kidney disease: inhibitors of calcification in blood and urine. Semin Dial. 2007;20:113-21.
4. Asplin JR. Hyperoxaluric calcium nephrolithiasis. Endocrinol Metab Clin North Am. 2002;31:927-49.
5. Schinke T, Amendt C, Trindl A, Pöschke O, Müller-Esterl W, Jahnen-Dechent W. The serum protein α 2-HS glycoprotein/fetuin inhibits apatite formation in vitro and in mineralizing calvaria cells: a possible role in mineralization and calcium homeostasis. J Biol Chem. 1996;271:20789-96.
6. Schäfer C, Heiss A, Schwarz A, et al. The serum protein α 2-Heremans-Schmid glycoprotein/fetuin-A is a systemically acting inhibitor of ectopic calcification. J Clin Invest. 2003;112:357-66.
7. Prezioso D, Saita A, Motta M, et al. Serum fetuin-A and recurrent urolithiasis in young adults. Arch Ital Urol Androl. 2013;85:180-3.
8. Price PA, Nguyen TMT, Williamson MK. Biochemical characterization of the serum fetuin-mineral complex. J Biol Chem. 2003;278:22153-60.
9. Price PA, Lim JE. The inhibition of calcium phosphate precipitation by fetuin is accompanied by the formation of a fetuin-mineral complex. J Biol Chem. 2003;278:22144-52.
10. Heiss A, DuChesne A, Denecke B, et al. Structural basis of calcification inhibition by α 2-HS glycoprotein/fetuin-A: formation of colloidal calciprotein particles. J Biol Chem. 2003;278:13333-41.
11. Schäfer C, Jahnen-Dechent W, Brandenburg V. Klinische Relevanz des Serumproteins Fetuin A – einem Regulator der Kalzifizierung. Laborwelt. 2005;6(5):9-12.
12. Wu YX, Li CY, Deng YL. Patients with nephrolithiasis had lower fetuin-A protein level in urine and renal tissue. Urolithiasis. 2014;42:29-37.
13. Stejskal D, Karpisek M, Vrtal R, et al. Urine fetuin-A values in relation to the presence of urolithiasis. BJU Int. 2008;101:1151-4.
14. Heiss A, Pipich V, Jahnen-Dechent W, Schwahn D. Fetuin-A is a mineral carrier protein: small angle neutron scattering provides new insight on Fetuin-A controlled calcification inhibition. Biophys J. 2010;99:3986-95.
15. Zhou H, Pisitkun T, Aponte A, et al. Exosomal Fetuin-A identified by proteomics: a novel urinary biomarker for detecting acute kidney injury. Kidney Int. 2006;70:1847-57.
16. Mehrsai A, Guitynavard F, Nikoobakht MR, Gooran S, Ahmadi A. The relationship between serum and urinary Fetuin-A levels and kidney stone formation among kidney stone patients. Cent European J Urol. 2017;70:394-9.
17. 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(4):291-3.

Cite this article as: Patankar RR, Dayapule S, Anand A, Davalla S. Evaluation of the role of serum and 24-hour urinary fetuin-A levels in patients with urolithiasis. Int Surg J 2026;13:2131-4.