International Journal of Advanced Biological and Biomedical Research
Available online at http:www.ijabbr.com
Volume 9, Issue 4 (2021) pp. 352-361 **DOI**: 10.22034/ijabbr.2021.537924.1366

*Original Article*

# Evaluation of Relationship between Vitamin D Supplementation Treatment and Hypercalciuria in Patients with Kidney Stones

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Received: 31 August 2021, Revised: 04 October 2021, Accepted: 17 September 2021

**ABSTRACT**

**Background:** Vitamin D, especially calcitriol (its active metabolite), increases gastrointestinal calcium absorption. Because urinary calcium excretion is associated with calcium absorption in the gastrointestinal tract; vitamin D metabolites could theoretically cause hypercalciuria. The aim of this study was to investigate the relationship between treatment and vitamin D supplementation on the rate of hypercalciuria in patients.

**Method:** In the present double-blind randomized clinical trial, 90 patients (male-female) with urinary stones and serum vitamin D levels less than 30 ng/mL were evaluated. Patients were randomLy divided into two groups of 45 patients. One group was given 50,000 units of oral vitamin D weekly for up to 8 weeks. For the other group, the drug was given as a placebo for up to 8 weeks. Sampling was performed one month after the end of treatment. The data garnered from hospital records were inserted into SPSS software for analysis.

**Results:** In the present study, the mean age of the subjects was 39.78 years. Also, out of 90 patients, 52 were male and 38 were female. Blood PTH levels decreased significantly after treatment in vitamin D group ($P < 0.001$). Also, serum levels of vitamin D in this group showed a significant increase ($P < 0.001$). However, in this study urinary calcium levels after treatment did not show significant changes ($P = 0.680$).

**Conclusion:** The present study showed that in people with a history of kidney stones, taking vitamin D supplement alone for people with lower than standard serum levels of vitamin D did not show any significant difference in calcification. As a result, the therapeutic dose of this drug is recommended in patients with kidney stones according to the condition.

**Keywords:** Kidney Stones, Vitamin D, Hypercalciuria.

## 1. Introduction

Kidneys and urinary tract are responsible organs for some basic secretory, regulatory and excretory functions such as urine formation, waste excretion, regulation of electrolyte and acid excretion, control of water excretion, self-regulation of blood pressure, and renal cleansing. The kidneys act as the principle excretory organ to remove metabolic waste like creatinine, phosphate, sulfates, uric acid, and urea from the body. It is necessary to excret all urea in the urine; otherwise, its accumulatin occurs in different forms like stones in tissues [1-3].

Urinary stones comprise polycrystalline aggregates made from various amounts of crystalloids and organic matrix. Stone formation requires supersaturated urine which in turn depends on urinary pH, ionic strength, concentration of solutes, and urine composition. During various physiological states, urine contents vary greatly from a relatively acidic urine early in the morning to an alkaline urine after a meal. The kind of combination can also affect the availability of ions, for example sodium combines with oxalate to reduce its ionic free form, whereas sulfate combines with calcium. The main theories of rock formation are nucleation theory, matrix theory, and the theory of inhibitors of crystal formation [4, 5].

Stones built on the surface of the kidney papillae or inside the collecting system do not necessarily cause clinical signs. Asymptomatic stones may be detected during radiographic examinations for other causes. Some common causes of isolated hematuria are stones, benign and malignant neoplasms, renal cysts, and urinary tract infections. Yet, the stones are frequently crushed to enter the ureter. They may also block the connection of the ureter to the pelvis and cause pain and obstruction [5].

Silicate rocks which are rarely found are normally associated with long-term use of silicate-containing antacids such as magnesium silicate (MgSiO3) and aluminum-magnesium silicate (Mg3Al2(SiO3)6. Triamterene stones which are also are clear are associated with anti-hypertensive medical treatments containing triamterene. Other drugs with possible stone components are Glafenine, Antrafenine, Vitamin D and acetazolamide, laxatives, and high-dose aspirin [5, 6].

The most important parts of kidney stones are mainly calcium oxalate and calcium phosphate. In calcium stones, an increased excretion of calcium in the urine (hypercalciuria) is a main risk factor for kidney stones. Similarly, in most cases of idiopathic hypercalciuria, an increase in intestinal calcium absorption was observed in some preliminary studies [7, 8].

Although intestinal calcium absorption depends on the intracellular concentration of calcium, the key factor in intracellular calcium absorption is 1,25dihydroxyvitamin D or calcitriol, i.e., the active form of vitamin D [9]. Actually, vitamin D, whether made by 7-dehidrocholesterolin the skin or absorbed through diet or supplements, must be first activated as 25-hydroxyvitamin D in the liver and then acts as calcitriol in the kidneys to leave its biological effects. Calcitriol binds to the vitamin D receptor (VDR) in intestinal cells to increase calcium transport through the gastrointestinal epithelium using the potential transient receptor transporter, vanilloid 6 (TRPV6) [10].

Moreover, calcitriolcan reduces parathyroid hormone (PTH) synthesis by binding VDR in parathyroid cells. In turn, PTH increases calcium influx through the gatekeeper TRPV5 in distal tubular renal cells. As a result, reduction of PTH by

calcitriol may be associated with increased urinary calcium excretion[11].

Despite the key role of vitamin D in maintaining bone health as well as other physiological functions of the body, most physicians avoid treating vitamin D deficiency in people with kidney stones, mainly because of the potential risk of increased urinary calcium excretion in such patients. This may stem from the belief that vitamin D is often considered a possible cause of kidney stone formation. So far, a number of epidemiological studies have reported a relationship between serum vitamin D levels and the risk of kidney stones [12, 13].

In addition, there is clear evidence on the correlation between serum calcitriol levels and net intestinal calcium uptake [14, 15]. In pathological settings, a positive correlation between urinary calcium excretion and calcitriol in sarcoidosis and primary hyperparathyroidism has been introduced as the two diseases are respectively responsible for increased calcitriol production by granuloma cells and kidneys [16, 17].

However, no significant relationship was observed between vitamin D intake and the risk of kidney stones in men, while the reverse was reported in women [18]. Another significant relationship was observed between increased serum vitamin D levels and kidney stone formation [14]. yet, proportional and low daily intake of vitamin D did not increase the risk of hypercalcemiaoria [19].

Reviewing the literature reveals vitamin D levels have always had a significant effect on blood calcium levels. In this study, it was attempted to analyze this association with hypercalciuria and evaluate urine stones to find out whether vitamin D supplementation could affect hypercalciuria.

## 2. Materials and Method

In this experiment which was carried out as a double-blind randomized clinical trial, a total of ninety 18-65-year-old patients (male and female) with urinary stones (Figure 1) who referred to Zahedan Nephrology Clinic formed the sample. The definitive diagnosis of stone was given and since the serum level of vitamin D was less than 30 ng/mL, they were selected as the study group.

Criteria for inclusion of patients in the study were patients ranging18-65 years old, admitting to participate in the project, signing a written consent, having no specific disease such as heart failure, kidney or liver disease and no inflammatory or infectious diseases, not taking drugs such as diuretics, corticosteroids, and immunosuppressive drugs, not taking vitamin D supplements before the study, not having a cancer, having a life expectancy (<3 months), not taking warfarin or other anticoagulants, not taking non-steroidal anti-inflammatory drugs, having no myocardial infarction during the last three months of the study, showing no sign of malabsorption syndromes, and not undertaking any surgery in the last three months of the study. Moreover, the exclusion criteria included taking medicines such as diuretics, potassium citrate, being pregnant, having a recent excretion of stones, having ureteral stones which lead to obstruction, showing urinary tract infection in the last two weeks of the study, suffering systemic infection in the last two weeks of the study, showing non-observance of the intervention, and expressing dissatisfaction to continue the study.

### *2.1. Sample size and sampling method*

The sample size was measured using the mean comparison formula (Formula 1), where α: 0.05 and β: 0.2 and the data obtained from the previous study (25). Finally, 44 people were considered in

each group, but in the present study, 45 people were examined in each group.
Formula 1: n = (Zα/2+Zβ)2 *2*σ2 / d2

*2.2. Sampling procedure*

First, the blood samples were taken. Then, patients were randomLy divided into two groups, each with 45 patients. For 45 patients with vitamin D ((25 (OH)) VitD levels less than 30 (ng/mL), oral administration of 50,000 units of vitamin D/week was given for up to 8 weeks. Within the same period, the other group took placebo. One month after the end of vitamin D and placebo administration, re-sampling was performed from both groups. Finally, a 24-hour urine test sample was taken to evaluate urinary calcium levels.

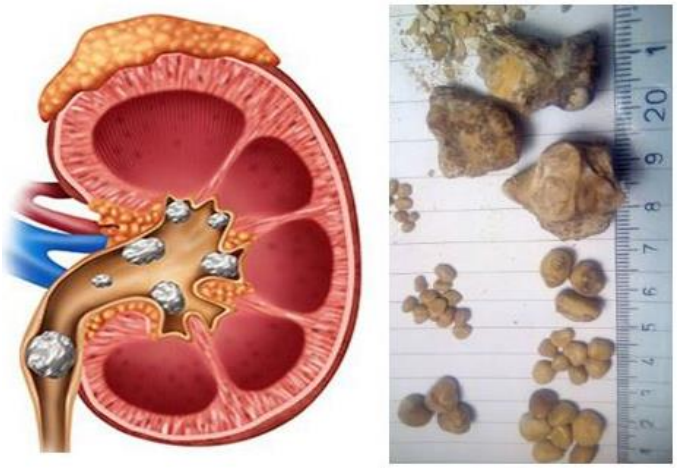

**Figure 1.** Profile of human kidney and kidney stones

*2.3. Data analysis*

The gathered data were analyzed using SPSS software. Central indices including mean and even median and mode, where necessary, and statistical dispersion including standard deviation and even amplitude and coefficient of variation, where necessary, were used to describe the data. Paire-t test, T-test, and even other parametric or non-parametric statistical tests, where necessary, were also used according to the nature of the data.

## 3. Results

Data analysis showed no significant difference in terms of vitamin D and placebo intake and even age and gender of the participants in both groups (Tables 1 and 2). In determining and comparing the amount of urinary calcium excretion in the group taking vitamin D before and after the intervention, only PTH and serum vitamin D level showed a significant increase after taking supplemen (Table 3), whereas before and after taking placebo, no significant difference was observed in the urinary and blood parameters which were related to urinary stones in measuring and comparing the amount of urinary calcium excretion in the control group before and after the intervention (Table 4).

Similarly, in determining and comparing variation in urinary calcium excretion in both groups after the intervention, none of the blood and urine parameters related to urinary stones was significantly different before the study (P> 0.05) (Table 5), while, the amount of PTH and serum levels of vitamin D in both groups was significantly different (Table 6).

Analysis of the mean changes in urinary stone parameters in the two groups before and after receiving the

drug showed a significant difference in the mean changes of serum vitamin D after receiving the supplement (Table 7).

**Table 1.** Evaluation and comparison of the mean age by year in the study groups

| Source | Mean ± Standard deviation | P value for test |
|---|---|---|
| **Get vitamin D.** | 41.91±10.63 | 0.072* |
| **placebo** | 37.66±11.43 | |

*independent sample t test

**Table 2.** Evaluation and comparison of gender in the study groups

| Gender | Group | | P Value |
|---|---|---|---|
| | Get vitamin D. Number(%) | Placebo Number(%) | |
| **Male** | 27(60) | 25(55.6) | |
| **Female** | 18(40) | 20(44.4) | 0.67* |
| **Total** | 45(100) | 45(100) | |

*chi square

**Table 3**. Evaluation and comparison of urinary stone parameters in vitamin D recipients before and after supplementation

| S.O.V | Mean ± Standard deviation | | P Value* |
|---|---|---|---|
| | Before treatment | After treatment | |
| **Serum creatinine (mg/dL)** | 1.02±0.14 | 1.06±0.15 | 0.243 |
| **Serum calcium (mg/dL)** | 9.12±0.16 | 9.14±0.22 | 0.513 |
| **Parathyroid hormone (ng/L)** | 87.15±42.50 | 58.17±23.03 | <0.001 |
| **Serum Vitamin D (ng/mL)** | 12.23±10.63 | 40.63±2.51 | <0.001 |
| **Urinary creatine (mg)** | 452.311±202.33 | 430.177±196.37 | 0.600 |
| **Uric acid (mg)** | 478.66±38.51 | 481.28±35.31 | 0.737 |
| **Urinary calcium (mg)** | 166.77±14.37 | 169.15±12.81 | 0.410 |
| **Urinary sodium (mEq/L)** | 216.64±113.09 | 209.155±110.52 | 0.751 |

*paired t test

**Table 4.** Evaluation and comparison of parameters related to urinary stones in placebo recipients before and after receiving

| S.O.V | Mean ± Standard deviation | | P Value* |
|---|---|---|---|
| | Before treatment | After treatment | |
| **Serum creatinine (mg/dL)** | 1.04±0.2 | 1.08±0.18 | 0.327 |
| **Serum calcium (mg/dL)** | 9.10±0.1615 | 9.17±0.23 | 0.094 |
| **Parathyroid hormone (ng/L)** | 104.177±42.93 | 92±40.06 | 0.168 |
| **Serum Vitamin D (ng/mL)** | 11.43±2.17 | 12.41±2.81 | 0.068 |
| **Urinary creatine (mg)** | 423.97±180.36 | 433.44±179.58 | 0.804 |
| **Uric acid (mg)** | 493.08±35.66 | 480.24±33.77 | 0.083 |
| **Urinary calcium (mg)** | 169.66±12.64 | 168.022±13.19 | 0.548 |
| **Urinary sodium (mEq/L)** | 218.82±119.92 | 210.64±110.94 | 0.738 |

*paired t test

**Table 5.** Evaluation and comparison of urinary stone parameters in vitamin D recipients and placebo recipients before the study

| S.O.V | Mean ± Standard deviation | | P Value* |
|---|---|---|---|
| | Get vitamin D. | Placebo | |
| **Serum creatinine (mg/dL)** | 1.02±0.14 | 1.04±0.2 | 0.501 |
| **Serum calcium (mg/dL)** | 9.12±0.16 | 9.10±0.15 | 0.599 |
| **Parathyroid hormone (ng/L)** | 87.15±42.5 | 104.177±42.93 | 0.062 |
| **Serum Vitamin D (ng/mL)** | 12.23±10.63 | 11.43±2.17 | 0.118 |
| **Urinary creatine (mg)** | 452.311±202.33 | 423.97±180.36 | 0.485 |
| **Uric acid (mg)** | 478.66±38.51 | 493.08±35.66 | 0.069 |
| **Urinary calcium (mg)** | 166.77±14.37 | 169.66±12.64 | 0.314 |
| **Urinary sodium (mEq/L)** | 216.64±113.09 | 218.82±119.92 | 0.930 |

*independent sample t test

**Table 6.** Evaluation and comparison of urinary stones parameters in vitamin D recipients and placebo recipients after the study

| S.O.V | Mean ± Standard deviation | | P Value* |
|---|---|---|---|
| | Get vitamin D. | Placebo | |
| **Serum creatinine (mg/dL)** | 1.06±0.15 | 1.08±0.18 | 0.436 |
| **Serum calcium (mg/dL)** | 9.14±0.22 | 9.17±0.23 | 0.578 |
| **Parathyroid hormone (ng/L)** | 58.17±23.03 | 92±40.06 | <0.001 |
| **Serum Vitamin D (ng/mL)** | 40.63±2.51 | 12.41±2.81 | <0.001 |
| **Urinary creatine (mg)** | 430.117±196.37 | 433.44±179.58 | 0.935 |
| **Uric acid (mg)** | 481.28±35.31 | 480.24±33.77 | 0.886 |
| **Urinary calcium (mg)** | 169.15±12.81 | 168.022±13.19 | 0.680 |
| **Urinary sodium (mEq/L)** | 209.155±110.52 | 210.64±110.94 | 0.949 |

*independent sample t test

**Table 7.** Evaluation and comparison of the mean changes of parameters related to urinary stones before and after receiving vitamin D and placebo

| S.O.V | Mean ± Standard deviation | | P Value* |
|---|---|---|---|
| | Get vitamin D. | Placebo | |
| **Serum creatinine (mg/dL)** | 0.037±0.19 | 0.04±0.27 | 0.961 |
| **Serum calcium (mg/dL)** | 0.026±0.30 | 0.071±0.0.27 | 0.467 |
| **Parathyroid hormone (ng/L)** | -28.97±47.52 | -12.17±61.61 | 0.151 |
| **Serum Vitamin D (ng/mL)** | 28.39±3.82 | 0.98±2.89 | <0.001 |
| **Urinary creatine (mg)** | -22.133±255.957 | 9.46±248.43 | 0.554 |
| **Uric acid (mg)** | 2.62±49.91 | -12.84±44.83 | 0.126 |
| **Urinary calcium (mg)** | 2.37±21.72 | -1.64±19.2 | 0.355 |
| **Urinary sodium (mEq/L)** | -7.48±142.63 | -8.17±144.70 | 0.982 |

*independent sample t test

## 4. Discussion

In the present study, it was found that taking vitamin D supplements in patients with vitamin D deficiency cannot increase calcium rate. In other words, taking vitamin D supplements for one month does not affect urinary calcium excretion in patients suffering suspected kidney stones. Similar studies also did not show a risk of hypercalciuria after taking vitamin D supplements or an

increased serum level of vitamin D [18, 20].

Since taking vitamin D supplement made no variation in urinary calcium levels, it could not increase the risk of kidney stones [21]. Also, no correlation was found between hypercalciuria and the dose of vitamin D. On the other hand, the episodes of hypercalciuria were either transient or recurrent [22]. Contrary to the present study, some studies have recorded a significant dose-dependent increase in incidence of nephrolithiasis with vitamin D supplements[23]. Although taking a diet containing 250 µg/week dose of vitamin D was safe, a 4-week diet followed by monthly doses of 1250 µg probably increased the risk of hypercalciuria [23]. Taking vitamin D3 with calcium supplemen can also significantly reduce stone formation and cause a significant reduction in urinary calcium, so it has a protective role in combination therapy [24].

Moreover, taking oral calcium and vitamin D made no changes in blood calcium and urinary calcium levels. In fact, an increased risk of kidney stones following combination therapy (vitamin D and calcium) is directly related to increased calcium levels in the urine. Yet, there is a great controversary on taking vitamin D supplements and the risk of hypercalciuria, possibly due to differences in study protocol, especially dose and duration of vitamin D treatment along with taking other calcium sources[13]. According to the present study, despite the great possibility of higher risks at taking higher doses, there was no significant relationship between taking a normal dose of vitamin D and an increased risk of kidney stones [25-27].

Actually, as an essential vitamin for the body, vitamin D or calciferol is a fat-soluble vitamin that helps the growth and strength of bones by controlling the balance of calcium and phosphorus. This vitamin increases the absorption of phosphorus and calcium from the intestines and in turn, reduces renal excretion to help bone metabolism. Also, it promotes cell growth by translating cell nucleus genes. Although the sunlight is its most important source, fats such as salmon are rich sources of vitamin D. Besides the sunlight, cereals, some vegetables and fruits, butter, cod liver oil, egg yolk, cream, liver, and sardines are other important sources of this vitamin [9, 28]. Thus, through planning nutrition training and improving habits in patients with stones, it is possible to reduce the incidence and recurrence of this disease or at least, increase its recurrence interval. Considering the problems of kidney stone treatment and its high costs, nutritional recommendations can be an easy and reasonable way to lower the risk of its incidence for both the individual and the community.

### *4.1. Study Limitations*

One of the most important limitations of this study was the lack of accurate evaluation of micronutrients in the daily diet of patients. Other limitations were the low number of participants, short follow-up, and lack of a food questionnaire to obtain participants' accurate eating habits. Therefore, to clarify the effect of vitamin D supplements on kidney stones, further studies are needed on greater populations with respect to different doses of vitamin D taken for different time periods.

## 5. Conclusion

Based on the results of the present study, people with urinary stones and vitamin D levels below the standard, it is useful to take a balanced amount of vitamin D supplement, with no risk of calcification.

Most current methods used to treat kidney and urinary tract stones focus on the stone itself, but they cannot prevent the formation of stones. Therefore, further investigation on factors affecting the formation of kidney stones is a necessary priority for preventing the disease.

**Acknowledgment**

This work was done in Zahedan University of Medical Scinece, The Islamic Republic of Iran. The authors appreciate all staffs on their good collaborations.

**Conflict of Interest Statement:**

The authors declare no competing interests.

**Consent for publications**

The authors have read and approved the submitted manuscript.

**Availability of data and material**

The authors declare that all the data is embedded in the manuscript.

**Authors' contributions**:

All the authors read and approved the final manuscript.

**Ethics approval and consent to participate:**

In the present study, all ethical principles were observed in accordance with the general guideline of ethics in medical sciences research with human subjects in the Islamic Republic of Iran (1-5, 7, 10, 11, 14, 25-31).

**Funding information**:

This work was supported by the Zahedan University of Medical Scinece, Zahedan, Iran.

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**How to cite this article**: Elham Javadian, Ali Alidadi, Mahmoud Ali Kaykhaei. Evaluation of Relationship between Vitamin D Supplementation Treatment and Hypercalciuria in Patients with Kidney Stones. *International Journal of Advanced Biological and Biomedical Research*, 2021, 9(4), 352-361. Link: http://www.ijabbr.com/article_246563.html