The Prevalence of Vitamin D Deficiency, Its Predisposing Factors and Association with 24-hour Urine Metabolites Among Iranian Kidney Stone Formers

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Original Paper

Introduction. To study the prevalence of vitamin D deficiency in kidney stone formers and its predisposing factors and to assess the relationship between serum 25-Hydroxyvitamin D and urine metabolites.
Methods. Kidney stone formers were selected from the records of the kidney stone prevention clinic in Labbafinejad hospital, Tehran, Iran. Vitamin D deficiency was defined as 25-Hydroxyvitamin D < 20 ng/mL. The association between vitamin D deficiency and predisposing factors, serum, and urine metabolites was evaluated.
Results. In 1005 patients (66.4% men and 33.6% women), the prevalence of vitamin D deficiency was 44.8%. Vitamin D deficiency was more prevalent in patients under 50 years ($P < .001$) and patients with hyperparathyroidism ($P < .05$). The lowest prevalence of hyperparathyroidism was in the 25-Hydroxyvitamin D range of 40 to 49.9 ng/mL, followed by the range of 30 to 39.9 and 20 to 29.9 ng/mL. Patients with vitamin D deficiency had lower serum creatinine ($P < .02$), lower 24-hour urine calcium ($P < .01$), and lower 24-hour urine oxalate ($P < .05$).
Conclusion. Iranian kidney stone formers have a relatively high prevalence of vitamin D deficiency. Our population seems to have different predisposing factors for vitamin D deficiency, i.e., higher prevalence among younger patients and no association between obesity and gender with vitamin D status. According to the parathyroid hormone, the favorable serum 25-Hydroxyvitamin D level was 20 to 49.9 ng/mL in our kidney stone formers.

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INTRODUCTION

Vitamin D deficiency (VDD) is a health issue worldwide.[1] The prevalence of VDD varies in different countries, life stage groups, and disease conditions.[1] During the last decade, the role of vitamin D in various medical conditions' pathophysiology has received considerable attention. Vitamin D has a crucial role in calcium absorption, calcium hemostasis, bone health, and, subsequently, osteoporosis prevention.[2] Besides, VDD is associated with the pathogenesis of different chronic diseases, such as diabetes (type 1 and 2) and various cancers.[3] Assessment of the current situation and identification of its risk factors in each region is mandatory to prevent VDD.[4]

Current studies suggest that in the case of normal parathyroid hormone (PTH) levels, a minimum 25(OH)D serum level of 20 ng/mL is sufficient for

optimal bone health and muscle function. However, the normal level of vitamin D is controversial, and some references recommend a minimum 25(OH)D level of 30 ng/mL to minimize the risk of osteomalacia.[5]

Some studies have investigated vitamin D in kidney stone formers (KSFs) and reported a relatively high VDD prevalence in these patients.[6-9] There is no information regarding the prevalence of VDD in Iranian kidney stone formers. This study's objective was to investigate the prevalence of VDD and its predisposing factors in patients with kidney stones. We also aimed to assess the relationship between serum 25(OH)D with metabolic risk factors in the serum and urine.

MATERIALS AND METHODS

This retrospective study was performed on KSF patients referred to the Labbafinejad Kidney Stone Prevention Clinic from March 2015 to May 2019. All patients who were ≥ 18 years old and had undergone serum assessment for 25-hydroxy vitamin D (25(OH)D) were included in this study. Patients who had any chronic disease that could interfere with serum vitamin D (such as sarcoidosis), a history of chronic kidney disease, a known history of primary hyperparathyroidism (HPT), or consumed vitamin D supplements six months prior to serum measurements were excluded. Data was extracted from patients' clinical records. The extracted data (including all variables and laboratory tests) was checked or recorded simultaneously. All investigations were carried out according to the guidelines of the Helsinki Declaration (Fortaleza, Brazil, October 2013). The Ethics Committee of the Urology and Nephrology Research Center of Shahid Beheshti University of Medical Sciences approved this study (ethic code, IR. SBMU.UNRC.1395.15).

Serum 25(OH)D and PTH measurements were performed according to our previous publication.[10] VDD was defined as serum 25(OH)D < 20 ng/mL or < 50 nmol/L, according to the Institute of Medicine (IOM) recommendations in 2011.[11] Serum PTH more than 65 pg/mL was considered as HPT.[10] Primary hyperparathyroidism was defined as serum PTH > 65 pg/mL, coexisted with high or borderline high serum calcium, and sufficient 25(OH)D levels.[12] Twenty four-hour urine samples were analyzed in terms of urine volume, creatinine, urea, uric acid, phosphate, calcium, oxalate, citrate, sodium, potassium, and magnesium to determine the association between these factors and patients' vitamin D status.

Predisposing factors, including demographic charactristics and body mass index (BMI), were gathered from patients' records. BMI was categorized based on the World Health Organization definition into normal (BMI of 18.5 to 24.9 kg/m^2), overweight (BMI of 25 to 29.9 kg/m^2), and obese (BMI greater than 30 kg/m^2).[13]

Statistical analysis was performed using SPSS version 25.0 (IBM, Chicago, Illinois, USA), and graphs were plotted using GraphPad Prism version 7.01 for Microsoft Windows (GraphPad Software, CA, USA). Continuous variables are reported as mean (standard deviation) and categorical data as frequency (percentage). The association between vitamin D status and the numeric variables was assessed using the Independent-Sample T-test. The Chi-square and Fisher exact tests were used to analyze the association between vitamin D and categorical variables. *P* value < .05 was considered statistically significant.

RESULTS

From patients referred to the Labbafinejad Kidney Stone Prevention Clinic during 2015 to 2019, 1005 patients (667 men (66.4%) and 338 women (33.6%)) met the eligibility criteria. The mean age of patients was 48.61 ± 12.77 years old, and most of the patients (75.6%) were from the capital of Iran, where the clinic is located. The mean serum 25(OH)D was 25.37 ng/mL (95% CI: 24.27 to 26.47), with a median value of 21 ng/mL. Figure 1 shows the distribution of serum 25(OH)D subgroups in our patients. The most frequent subgroup was 10 to 19.9 ng/mL, followed by 20 to 29.9 ng/mL. The overall prevalence of VDD in the study population was 44.8% (450 out of 1005 patients).

Table 1 shows the comparison between demographic and anthropometric data of KSFs among vitamin D deficient and vitamin D sufficient patients. As shown in the table, VDD was more prevalent in patients aged less than 50 years old than those aged over 50 (*P* < .001). The prevalence of VDD was not different between men and women. Neither BMI nor weight had any association with VDD. Considering serum PTH, patients with HPT

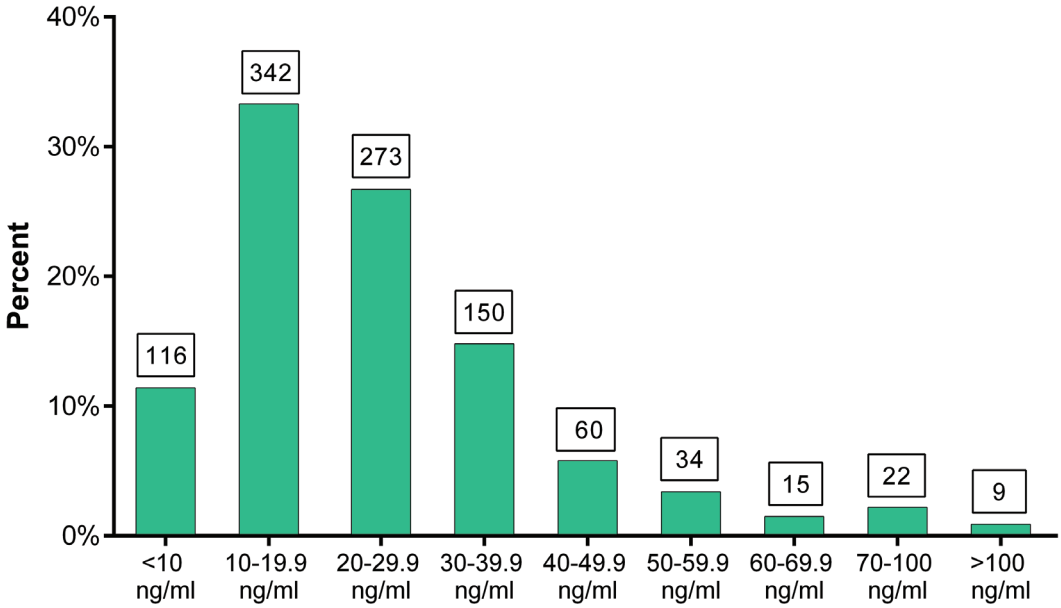

Figure 1. Distribution of Serum 25-Hydroxyvitamin D Subgroups Among Kidney Stone Formers (The values on the Bars represents the number in each group)

Table 1. Comparing Demographic Variables Between Vitamin D Deficient and Vitamin D Sufficient Kidney Stone Formers (All values are number (percentage) and *P* values stand for Chi-square test unless otherwise mentioned.)

	Vitamin D Deficient Kidney Stone Formers	Vitamin D Sufficient Kidney Stone Formers	*P*
Age, y			
< 50	262 (50.6)	256 (49.4)	< .001
≥ 50	188 (38.6)	299 (61.4)	
Gender			
Women	145 (42.9)	193 (57.1)	> .05
Men	305 (45.7)	362 (54.3)	
Weight, kg†	81.3 (14.1)	79.3 (14.9)	> .05‡
BMI			
Normal (18.5 to 24.9)	54 (45.8)	64 (54.2)	
Overweight (25 to 29.9)	138 (46.6)	158 (53.4)	> .05
Obese (≥ 30)	120 (49.4)	123 (50.6)	
Serum PTH			
Hyperparathyroidism	76 (49.7)	77 (50.3)	< .05
Normal PTH	213 (40.7)	310 (59.3)	
Marital Status			
Single	77 (44.5)	96 (55.5)	> .05
Married	373 (44.8)	459 (55.2)	
Education			
Illiterate	88 (41.9)	122 (58.1)	
Literate	279 (45.0)	341 (55.0)	> .05
Academic	83 (47.4)	92 (52.6)	

Abbreviations: BMI, body mass index; PTH, parathyroid hormone.
†The values stand for mean (standard deviation).
‡The *P* value stands for Independent-Samples T test.

had a higher prevalence of VDD compared with patients with normal PTH ($P < .05$). Education and Marital status did not have any association with vitamin D status.

Figure 2 depicts the mean serum 25(OH)D by age subgroups, clustered by gender. As shown in the figure, the mean serum 25(OH)D was higher in women in the subgroup with more than 70 years.

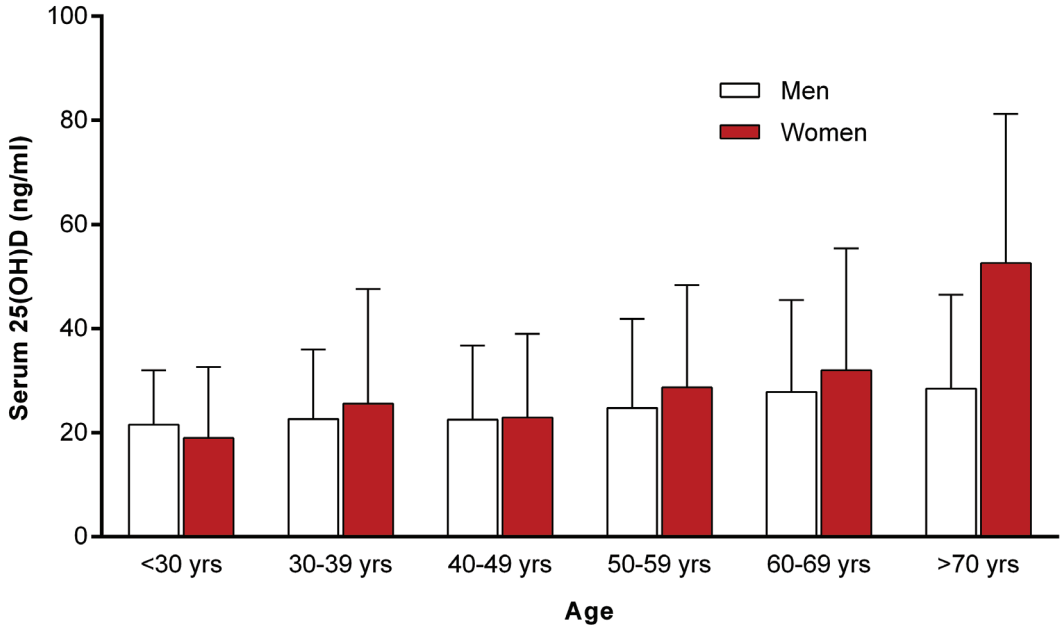

Figure 2. Mean Serum 25-Hydroxyvitamin D by Age Subgroups, Clustered by Gender in the Study Population

Such a difference was not noticeable in other age subgroups.

Figure 3 shows the prevalence of HPT in subgroups of serum 25(OH)D status. Overall, the prevalence of HPT was 15.2% (153 out of 676 patients with serum PTH results). Considering serum 25(OH) D status subgroups, a higher prevalence of HPT was seen in the subgroup with serum 25(OH)D of less than 10 ng/mL. The lowest prevalence of HPT was in the subgroup of 40 to 49.9 ng/mL, followed by the subgroups of 30 to 39.9 ng/mL, and 20 to 29.9 ng/mL.

Table 2 compares the value of serum and 24-hour urine metabolites between vitamin D deficient and sufficient patients. The results showed that serum creatinine was lower in vitamin D deficient patients ($P < .05$). Regarding 24-hour urine analyses, vitamin D deficient patients had lower 24-hour urine calcium ($P < .05$), and lower 24-hour urine oxalate ($P < .05$).

DISCUSSION

The pandemic of VDD has raised considerable concern because of the wide range of vitamin

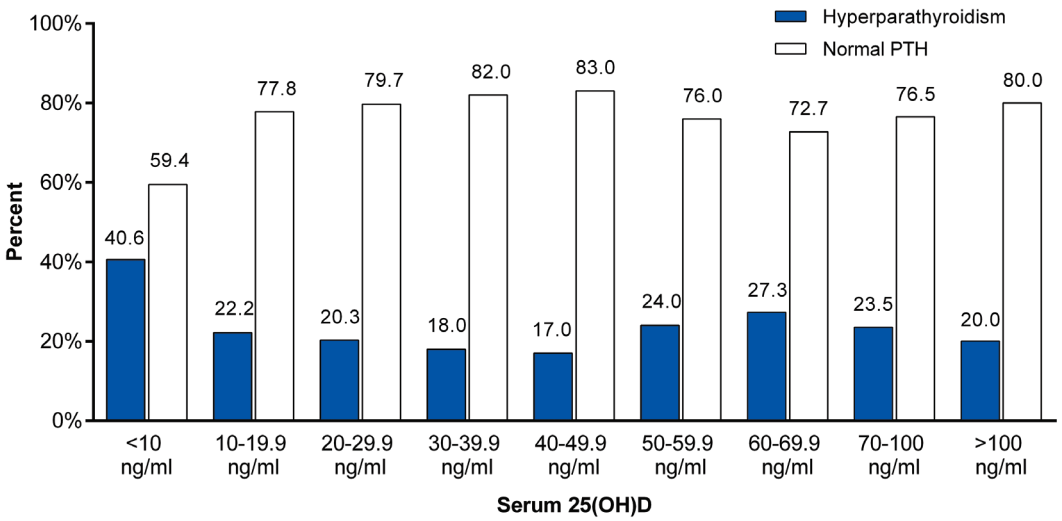

Figure 3. Prevalence of Hyperparathyroidism by Subgroups of Serum 25-Hydroxyvitamin D Status

Table 2. The Association Between Serum and 24-hour Urine Metabolites with Serum 25-Hydroxyvitamin D Status

	Vitamin D Deficiency	Vitamin D Sufficiency	*P*
Serum Creatinine, mg/dL	1.11 (0.24)	1.16 (0.27)	< .01
Serum Calcium, mg/dL	9.52 (0.48)	9.57 (0.49)	> .05
24-hour Urine Volume, mL	1782.7 (732.5)	1813.1 (663.1)	> .05
24-hour Urine Creatinine, mg	1.18 (0.42)	1.18 (0.41)	> .05
24-hour Urine Calcium, mg	183.62 (100.07)	201.85 (119.27)	< .05
24-hour Urine Urea, g	24.95 (11.00)	27.64 (42.39)	> .05
24-hour Urine Sodium, meq	157.29 (70.77)	158.38 (79.02)	> .05
24-hour Urine Magnesium, mg	77.67 (39.14)	78.98 (36.78)	> .05
24-hour Urine Citrate, mg	536.94 (299.08)	565.01 (344.88)	> .05
24-hour Urine Oxalate, mg	34.91 (16.86)	37.53 (19.75)	< .05
24-hour Urine Uric Acid, mg	467.32 (194.40)	454.35 (197.74)	> .05

Independent sample t-test has been used for all variables.

D's biological actions in the body.[1] Finding the predisposing factors and the high-risk population for VDD could help to treat and prevent it. As mentioned earlier, there is a controversy regarding the VDD definition.[5] We defined VDD as serum 25(OH)D level of less than 20 ng/mL. Therefore, here we only presented the results of studies that used the same definition for VDD as in our study.

The prevalence of VDD was 44.8% in our patients. This value is a relatively high prevalence regarding previous studies on kidney stone formers, which reported a range of 18.9 to 56% for VDD prevalence.[6-8, 14,15] However, according to two recent meta-analyses by Tabrizi *et al.*[4] and Vatandost *et al.*,[16] our result showed a lower value than overall Iranian prevalence. These meta-analyses, which used the same cut-point for VDD as our study, reported a prevalence of 61.97% [4] and 57% [16] among the Iranian population. This finding is in disagreement with recent studies that showed a higher prevalence of VDD in stone formers compared with the normal population.[14, 15] This controversy may be due to the difference between our study population and that of the meta-analyses mentioned above. As noted by Tabrizi *et al.*, the prevalence of VDD was significantly different between different geographical regions among the Iranian population.[4] Since most of our patients were from the capital of Iran, comparing our results with the published meta-analyses results may have some limitations. Future case-control studies comparing the prevalence of VDD between urolithiasis patients and general population in each region are suggested to overcome this limitation.

Aging has been mentioned as a predisposing factor of low vitamin D status.[1] The circulatory level of vitamin D reduces with age because of thinner skin, decreased cutaneous production, and lower exposure of older adults to sunlight.[1] However, our results showed that VDD is more prevalent among patients less than 50 years old (Table 1). In line with our findings, the results of Vatandost *et al.*[16] showed a higher prevalence of VDD in the Iranian population of 20 to 50 years compared with more than 50. The consumption of vitamin D supplements due to musculoskeletal complications might have been higher among this group, although not mentioned as drug or medication history.[17] Furthermore, retired Iranian elderly populations usually spend most of their time outdoors, resulting in higher exposure to sunlight.[18]

Clothing practices are proposed as one of the risk factors that could reduce the production of vitamin D in the skin. Some studies stated that covering all the body except the face and hands is one of the risk factors contributing to VDD in the women live in the Middle East region and Africa.[19] The meta-analyses on the Iranian population also noticed a higher prevalence of VDD in women compared with men.[4,16] However, there are controversial results in the current literature. Heshmat *et al.*, in a multi-central study, found no difference between men and women.[20] The results of our study either revealed no difference between men and women (Table 1). Moreover, as shown in Figure 2, serum 25(OH)D level was nearly the same in younger men and women, whereas women of more than 70 years had higher serum 25(OH)D levels. This finding is also in line with Heshmat el.[20] Factors that could explain these findings are air pollution limiting sun exposure in both genders, men's

indoor activities, or seeking more medical care in older women.

Obesity has been mentioned as another predisposing factor for VDD. It is due to the deposition of vitamin D in fat tissue, which decreases its bioavailability in the fat mass of the body.[21, 22] However, neither weight nor BMI was associated with the prevalence of VDD in our study. According to the literature, BMI has some limitations in diagnosing obesity and higher body fat percentage. The studies showed that some people with normal BMI have higher than normal body fat, called 'metabolically obese, normal-weight' phenotype.[23] The higher body fat in these people could result in lower serum vitamin D. This hypothesis needs more studies.

As shown in Table 1, patients with HPT had a higher prevalence of VDD, which is in line with the literature.[1] The inverse association between serum 25(OH)D and PTH levels is suggested to be a tool to define VDD.[1] The serum vitamin D level at which serum PTH reaches the lowest serum values is defined as the normal serum vitamin D cut-point.[1] Our results revealed that the lowest prevalence of HPT was seen in the serum 25(OH)D range of 20 to 49.9 ng/mL (Figure 3). This range could be the best 25(OH)D level for KSF patients, although more studies are warranted for this conclusion.

We found higher serum creatinine levels in patients with sufficient 25(OH)D status (Table 2), with both VDD and vitamin D sufficient groups had normal serum creatinine levels. Most of the studies showed that VDD exacerbates kidney function. However, a study by Agarwal *et al.* showed that short-term vitamin D receptor activation, using a vitamin D analog, increases creatinine production resulting in increased serum creatinine. The intervention did not affect the glomerular filtration rate in chronic kidney disease patients.[24] This effect was due to the increased generation of creatinine in study participants. It is not clear whether VDD increased serum creatinine due to the lower activation of vitamin receptors in our patients or not.

The current results revealed higher urinary calcium in vitamin D sufficient patients, which resulted from univariate analysis. The literature has controversial results regarding the association between serum 25(OH)D and urine calcium.[7,15,25-28] Our previous study showed that urine calcium increased in vitamin D supplemented patients; however, this increase was not associated with the rise in serum vitamin D. Since different dietary and metabolic variables could affect urine calcium, these variables should be considered in future studies on the association between serum 25(OH)D and urine calcium.

A few studies have studied the association between serum 25(OH)D and urine oxalate. As mentioned in Table 2, patients with sufficient vitamin D status had higher urine oxalate. A low intake of calcium could increase urine oxalate.[29] Giannini *et al.* suggested that increased intestinal calcium absorption by vitamin D could induce higher intestinal absorption of oxalate, leading to higher urine oxalate. Limited data on this association warrants further studies.

This study is the first, which determined the prevalence of VDD in Iranian kidney stone formers. However, it had some limitations. The exact time and season of serum vitamin D evaluation is not recorded in the clinic database and is not necessarily the same as the patients' visit date, so it was impossible to precisely determine the prevalence of VDD in different seasons of the year. Additionally, because of the retrospective study design, it was implausible to have a control group without kidney stone disease to compare VDD prevalence between KSFs and the normal population. To overcome this limitation, we decided to compare the prevalence of VDD of kidney stone formers with published studies of the general population that used the same cut-points for vitamin D status. Another limitation was the lack of information regarding dietary habits or comorbid conditions.

CONCLUSION

In conclusion, Iranian KSF patients had a relatively high prevalence of VDD. Our population seems to have different predisposing factors for VDD, i.e., higher prevalence among younger patients, and no association of obesity and gender with vitamin D status. Since the lowest prevalence of HPT was seen in the serum 25(OH)D range of 20 to 49.9 ng/mL, this range could be the favorable serum 25(OH)D level in KSFs. More studies are warranted regarding the association between serum vitamin D and 24- hour urine metabolites, especially urine oxalate and calcium.

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DISCLOSURE OF INTEREST

The authors report no conflict of interest.

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