



# Correlation of Calcium Metabolic Axis with Urinary Stone Characteristics

Anahita Ansari Djafari <sup>1</sup>, Muhammadhosein Moradi <sup>2</sup>, Mohaddese Malek Mohammadi <sup>3</sup>, Babak Javanmard <sup>4</sup> and Hamidreza Rismanchi <sup>3,\*</sup>

<sup>1</sup>Department of Urology, Shohada-e-Tajrish Educational Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>2</sup>Student Resesarch Committe, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>3</sup>School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>4</sup>Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

\*Corresponding author: School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: [rismanchih@gmail.com](mailto:rismanchih@gmail.com)

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## Abstract

**Background:** Urinary stone disease (USD) refers to the presence of stones or salt crystals within the urinary tract, with calcium stones accounting for approximately 80% of cases. Increased urinary calcium and phosphorus excretion predispose individuals to urinary stones, with hypercalciuria being the most significant risk factor. Vitamin D plays a pivotal role in modifying urine calcium and phosphorus excretion, and it enhances calcium and phosphorus reabsorption in the kidneys. Urinary stone disease is a recognized risk factor for chronic kidney disease (CKD) and may also lead to life-threatening complications such as perinephric abscesses, urosepsis, and urinary tract malignancies. The role of serum vitamin D and its effects on serum calcium and phosphorus in urinary stone formation have been subjects of controversy.

**Objectives:** This study aims to evaluate the associations between serum calcium, phosphorus, and vitamin D levels and urinary stones.

**Methods:** This retrospective study involved two groups of 90 patients, one with urinary stones and the other without. Demographic and biochemical data, including serum calcium, phosphorus, and 25-(OH) vitamin D levels, were recorded for all patients. Patients were categorized into four groups based on their serum vitamin D levels: Excess, sufficient, insufficient, and deficient. The presence and characteristics of urinary stones were assessed using non-contrast CT scans.

**Results:** The mean age of the patients was  $54.62 \pm 15.46$  years. Laboratory investigations revealed mean serum calcium, phosphorus, and vitamin D levels of  $9.56 \pm 0.65$  mg/dL,  $3.53 \pm 0.79$  mg/dL, and  $25.05 \pm 12.96$  ng/mL, respectively. This study demonstrated a significant correlation between serum calcium levels and the maximum diameter of urinary stones (correlation = 0.313, P-value = 0.005). No other significant associations were found between serum calcium, serum phosphorus, and serum vitamin D levels and the number of kidney stones, stone laterality, and type of kidney stone. There was also no significant difference between the two groups.

**Conclusions:** In conclusion, the role of serum calcium, phosphorus, and 25-(OH) vitamin D levels in urinary stone formation remains controversial. This study suggests that there is no significant association between serum calcium, phosphorus, or 25-(OH) vitamin D and urinary stones, except for a positive association between serum calcium and the diameter of the stone.

**Keywords:** Urinary Calculi, Kidney Calculi, Vitamin D, Calcium, Phosphorus

## 1. Background

Urinary stone disease (USD) refers to the presence of stones or crystalline material within the urinary tract. It affects approximately 12% of the global population, with a lifetime risk of formation at 8.8%, and it is more commonly observed in men. The risk of urinary stone formation increases with age, with the highest incidence occurring between the fourth and sixth decades of life

(1). The incidence of urinary stone formation is nearly 0.5% per year in North America and Europe, and 50% of patients with a history of urinary stones may be at risk of developing a second stone within the next 10 years (2, 3). Various factors may contribute to the formation of urinary calculi, including socioeconomic status, dietary habits, fluid intake, and underlying medical conditions such as hypertension and diabetes mellitus (3-5).

Urinary stone disease is recognized as a risk factor for chronic kidney disease (CKD), and over time, it can progress to end-stage renal disease due to scarring resulting from hydronephrosis (6). Urinary stones can lead to life-threatening complications such as urinary tract infections, perinephric abscesses, and urosepsis. If not appropriately treated, these complications have the potential to be fatal (7). Additionally, some studies have observed an association between urinary stone formation and an increased risk of papillary renal cell carcinoma (RCC) and transitional cell carcinoma (TCC) (8-10).

There are several types of urinary stones, with calcium stones accounting for approximately 80% of cases. Hypercalciuria poses a significant risk for the formation of calcium urinary stones as it leads to the crystallization of calcium salts in association with oxalate and phosphate. Hypercalciuria may result from various factors, including increased calcium absorption in the gut, hyperparathyroidism, immobilization, and excessive sodium and animal protein consumption in the diet, either individually or in combination (11).

Vitamin D plays a crucial role in calcium and phosphorus homeostasis by mediating the intestinal absorption of calcium in the gut. Additionally, vitamin D plays a pivotal role in increasing the reabsorption of calcium and phosphorus in the kidneys, thereby modifying urinary calcium and phosphorus excretion (12-14). While hypercalciuria is established as a risk factor for USD, investigations concerning the association of serum calcium, phosphorus, and vitamin D levels with urinary stones and their characteristics are lacking. Therefore, it is imperative to optimize risk factor management due to the significance of urinary stone complications, such as chronic kidney disease (CKD) and subsequent end-stage renal disease (ESRD) resulting from hydronephrosis-induced scarring.

## 2. Objectives

This study aims to assess the correlation among serum calcium, phosphorus, and vitamin D levels with urinary stones.

## 3. Methods

### 3.1. Study Design and Population

This case-control study involved 180 randomly selected participants through conventional sampling. The participants consisted of 90 patients with urinary stones and 90 individuals without urinary stones who were referred to a university referral hospital in Tehran from

June 2021 to June 2023. The case group included patients above 18 years old diagnosed with urinary stones based on computed tomography (CT) scan studies and referred to the urology clinic. The control group was selected from participants who had neither complaints nor a history related to urinary stones. Pregnant participants and those with underlying complications affecting calcium, phosphorus, or 25-(OH) vitamin D metabolism, such as chronic kidney diseases (CKD), end-stage renal disease (ESRD), hyperparathyroidism, kidney transplant recipients, malignancies, and malabsorption diseases, were excluded from this study. Furthermore, patients receiving diuretics, corticosteroids, calcium and vitamin D supplementation, or phosphorus chelates within 3 months of enrollment were also excluded.

The diagnosis of urinary stones was established based on imaging investigations, including ultrasonography and non-contrast abdominopelvic spiral CT scans, in patients with related complaints. Information, including demographics (sex and age) and biochemical data (serum calcium, phosphorus, 25-(OH) vitamin D), were collected from all participants in this study. After the diagnosis was established, all patients with urinary stones underwent non-contrast abdominopelvic spiral CT scans, and complementary data regarding the stones' properties, including type (struvite or non-struvite), number, side of involvement, and maximum size, were obtained.

Serum 25-(OH) vitamin D was measured using the radioimmunoassay technique for all participants in the academic referral hospital laboratory. Calcium and phosphorus levels were measured using isotope-dilution mass spectrophotometry.

### 3.2. Descriptions

#### 3.2.1. 25-(OH) Vitamin D

The 25-(OH) vitamin D was classified into 4 groups based on the national institutes of health (NIH) guidelines (15) as follows: (1) Levels of 50 nmol/L (20 ng/mL) to 125 nmol/L (50 ng/mL) were considered sufficient; (2) levels below 30 nmol/L (12 ng/mL) were considered deficient; (3) levels between 50 nmol/L (20 ng/mL) and 30 nmol/L (12 ng/mL) were considered insufficient; and (4) levels above 125 nmol/L (50 ng/mL) were considered excess.

#### 3.2.2. Calcium and Phosphorus

Normal serum levels were defined between 8.5 mg/dL to 10.5 mg/dL for calcium and 2.5 mg/dL to 4.5 mg/dL for phosphorus (16).

### 3.3. Ethical Consideration

All procedures involving humans were carried out following the guidelines of the Helsinki Declaration and

its later editions. Written informed consent was obtained from the participants.

This study was approved by the Ethics Committee of the Research Center of Shahid Beheshti University of Medical Sciences (ethics code, IR.SBMU.MSP.REC.1399.696).

### 3.4. Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 26 (IBM, New York, USA). Descriptive analysis was presented using mean and standard deviation for quantitative data, while counts and percentages were used for qualitative data. Independent sample *t*-test, Mann-Whitney U, and chi-square tests were used to compare the data between the 2 groups. Spearman and Pearson correlation tests were also used to assess the presence of correlations between quantitative variables. A *P*-value of  $< 0.05$  was considered significant.

## 4. Results

The mean age of the patients was  $55.07 \pm 15.17$  years, comprising 129 (71.6%) males. The mean age of patients with urolithiasis was  $53.57 \pm 15.60$  years, with 63 males (70%), and  $56.57 \pm 14.79$  years for participants without urinary stones, with 66 male individuals (73.3%).

Laboratory investigations revealed mean serum calcium, phosphorus, and 25-(OH) vitamin D levels of  $9.56 \pm 0.65$  mg/dL,  $3.53 \pm 0.79$  mg/dL, and  $25.05 \pm 12.96$  ng/mL overall, with  $9.14 \pm 0.53$  mg/dL,  $3.54 \pm 0.73$  mg/dL, and  $26.26 \pm 12.94$  ng/mL for patients with urolithiasis, and  $8.96 \pm 0.75$  mg/dL,  $3.54 \pm 0.87$  mg/dL, and  $27.83 \pm 13.01$  ng/mL for participants without urolithiasis. Sufficient vitamin D levels were observed in 64.4% of the participants, with 62.2% in the control group and 66.7% in the case group reporting sufficient vitamin D levels. [Figure 1](#) presents the prevalence of urinary stones among participants with different levels of serum vitamin D. No significant differences were observed between the two groups regarding age, sex, and laboratory findings. Patients' demographics and laboratory findings are presented in [Table 1](#).

Single and multiple urinary stones were observed in 57 (63.33%) and 33 patients (36.67%), respectively. Non-struvite urinary stones were observed in 79 patients (87.8%), with the largest diameter measuring  $17.02 \pm 7.70$  mm. Unilateral stones were found in 74 patients (82.2%), with 31 cases (34.4%) on the right side and 43 cases (47.8%) on the left side, while bilateral kidney stones were seen in 16 patients (17.8%). [Table 2](#) presents urinary stone characteristics.

Assessing the association between stone characteristics and laboratory findings revealed a

significant correlation between serum calcium levels and the maximum diameter of the kidney stone (correlation = 0.313, *P*-value = 0.005). No other significant associations were found between serum calcium, serum phosphorus, and serum vitamin D levels with the number of kidney stones, stone laterality, and the type of kidney stone ([Figure 2](#)).

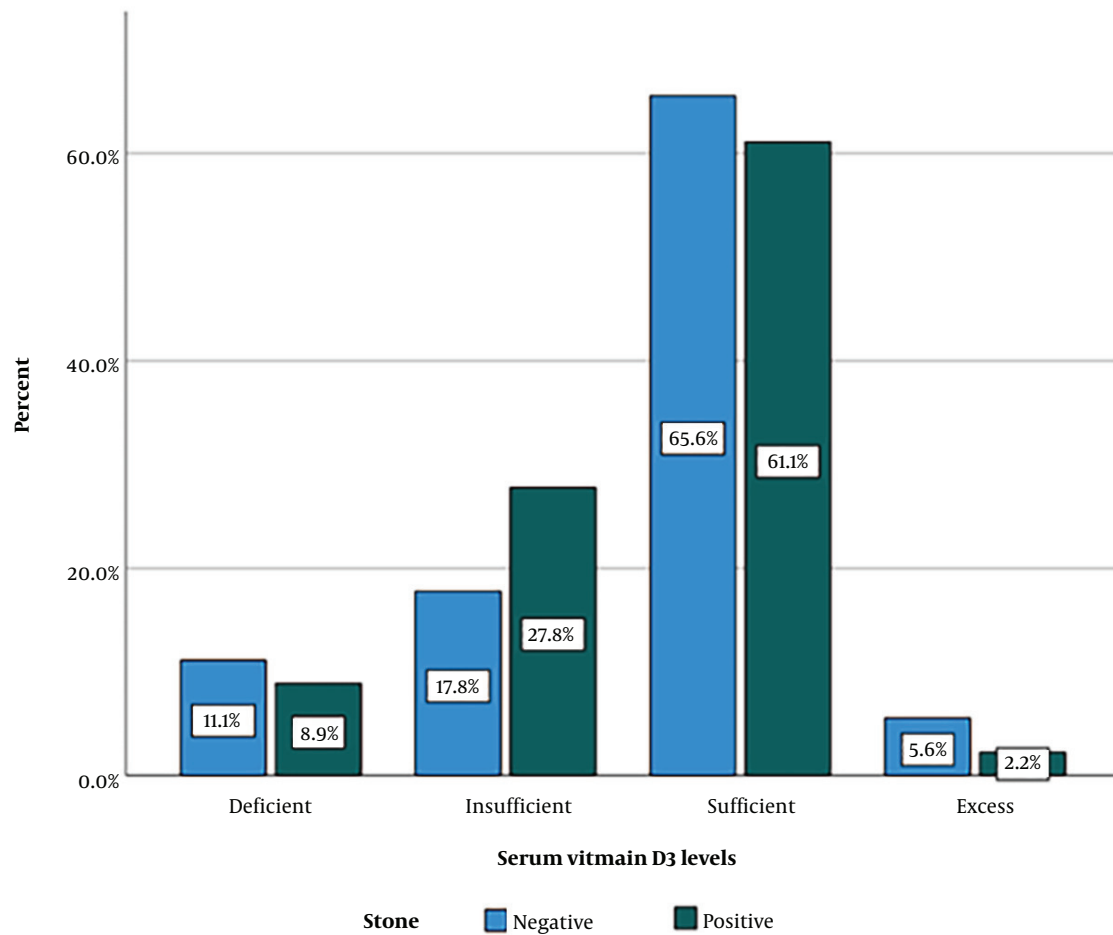
## 5. Discussion

Hypercalciuria is recognized as the most common metabolic risk factor for calcium stones. Excessive urinary calcium excretion, referred to as absorptive hypercalciuria, is one of the factors responsible for this (17). Vitamin D plays a crucial role in calcium and phosphorus homeostasis by influencing the intestine and kidneys. Its primary effect is on the intestine, where it enhances calcium absorption, particularly in the duodenum. Additionally, vitamin D promotes the reabsorption of calcium and phosphorus in the kidneys (12-14, 18). Consequently, maintaining calcium and phosphorus balance and understanding vitamin D's role in this balance are crucial in the context of urinary stone formation.

However, according to this study, no associations were observed between serum calcium, phosphorus, and 25-(OH) vitamin D levels and the incidence of urinary stones. In other words, serum calcium, phosphorus, and 25-(OH) vitamin D levels did not significantly differ between participants with and without urinary stones. Furthermore, there were no significant differences in the incidence of urinary stones among individuals with deficient, insufficient, sufficient, or excess serum vitamin D levels.

Studies have produced conflicting findings concerning the role of vitamin D in urinary stone formation. Some studies found no significant differences in serum vitamin D levels between groups with and without urinary stones (19-22). Nguyen et al. reported no statistically significant association between urinary stones and serum vitamin D levels within the range of 20 to 100 ng/mL (23). Additionally, a meta-analysis revealed similar serum 25-(OH) vitamin D levels in both groups (24).

Conversely, several studies reported contrasting results (25). Ticinesi et al. and Girón-Prieto et al. separately found lower vitamin D serum levels in urinary stone formers compared to the control group and suggested that vitamin D deficiency increases the risk of urinary stone formation due to elevated iPTH levels (26, 27). Tavasoli and Taheri proposed that kidney tissue's oxidative stress and inflammation due to vitamin D deficiency



**Figure 1.** Bar chart showing the presence of urolithiasis based on serum vitamin D levels.

could contribute to calcium oxalate stone formation in the kidney (28).

However, in another meta-analysis, Wang et al. indicated that serum vitamin D levels in kidney stone formers were significantly higher than in controls (29). In a similar study, vitamin D serum levels were significantly higher in groups with bilateral stones than in patients with unilateral stones. Similar to our investigation of the correlation between serum calcium levels and the risk of urinary stone incidence, Moudi et al. found no significant correlation between serum calcium levels and urinary stone incidence in their study (30).

In our study, we identified a significant correlation between serum calcium levels and stone size, with higher serum calcium levels associated with larger urinary stones. Nevertheless, we found no significant correlation between serum phosphorus and vitamin D levels and the size of

urinary stones. Additionally, our study indicated that higher serum calcium and vitamin D levels were not risk factors for an increased number of stones in the urinary tract.

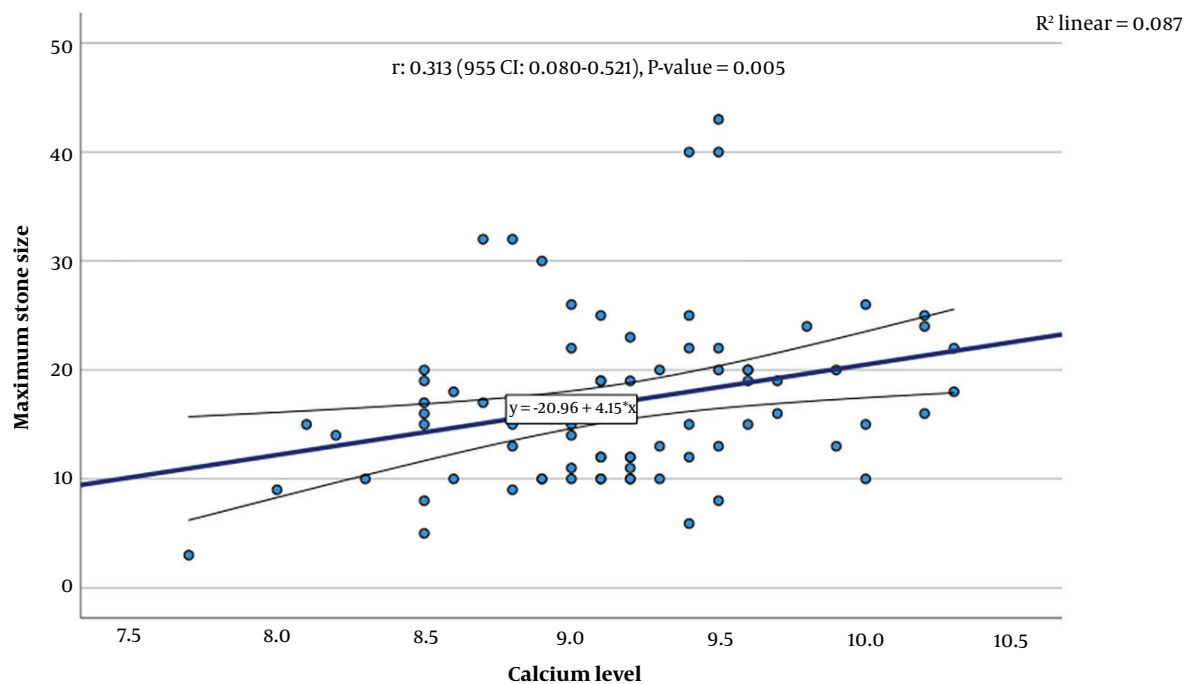
We also assessed the risk of higher serum calcium and vitamin D levels in the occurrence of bilateral urinary stones. However, we did not observe any elevated risks for the formation of bilateral kidney stones with increasing levels of calcium and vitamin D. Furthermore, there were no significant differences in serum calcium and vitamin D levels among patients with right and left kidney stones. Moreover, laboratory findings did not differ among patients with different urinary stone types.

This study represents the first attempt to evaluate the association between serum calcium, phosphorus, and vitamin D levels and stone size, number of stones, and stone types (struvite and non-struvite). However, it has

**Table 1.** Baseline Demographic and Laboratory Characteristics of the Participants <sup>a</sup>

Characteristics and Levels	Total (N = 180)	US+ (N = 90)	US- (N = 90)	P-Value
<b>Demographics</b>				
Age (y)	55.07 ± 15.14	53.57 ± 15.60	56.57 ± 14.79	0.066
Sex				0.620
Male	129 (71.6)	63 (70)	66 (73.3)	
Female	51 (28.4)	27 (30)	24 (26.7)	
<b>Laboratory investigations</b>				
Serum calcium (mg/dL)	9.56 ± 0.65	9.14 ± 0.53	8.96 ± 0.75	0.105
Serum phosphorus (mg/dL)	3.53 ± 0.79	3.54 ± 0.73	3.54 ± 0.87	0.462
25-(OH) Vitamin D (ng/mL)	25.05 ± 12.96	26.26 ± 12.94	27.83 ± 13.01	0.321
Vitamin D status				0.313
Deficient	18 (10)	8 (8.9)	10 (11.1)	
Insufficient	39 (21.7)	24 (26.7)	15 (16.7)	
Sufficient	116 (64.4)	56 (62.2)	60 (66.7)	
Excess	7 (3.9)	2 (2.2)	5 (5.6)	

Abbreviation: US, urinary stone.

<sup>a</sup> Quantitative and Qualitative data are presented as mean ± SD and No. (%) respectively.**Figure 2.** The correlation between serum calcium levels and maximum stone size.

**Table 2.** Stones Characteristics Among Patients with Urinary Stones

Variables and Levels	No. (%)
<b>Number of stones</b>	
Single	57 (63.3)
Multiple	
2	26 (28.9)
3	2 (2.2)
4	3 (3.3)
5	1 (1.1)
6	1 (1.1)
<b>Side</b>	
Unilateral	
Right	31 (34.4)
Left	43 (47.8)
Bilateral	16 (17.8)
<b>Type</b>	
Struvite	11 (12.2)
Non-struvite	79 (87.8)

several limitations. Studies investigating the impact of serum vitamin D, calcium, and phosphorus levels on urinary stone properties, such as size, location, and type, are scarce. More comprehensive studies with larger sample sizes are needed to explore the role of serum calcium and phosphorus levels in the formation of urinary stones.

In conclusion, we found that higher serum calcium levels were associated with larger urinary stone size. However, no other associations between serum vitamin D, calcium, and phosphorus levels and urinary stones were observed, including stone properties such as location and type.

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### Footnotes

**Authors' Contribution:** Study design and conceptualization, A.A.D.; Acquisition of data, M.M.M; Statistical analysis and interpretation of data, M.M; Drafting the manuscript, H.R, and M.M; Critical Revision, A.A.D, and B.J.

**Conflict of Interests:** The authors declare no conflict of interest.

**Data Availability:** The datasets presented in this study are available upon reasonable request from the corresponding author after publication.

**Ethical Approval:** All procedures involving humans were carried out according to the guidelines of the Helsinki Declaration and its later editions. This study was approved by the Ethics Committee of the Research Center of Shahid Beheshti University of Medical Sciences (ethics code, [IR.SBMU.MSP.REC.1399.696](https://doi.org/10.1399.696)).

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