Original Article
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The Relationship Between Urinary System Stone Disease and Serum Fetuin-A Glycoprotein

Üriner Sistem Taş Hastalığı ile Serum Fetuin-A Glikoproteini Arasındaki İlişki

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ABSTRACT

Objective: This study aimed to investigate the relationship between Fetuin-A glycoprotein, a known systemic and localized calcification inhibitor, and urinary system stone disease.

Material and Methods: A total of 63 patients with urinary stone disease and 70 healthy controls were included. Serum Fetuin-A levels were measured using enzyme-linked immunosorbent assay, and various biochemical parameters were analyzed. Statistical comparisons were performed by using Pearson correlation to determine relationships, with significance set at $p<0.05$.

Results: The mean serum Fetuin-A levels were slightly higher in the stone disease group (503.5 ± 87.6 mg/dL) compared to the control group (462.7 ± 101.6 mg/dL); however, the difference was not statistically significant ($p>0.05$). The mean age was 42.87 ± 11.0 years in the stone group and 41.6 ± 11.7 years in the control group ($p=0.497$). In the stone group, 65% were male and 35% female, while in the control group, 66% were male and 34% female, with no significant difference in gender distribution ($p=0.831$). Body mass index (BMI) was 25.3 ± 2.57 kg/m^2 in the stone group and 26.9 ± 3.08 kg/m^2 in the control group, also showing no significant difference ($p=0.067$). No correlations were found between serum Fetuin-A levels and other parameters such as age, BMI, or biochemical markers.

Conclusion: Although some previous studies have suggested a relationship between Fetuin-A levels and urinary stone disease, this study found no significant association. Further research focusing on genetic polymorphisms of Fetuin-A may clarify its role in stone formation.

Keywords: kidney calculi, urinary calculi, fetuins

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ÖZET

Amaç: Bu çalışmada, sistemik ve lokal bir kalsifikasyon inhibitörü olan Fetuin-A glikoproteini ile üriner sistem taş hastalığı arasındaki ilişki araştırılmıştır.

Gereç ve Yöntemler: Çalışmaya 63 üriner sistem taş hastası ve 70 sağlıklı kontrol grubu dahil edilmiştir. Serum Fetuin-A seviyeleri ELISA yöntemiyle ölçülmüş ve çeşitli biyokimyasal parametreler analiz edilmiştir. İki grup arasındaki ilişkiyi belirlemek için Pearson korelasyonu kullanıldı ve istatistiksel anlamlılık $p<0,05$ olarak belirlendi.

Bulgular: Serum Fetuin-A seviyeleri taş hastalarında (503,5 ± 87,6 mg/dL), kontrol grubuna (462,7 ± 101,6 mg/dL) göre hafifçe yüksek bulunmuş ancak istatistiksel olarak anlamlı fark saptanmamıştır ($p>0,05$). Taş hastalarının yaş ortalaması 42,87 ± 11 yıl, kontrol grubunun ise 41,6 ± 11,7 yıl idi ($p=0,497$). Taş hastalarının %65'i erkek, %35'i kadın; kontrol grubunun %66'sı erkek, %34'ü kadın olup cinsiyet dağılımı açısından anlamlı fark bulunmamıştır ($p=0,831$). Vücut kitle indeksi (VKİ) taş hastalarında 25,3 ± 2,57 kg/m^2, kontrol grubunda 26,9 ± 3,08 kg/m^2 olup bu fark da anlamlı değildi ($p=0,067$). Serum Fetuin-A seviyeleri ile yaş, VKİ veya biyokimyasal belirteçler arasında bir ilişki saptanmamıştır.

Sonuç: Daha önceki bazı çalışmalar Fetuin-A seviyeleri ile üriner sistem taş hastalığı arasında bir ilişki olduğunu öne sürse de, bu çalışmada anlamlı bir ilişki tespit edilmemiştir. Fetuin-A'nın genetik polimorfizmleri üzerinde yapılacak ileri çalışmalar, taş oluşumundaki rolünü daha iyi açıklayabilir.

Anahtar Kelimeler: böbrek taşı, üriner taş, fetuin

INTRODUCTION

Urinary system stone disease is a significant clinical condition with an increasing global prevalence, causing substantial health issues. Epidemiological studies have shown that this disease affects approximately 10% of the population and significantly reduces quality of life (1). The formation of urinary stones involves various factors, including genetic predisposition, metabolic imbalances, environmental influences, and dietary habits (2). However, the biochemical mechanisms underlying stone formation are not yet fully elucidated (3).

Fetuin-A, a glycoprotein produced by the liver, prevents calcium phosphate precipitation and plays a critical role in inhibiting soft tissue calcification (4). While the protective effects of Fetuin-A in the vascular system are well-documented, its role in urinary stone disease remains underexplored. Some studies suggest that a deficiency in Fetuin-A may increase the risk of calcification, potentially influencing the mechanisms of stone formation (5). However, conflicting findings in the literature highlight the need for further investigation (6).

This study aims to evaluate the relationship between serum Fetuin-A levels and urinary system stone disease. The findings may enhance our understanding of stone formation mechanisms and contribute to the development of preventive strategies in the future. Addressing this gap in the literature underscores the significance of research in this field.

MATERIAL AND METHODS

Study Population

After obtaining local ethical approval, the study was initiated (SEEAH 2009 17/12-08). Between 2010 and 2011, 63 patients diagnosed with urinary system stone disease and 70 control individuals with no history of urinary stone disease were included in this study. Participants were selected from those attending urology outpatient clinic or being treated as inpatients. The control group consisted of individuals of similar age without urinary stone disease. Patients with urinary tract infections or a history of acute stone episodes were excluded from the study. Patients previously treated for stone disease were included only after at least one month had passed since their treatment. All participants were aged 18 years or older, with an age range of 18 to 82 years. Informed consent was obtained from all participants before their inclusion in the study.

Diagnostic Methods

Stone diagnosis and exclusion were performed using at least one of the following imaging methods: direct urinary system radiography, ultrasonography (USG), intravenous pyelography (IVP), or abdominal computed tomography (spiral CT with 5 mm sections). The collected data included participants' age, sex, body mass index (BMI), history of stones, and family history. Biochemical analyses involved measuring serum creatinine, uric acid, calcium, phosphorus, magnesium, sodium, potassium, and parathyroid hormone levels. Morning urine pH was determined using a stick test and documented for analysis.

Measurement of Serum Fetuin-A Levels

Venous blood samples (4-5 mL) were collected from all participants in the morning after fasting. The serum Fetuin-A (AHSG) concentrations were measured using an enzyme-linked immunosorbent assay (ELISA) kit (BioVendor – Asheville, North Carolina, USA). After centrifugation, serum samples were stored at -20°C for up to two weeks. Prior to analysis, the samples were thawed and diluted 10,000 times. These diluted samples were added to microwells coated with polyclonal anti-human AHSG/Fetuin-A-specific antibodies. After incubation, peroxidase-conjugated polyclonal anti-human AHSG/Fetuin-A antibodies were added. Subsequent incubation and washing procedures were followed by absorbance measurement at 450 nm using an automatic microplate reader. Concentrations were determined using a standard curve for human AHSG/Fetuin-A, and the actual concentrations were calculated. Mean, median, standard deviation, minimum, and maximum values of Fetuin-A levels were compared between patient and control groups.

Statistical Analysis

The study utilized Statistical Package for the Social Sciences (SPSS) software. For the comparison of biochemical parameters between groups, independent samples t-test (Welch) was used for normally distributed parameters, while the Mann-Whitney U test was applied for non-normally distributed parameters. The chi-square test was used for categorical data comparisons, while Pearson correlation was applied to determine relationships between variables. Statistical significance was considered at $p<0.05$. This comprehensive methodology enabled the evaluation of the relationship between serum Fetuin-A levels and urinary system stone disease, providing reliable results and supporting the study's aims.

RESULTS

The study included 63 patients with urinary system stone disease and 70 healthy individuals without any history of urinary system stone disease. The demographic and clinical characteristics of the study participants, including age, BMI, and gender distribution, are detailed in (Table 1). The mean age of the stone disease group was 42.87 ± 11 years, compared to 41.6 ±11.7 years in the control group. Gender distribution was similar between the groups, with females constituting 65.08% and males 34.92% in the patient group, compared to 66.67% females and 33.33% males in the control group.

Table 1. Profile of the Study Groups

	Stone Disease Group		Control Group	
	n	Mean ± SD	n	Mean ±SD
Age	63	42.87 ± 11	70	41.6 ±11.7
BMI (kg/m2)	63	25.3 ±2.57	70	26.9 ±3.08
Gender	n	%	n	%
Male	41	65.08	44	66.67
Female	22	34.92	26	33.33

Blood samples were analyzed for serum creatinine, uric acid, potassium, sodium, calcium, magnesium, phosphorus, and parathyroid hormone (PTH) levels in both groups. No statistically significant differences were observed between the groups for any of these biochemical parameters as shown in Table 2. Similarly, the urinary pH, measured from fresh morning urine samples, showed no differences between the two groups.

Table 2. Distribution of Serum Parameters Between Groups (Group 1: Stone Disease Group, Group 2: Control Group)

Parameter	Group 1: (Mean ± SD)	Group 2: (Mean ± SD)	p-value
Creatinine (mg/dL)	1.03 ± 0.24	0.97 ± 0.15	0.251
Uric Acid (mg/dL)	5.08 ± 1.04	5.37 ± 1.52	0.392
Sodium (mEq/L)	140.84 ± 3.32	141.22 ± 4.66	0.717
Potassium (mEq/L)	4.58 ± 0.35	4.62 ± 0.6	0.754
Calcium (mg/dL)	9.95 ± 0.57	9.92 ± 0.5	0.829
Phosphorus (mg/dL	3.42 ± 0.58	3.3 ± 0.69	0.469
Magnesium (mg/dL)	2.17 ± 1.89	1.79 ± 0.18	0.282
PTH (pg/mL)	61.4 ± 24.8	57 ± 20.2	0.417 *

** Group 1 Median value: 55, IQR: 29*

** Grup 2 Median value: 54, IQR: 23*

Serum Fetuin-A Levels

The mean serum Fetuin-A levels were higher in the stone disease group (503.46 ± 87.6 mg/dL) compared to the control group (462.69 ± 101.56 mg/dL). However, this difference was not statistically significant as shown in Table 3 (p=0.358). Correlation analysis of serum Fetuin-A levels with other parameters, including age, BMI, serum creatinine, uric acid, albumin, sodium, potassium, magnesium, and PTH levels, revealed no significant relationships.

Table 3. Serum Fetuin-A Levels in Study Groups

Parameter	Stone Disease Group	Control Group	p-value
Mean (mg/dL)	503.46	462.69.	0.358
Standard Deviation	87.65	101.56	
Median (mg/dL)	540.84	487.65	
Maximum (mg/dL)	647.33	590.19	
Minimum (mg/dL)	364.83	291.80	

In summary, while serum Fetuin-A levels were slightly elevated in patients with urinary stone disease compared to healthy controls, this increase was not statistically significant.

DISCUSSION

Fetuin-A glycoprotein has been established as a critical inhibitor of calcification in the human body (7). Its normal serum concentration ranges from 0.4 to 1.0 g/L (8). The gene encoding Fetuin-A is located on chromosome 3q27, a region previously associated with metabolic disorders such as type 2 diabetes and metabolic syndrome (9). While Fetuin-A's role in vascular and soft tissue calcification is well-documented (10), its involvement in urinary stone disease remains underexplored. Emerging evidence suggests that Fetuin-A deficiency may contribute to calcium-rich stone formation by enhancing calcification mechanisms in the urinary system (11).

Studies have investigated the relationship between genetic polymorphisms of Fetuin-A and its role in pathological calcification. Aksoy et al. examined the 766 C/G (T256S) and 742 C/T (T248M) polymorphisms of Fetuin-A in 112 kidney stone patients and 73 healthy controls. While the 742 C/T polymorphism showed significant differences, the 766 C/G polymorphism did not. Furthermore, patients with the 766 CG genotype exhibited lower serum Fetuin-A levels compared to those with the CC genotype (12). These findings suggest that certain polymorphisms may influence serum levels and predispose individuals to stone formation.

Similarly, Emoto et al. demonstrated an inverse correlation between serum Fetuin-A levels and the extent of atherosclerotic calcification in 416 patients with type 2 diabetes. Their study highlights the systemic implications of Fetuin-A deficiency in promoting calcification processes (13). Ross et al. further confirmed the association between the 766 C/G polymorphism of Fetuin-A and arterial stiffness in patients with normal renal function but confirmed vascular calcification. Their genetic analysis provided evidence that the same polymorphism associated with vascular stiffness might contribute to pathological calcification mechanisms relevant to urinary stone disease (14).

In the present study, serum Fetuin-A levels were slightly higher in patients with urinary stone disease compared to healthy controls, although the difference was not statistically significant. This aligns with previous findings indicating that while Fetuin-A plays a role in calcification, its involvement in urinary stone formation is complex and multifactorial (15). Factors such as genetic polymorphisms, metabolic conditions, and environmental influences likely interact to determine an individual's susceptibility to stone disease.

Future research should focus on integrating genetic, environmental, and metabolic factors to provide a more comprehensive understanding of the pathophysiology of urinary stone disease. Expanding the sample size and employing advanced genetic and biochemical analyses could pave the way for new preventive and therapeutic strategies (16).

Limitations

This study has certain limitations that should be acknowledged. One significant constraint is the lack of analysis of stone subtypes (e.g., calcium oxalate, uric acid), as this data was not collected, limiting our ability to evaluate Fetuin-A's relationship with different stone compositions and potentially overlooking a key aspect of stone formation mechanisms. Additionally, the relatively small sample size, with only 63 patients and 70 controls, may have impacted the generalizability and statistical power of our findings. Including a larger sample could have enhanced the reliability of our analyses. Moreover, the incorporation of additional data, such as stone recurrence or family history, could have expanded the study's scope and offered a more comprehensive understanding of stone disease risk factors. These limitations highlight the need for cautious interpretation of our results and underscore the importance of larger samples and broader data collection in future research.

CONCLUSIONS

Fetuin-A glycoprotein, a calcification inhibitor, has been linked to various diseases. This study investigated its relationship with urinary system stone disease. Although hypothesized to influence urinary calcium excretion and stone formation, no significant difference in serum Fetuin-A levels was found between 63 stone patients and 70 controls. While previous studies suggested an association, our findings indicate otherwise. Future research should focus on genetic polymorphisms of Fetuin-A to better understand its role in stone disease.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Ethics Committee Approval: This study was approved by the Sisli Etfal Trainig and Research Hospital Local Ethics Committee (approval number: 0478-5637).

Author Contributions: The authors contributed equally to the study, which was a collaborative effort.

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