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The Serum Level of Vitamin D in Women With Urinary Incontinence Due to Pelvic Floor Disorder and Prolapse: A Regional Case-Control Study on Iranian Population

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Abstract

Objectives: Vitamin D is important for the muscular tone and bone metabolism. Due to the high prevalence of vitamin D deficiency in Iranian women, this study aimed to investigate the difference in vitamin D levels between patients with and without pelvic floor disorder (PFD) to assess the possible effect of vitamin D on PFD.

Materials and Methods: The present case-control study examined 209 women referring to Ayatollah Rouhani hospital of Babol in 2017. Patients were explored for prolapse and those with at least one disorder or without PFD were categorized as the case (n = 104) or control (n = 105) groups, respectively. Then, the serum level of 25-hydroxy vitamin D was compared between the groups.

Results: The mean age and abdominal circumference of the patients were significantly higher in the case group ($P < 0.001$ & $P = 0.046$, respectively) as compared to the control group. Meanwhile, the total mean ± SD serum level of vitamin D was 20.03±17.88 ng/mL and significantly higher in the case group (24.58 ± 20.75 ng/mL) than that of the control group (15.53±13.11 ng/mL), especially in patients with stress and urgency urinary incontinence (SIU/UIU) (both with a significance level of $P < 0.001$).

Conclusions: As a result of PFD, the group with UI, especially the one with SIU or UIU had the highest vitamin D level compared to the control and other groups. Nonetheless, the mean age and educational level were significantly higher and lower in this group, respectively. These results could be due to the multifactorial nature of vitamin D level, that is, it varies based on nutrition, place of residence, and other factors.

Keywords: Pelvic floor disorders, Vitamin D, UI, Women

Introduction

Aging is associated with a gradual reduction of muscle strength (1), which will also affect pelvic floor muscles, that is the levator ani and coccygeus skeletal muscles (2). The aging and increased life expectancy of the population have resulted in the increased incidence of aging-associated disorders such as pelvic floor disorder (PFD). As pelvic floor muscles support the pelvic organs, their malfunctioning causes several problems for the affected patients. The main symptoms of PFD include urinary incontinence (UI), fecal incontinence, and pelvic organ prolapse (POP), which reduce patients' quality of life and impose a great financial burden on them (3, 4).

The PFD is generally considered as a multifactorial disease and many factors such as patients' age, body mass index (BMI), parity, mode, and number of deliveries have been suggested as its predictors (5-7). Generally, any factor affecting the musculoskeletal integrity, contraction, and strength can cause PFD (8,9).

Vitamin D, a fat-soluble vitamin, has significant roles in different parts of the body. In addition to nutritional intake, it is considered a sunshine vitamin, as it can be absorbed and metabolized into the active form by the skin when exposed to the sunshine (10). The prevalence of vitamin D deficiency is expected to be low in regions with appropriate sun exposure such as Iran. Nevertheless, a high prevalence of vitamin D hypovitaminosis is reported among the Iranian population (11), especially in women (12). Furthermore, the risk of vitamin D hypovitaminosis increases with the age (13,14). Therefore, older women who are at a higher risk of PFD, further experience vitamin D hypovitaminosis, as well.

Vitamin D receptors (VDRs) can be found on cells including muscle cells (15), thus, this vitamin is important in skeletal muscle function (16). Similarly, evidence has suggested that the serum levels of vitamin D are associated with musculoskeletal health in elderly women (17) and vitamin D supplementation is found effective on neuromuscular function, muscular strength, and stability (18,19). Due to this association and the role of

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muscular dysfunction in pathophysiology of the UI, some studies have investigated the association of vitamin D and urogenital disorders such as UI (20) and overactive bladder (21) while others have focused on the effect of vitamin D supplementation on treatment of UI symptoms (22, 23). However, based on the review studies (24), the few investigations exploring this association (25-28) have several limitations and further studies are required to determine the definite correlation between vitamin D and PFD. Moreover, the prevalence of vitamin D hypovitaminosis and PFD are high among Iranian women and the relationship between these 2 variables has not been investigated in the Iranian population. Accordingly, the current study sought to investigate the difference in serum levels of vitamin D between patients with and without PFD to imply the possible role of vitamin D in PFD. Besides, to the best knowledge of the authors, there is no study exploring the correlation between UI and vitamin D in Iran. The researchers hypothesized that vitamin D hypovitaminosis was associated with PFD. In case of finding such a relationship, in the next step, they attempted to examine if PFD could be improved by vitamin D supplementation, which could be a simple and cost-effective measure towards reducing its incidence and economic/health burden.

Materials and Methods

Study Design

The present case-control research investigated the difference in vitamin D levels of women referring to gynecologic disorders and PFD general clinic of Ayatollah Rouhani hospital in Babol during fall and winter 2017. Before the patient recruitment, the objectives and methods were explained to all the patients. Those who were willing to participate in the study signed the written informed consent and were evaluated in terms of the inclusion/exclusion criteria.

The sample size of the study was calculated to be 100 individuals in each group by the following assumptions: $\sigma = 5$, $Z(1-\alpha/2) = 1.96$, $Z_\beta = 0.84$, vitamin D = 2 ng/dL, study power of 80%, and a 95% confidence level by the formula: $n = [2(z(1-\alpha/2) + z_\beta)^2 * \sigma^2]/d^2$. Finally, a total of 209 women were selected, considering the lost cases according to the inclusion/exclusion criteria.

The inclusion criteria consisted of patients aged >20 years, who referred to the general clinic of gynecologic disorders and PFD of Ayatollah Rouhani hospital in Babol for genitourinary tract dysfunction. Exclusion criteria contained any disorder preventing the absorption of vitamin D such as inflammatory bowel disease (IBD), gastric bypass surgery, chronic kidney or liver disease, any neurological disease affecting the urinary system or bowel movement including multiple sclerosis, degenerative muscle disease, or a history of cerebral vascular accident (CVA) with spinal cord injury and high-grade or chronic diabetes mellitus. All the cases with current or chronic infectious diarrhea, chronic cough, chronic constipation history of anorectal surgery or hysterectomy, recto-vaginal or vesicovaginal fistula and those patients who used estrogen and progesterone or vitamin D supplementation over the past 6 months were excluded from the study. Moreover, the inclusion criteria for the control group involved the adult women referring to the same clinic with complaints about problems other than PFD/UI and the exclusion criteria were similar to the case group in addition to having no UI problem.

Patients were examined by an experienced specialist for prolapse and UI. The diagnosis of UI and POP were based on Stroker's description (29) and categorized based on the UI severity index, that is, an index >3 or <3 was considered positive or negative, respectively. Organ prolapse was regarded as positive when people responded positively to the question: "*Have you ever experienced protrusion of something out of your vaginal area?*" The prolapse degree was determined based on grading (30). Then, demographic data, namely, information about the participants' age, height, weight, parity, and gravidity were recorded and all the enrolled patients were divided into 2 groups based on PFD: patients with at least one disorder or those without PFD were categorized as the case or control group, respectively.

One fasting serum sample (5 cc) was taken from all the women in the morning and all the samples were referred to the hospital's laboratory and were frozen immediately. The serum levels of 25-hydroxyvitamin D (25 (OH) D) level was measured by RIA method (Biosource Europes SA, Belgium). The vitamin D level was considered as (I) deficient when less than 15ng/mL; (II) insufficient when 15-29 ng/mL; and (III) sufficient when > 30 ng/mL (31). Then, the amount of total 25-hydroxyvitamin D was compared in both groups. The BMI was calculated by dividing weight (kg) to squared height (meters) and reported in kg/m^2. Besides, the obtained BMI was categorized as: (*a*) normal weight when <25 kg/m^2; (*b*) overweight when 25.1-29.9 kg/m^2; and (*c*) obese when > 30 kg/m^2 (30). The PFD was considered as the main outcome and vitamin D level was regarded as its predictor.

Statistical Analysis

The data were analyzed using the SPSS (Statistical Package for the Social Sciences) software, version 20. To report the results, quantitative variables were described by the mean ± standard deviation (SD) and categorical variables were also provided by frequency (percentage). As the results of the Kolmogorov-Smirnov test confirmed the normal distribution of data, variables were compared between the case and control groups using the *t* test, Fisher exact test, ANOVA, and chi-square test. The patients were categorized based on the following criteria: age <50 and >50 years; BMI categories <25, 25.1-29.9, and >30 kg/m^2; and serum vitamin D levels into <15, 15-29, and >30 ng/mL. Furthermore, patients in the case group were

classified into 2 groups of SIU and UIU and POP. The *P* values <0.05 were considered statistically significant for all the tests.

Results

Of the 209 participants, 104 women were in the case group and 105 patients in the control group. The mean ± SD age of the patients was 45.79 ± 17.58 years with a range of 20 to 80 years ($P < 0.001$) (Table 1). To compare the age between the groups, the patients were classified according to age categories < 50 and > 50 showing that most patients in the control group were <50 years old ($P < 0.001$) (Table 1).

The mean ± SD of BMI was 28.60 ± 4.88 kg/m^2 with a range of 16.51 to 43.06 kg/m^2. Comparison of the total and categorized BMI values showed no significant difference between the case and control groups ($P = 0.833$ & 0.604, respectively) (Table 1). In addition, the mean ± SD of abdominal circumference was 104.00 ± 10.36 cm, which was significantly higher in the case group as compared to the control group ($P = 0.046$).

Considering the educational level of the patients, 26.3% (n = 55) of them were illiterate whereas 34.0% (n = 71) had a primary school diploma. In addition, 15.7% (n = 33) of the patients had a secondary school diploma while 23.9% (n = 50) of them had a high school diploma or higher educational level. Comparison of the educational level between the groups showed a lower educational level in the case group compared to the control group ($P < 0.001$) (Table 1). With regard to the patients' occupation, 66% (n = 138) of them were housewives and there was no significant difference between the groups in this respect ($P = 0.284$) (Table 1). The complete list of demographics compared between the groups are shown in Table 1.

The mean ± SD serum level of vitamin D in all participants was 20.03 ± 17.88 ng/mL, which was significantly higher in the case group (24.58 ± 20.75 ng/mL) compared to the control group (15.53 ± 13.11 ng/mL) ($P < 0.001$). Of all participants, 108 (51.7%) of them were vitamin D deficient whereas 63 (30.1%) individuals were insufficient. And finally, 38 (18.2%) participants were vitamin D sufficient. Comparison of vitamin D categories between the case and the control groups revealed that the control group had a higher frequency of deficient vitamin D levels while the control group had a higher frequency of sufficient vitamin D levels ($P = 0.003$) (Table 1).

Classifying the case group into SIU/UIU (n = 61) and POP (n = 43) showed a statistically significant difference among the groups considering that the patients' age was considerably higher in the SIU/UIU group ($P < 0.001$). Besides, this group had a lower educational level ($P < 0.001$) and higher gravidity ($P = 0.023$). Meanwhile, comparison of vitamin D levels among the groups demonstrated a statistically higher vitamin D levels in SIU/UIU group compared to the POP group ($P < 0.001$) (Table 2).

As there was a significant difference in the SIU/UIU group, the researchers categorized this group into UIU,

Table 1. Comparing the Demographics and Serum Levels of Vitamin D Between the Case and the Control Groups

Variable	Category	Control Group (n=105)	Case group (n=104)	*P* Value
Age, years	Total, mean±SD	40.77±14.73	50.87±18.79	<0.001*
	20-50 years, No. (%)	80 (76.2%)	46 (44.2%)	<0.001†
	51-85 years, No. (%)	25 (23.8%)	58 (55.8%)	
Body mass index, kg/m^2	Total, mean±SD	28.67±5.46	28.52±4.24	0.833*
	Normal, No. (%)	23 (22.3%)	18 (17.5%)	
	Overweight, No. (%)	44 (42.7%)	50 (48.5%)	0.604†
	Obese, No. (%)	36 (35%)	35 (34%)	
Abdominal circumference, cm, mean±SD		102.58±12.69	105.44±7.07	0.046*
Parity, mean±SD		3.29±1.77	3.73±1.97	0.095*
Gravidity, mean±SD		3.49±1.76	4.14±2.16	0.019*
Mode of delivery, No. (%)	Normal vaginal delivery	62 (59%)	62 (59.7%)	
	Cesarean section	20 (19.1%)	12 (11.5%)	0.232†
	Both	23 (21.9%)	30 (28.8%)	
Educational Level, No. (%)	<High school diploma	64 (61%)	95 (91.3%)	<0.001†
	≥High school diploma	41 (39%)	9 (8.7%)	
Occupation	Housewife	73 (69.5%)	65 (62.5%)	0.284†
	Farmer or others	32 (30.5%)	39 (37.5%)	
25(OH)D (ng/mL)	Total, mean±SD	15.53±13.11	24.58±20.75	<0.001*
	Deficient, No. (%)	63 (60%)	45 (43.3%)	
	Insufficient, No. (%)	32 (30.5%)	31 (29.8%)	0.003†
	Sufficient, No. (%)	10 (9.5%)	28 (18.2%)	

Abbreviations: PFD, pelvic floor disorder; NVD, Normal vaginal delivery. C/S, cesarean section.
* The results of comparison between the groups by *t* test. † The results of comparison between the groups by chi-square test.

Table 2. Comparison of Demographics and Vitamin D Serum Levels Between the Groups According to the Case Groups Categories

Variable	Category	The Control Group (n=105)	Stress and Urgency Urinary Incontinence (n=61)	Pelvic Organ Prolapse (n=43)	*P* Value
Age, years	Total, mean±SD	40.77±14.73^{A}	52.14 ±20.13^{B}	49.06±16.78^{B}	<0.001*
	<50 years, No. (%)	80 (76.2%)	24 (39.3%)	22 (51.2%)	<0.001†
	>50 years, No. (%)	25 (23.8%)	37 (60.7%)	21 (48.8%)	
Body mass index, kg/m^2	Total, mean±SD	28.67±5.46	28.34±4.29	28.79±4.21	0.880*
	Normal, No. (%)	23 (22.3%)	14 (23.3%)	4 (9.3%)	
	Overweight, No. (%)	44 (42.7%)	26 (43.3%)	24 (55.8%)	0.363†
	Obese, No. (%)	36 (35%)	20 (33.3%)	15 (34.9%)	
Abdominal Circumference, cm, mean±SD		102.58±12.69	105.08±7.07	105.95±7.12	0.126*
Parity, mean±SD		3.29±1.77	3.91±1.97	3.46±1.95	0.119*
Gravidity, mean±SD		3.49±1.76^{A}	4.37±2.23^{B}	3.81±2.05^{A}	0.023*
Mode of delivery, No. (%)	Normal vaginal delivery	62 (59%)	32 (52.5%)	30 (69.8%)	0.182†
	Cesarean section	20 (19.1%)	8 (13.1%)	4 (9.3%)	
	Both	23 (21.9%)	21 (34.4%)	9 (20.9%)	
Educational Level, No. (%)	<High school diploma	64 (61%)	56 (91.8%)	39 (90.7%)	<0.001†
	≥High school diploma	41 (39%)	5 (8.2%)	4 (9.3%)	
Occupation	Housewife	73 (69.5%)	40 (65.6%)	25 (58.1%)	0.419†
	Farmer or others	32 (30.5%)	21 (34.4%)	18 (41.9%)	
25(OH)D (ng/ml)	Total, mean±SD	15.53±13.11^{A}	33.82±22.46^{B}	11.46±5.94^{AB}	<0.001*
	Deficient, No. (%)	63 (60%)	13 (21.3%)	32 (74.4%)	<0.001†
	Insufficient, No. (%)	32 (30.5%)	21 (34.4%)	10 (23.3%)	
	Sufficient, No. (%)	10 (9.5%)	27 (44.3%)	1 (2.3%)	

Abbreviations: PFD, pelvic floor disorder.

* The results of comparison between the groups by *t* test. † The results of comparison between the groups by chi-square test.

Table 3. Comparing the Demographics and Serum Levels of Vitamin D Between the Groups Based on Categories of Stress and Urgency Urinary Incontinence Group

Variable	Category	The Control Group (n=105)	Urgency Urinary Incontinence (n=32)	Stress Urinary Incontinence (n=16)	Stress and Urgency Urinary Incontinence (n=13)	Pelvic Organ Prolapse (n=43)	*P* Value
Age, years	Total, mean±SD	40.77±14.73^{A}	53.06±18.02^{B}	58.75±21.67^{B}	41.76±20.55^{A}	49.06±16.78^{AB}	<0.001*
	<50 years, No. (%)	80 (76.2%)	10 (31.3%)	5 (31.2%)	9 (69.2%)	22 (51.2%)	<0.001†
	>50 years, No. (%)	25 (23.8%)	22 (68.7%)	11 (68.8%)	4 (30.8%)	21 (48.8%)	
Body mass index, kg/m^2	Total, mean±SD	28.67±5.46	27.35±3.84	28.61±4.22	30.42±4.91	28.79±4.21	0.412*
	Normal, No. (%)	23 (22.3%)	8 (25.8%)	4 (25%)	2 (15.4%)	4 (9.3%)	
	Overweight, No. (%)	44 (42.7%)	15 (48.4%)	6 (37.5%)	5 (38.5%)	24 (55.8%)	0.606†
	Obese, No. (%)	36 (35%)	8 (25.8%)	6 (37.5%)	6 (46.1%)	15 (34.9%)	
Abdominal Circumference, cm, mean±SD		102.58±12.69	103.62±6.95	106.0±7.89	107.53±5.83	105.95±7.12	0.228*
Parity, mean±SD		3.29±1.77^{AB}	4.31±1.99^{B}	4.00±1.71^{B}	2.84±1.99^{A}	3.46±1.95^{AB}	0.040*
Gravidity, mean±SD		3.49±1.76^{AB}	4.90±2.36^{C}	4.37±1.70^{BC}	3.07±2.1^{A}	3.81±2.05^{AB}	0.023*
Mode of delivery, No. (%)	NVD	62 (59%)	16 (50%)	9 (56.3%)	7 (53.8%)	30 (69.8%)	0.428†
	C/S	20 (19.1%)	3 (9.4%)	3 (18.7%)	2 (15.4%)	4 (9.3%)	
	Both	23 (21.9%)	13 (40.6%)	4 (25%)	4 (30.8%)	9 (20.9%)	
Educational Level, No. (%)	<high school diploma	64 (61%)	29 (90.6%)	15 (93.8%)	12 (92.3%)	39 (90.7%)	<0.001†
	≥high school diploma	41 (39%)	3 (9.4%)	1 (6.3%)	1 (7.7%)	4 (9.3%)	
Occupation	Housewife	73 (69.5%)	23 (71.9%)	11 (68.8%)	6 (46.2%)	25 (58.1%)	0.338†
	Farmer or others	32 (30.5%)	9 (28.1%)	5 (31.3%)	7 (53.8%)	18 (41.9%)	
25(OH)D (ng/mL)	Total, mean±SD	15.53±13.11^{AB}	31.53±17.80^{C}	48.05±30.06^{D}	21.94±3.24^{B}	11.46±5.94^{A}	<0.001*
	Deficient, No. (%)	63 (60%)	6 (18.7%)	3 (18.8%)	4 (30.8%)	32 (74.4%)	<0.001†
	Insufficient, No. (%)	32 (30.5%)	10 (31.3%)	3 (18.8%)	8 (61.5%)	10 (23.3%)	
	Sufficient, No. (%)	10 (9.5%)	16 (50%)	10 (62.4%)	1 (7.7%)	1 (2.3%)	

Abbreviations: PFD, pelvic floor disorder.

* The results of comparison between the groups by ANOVA, † The results of comparison between the groups by chi-square test.

SIU, SIU, and UIU to see where the exact difference was. Accordingly, the results showed a significant difference in vitamin D levels, age, parity, gravidity, and educational level (Table 3).

Discussion

Comparison of demographics and serum level of vitamin D between the case group, that is, patients with UI due to PFD and the control group in this study revealed that the case group, especially the group with SIU/UIU had a higher serum level of vitamin D compared to the control group. However, the mean age and educational level were significantly higher and lower in this group, respectively. This difference in demographics of the patients in different groups could be a source of bias in the results for comparing vitamin D levels, as serum levels of vitamin D vary according to patients' age and that their educational level can also play a role in different health-care and nutritional habits of the patients (32).

Classification of the serum level of vitamin D based on the standard levels in Iranian population (31) showed that 51.7% of the whole population, 60% of the case, and 43.3% of the control groups were vitamin D deficient while only 18.2%, 9.5%, and 18.2% were vitamin D sufficient, respectively. These results show that, generally, the serum level of most the studied patients was very low while that of the control group was even lower. These results are in line with the findings of previous studies on the Iranian population (11,31), in general, and Iranian women (12,33), in particular, which indicate the high prevalence of hypovitaminosis. Various factors can affect the low serum levels of vitamin D in Iranian women including women's clothing that limits the sun exposure and synthesis of vitamin D by the sunshine, as well as dietary habits (34), which could both be the underlying factors of low serum level of vitamin D among the population of this study, especially in the control group. Although the results of the present study confirm those of the previous studies on the high prevalence of vitamin D hypovitaminosis in Iranian population, it has to be considered that the serum levels of vitamin D cannot be easily compared between the studies as its serum value can differ by the season and hour the blood sample was taken from the patients. Moreover, atmospheric components of the living place, sunscreen use, and skin pigmentation, as well as several chronic illnesses in the studied population were among the other factors affecting vitamin D serum value (35,36).

The findings of the study were contrary to the main hypothesis. Considering the pathophysiology of vitamin D and the presence of VDRs on muscle cells (15), it was hypothesized that vitamin D could play a role in the reduced muscular strength and integrity of PFD in cases with hypovitaminosis as far as musculoskeletal health and muscle function was concerned. Contrary to this hypothesis regarding that serum levels of vitamin D should be lower in patients in the case group, namely, those with PFD as compared to the control group (without PFD), the results showed that the mean serum level of the control group and the frequency of vitamin D deficient patients were higher in the control group. These results do not match the results of previous studies on the association of PFD and serum level of vitamin D (26-28), and also the correlation between the serum levels of vitamin D and urogenital disorders such as UI (20,37) and overactive bladder (21), which have determined lower serum levels of vitamin D in patients with PFD or UI problems. In this study, it was assumed that the patients were of the same social class as they referred to one center and that their dietary nutrition was also similar. However, as far as the serum levels of vitamin D depends greatly on the nutritional habits of the individuals and the researchers did not assess or match this factor between the case and the control groups, the variation in the nutritional habits of the study units could be one of the reasons for such contrary results. Another factor for the discrepancy between the results of the current study and the above-mentioned studies could be the different distribution of participants' age and demographics among different studies. The outcomes of the present study were however similar to the results of the study by Parker-Autry et al who compared the serum level of patients with and without PFD according to colorectal anal distress inventory (CRADI)-8 and incontinence impact questionnaire (IIQ-7) and found significantly higher serum levels of vitamin D in the control group (25). Although the main results of the present study are in conformity with the above-mentioned study, it is different from that of ours regarding the measurement method. The researchers of the current study recorded the patients' signs and symptoms according to the gynecologist's visit and physical examination according to which the results indicated that patients with SUI and UIU had a higher serum level of vitamin D than the other groups. The mechanism for the association of vitamin D deficiency and UI is suggested to underlie the effect of vitamin D on the detrusor wall, which contributes to the UI symptoms (25). On the contrary, a reverse association was observed between UI and serum levels of vitamin D in the present study, as patients with UI had higher serum levels of vitamin D in patients with stress and urgency UI than the other groups. These opposing results could be attributed to the fact that serum levels of vitamin D were (very) low in almost all the participants and even in the groups higher than the other, the serum level of vitamin D was in the insufficient class.

The strengths of the present study included the examination of all the patients by a specialist for recording the signs and symptoms and comparing the results of the case group with a control group. Nevertheless, in the present study like most studies evaluating serum levels of vitamin D the recorded serum value of vitamin D varied based on various factors such as the time of sampling, sunlight exposure, and nutritional habits of

the participants, which could not be easily controlled. In addition, the control group did not match in terms of age, educational level, and the demographic characteristics, and thus the significant differences in demographics of the groups could be a source of bias. Furthermore, selection of patients from one center, namely, a specific population limits the generalizability of the results.

Conclusions

The group with UI due to PFD, especially those with SUI or UIU had the highest vitamin D compared to the control and other groups. Nonetheless, the mean age was significantly higher and the educational level was found to be lower in this group as well. These results are not in line with the findings of previous studies and the initial hypothesis on the effect of vitamin D in musculoskeletal pathophysiology of PFD, which could underlie the fact that vitamin D level is determined based on various factors such as nutritional habits, time of sampling, place of residence, etc. that should have been matched between the groups investigated. Moreover, the vitamin D serum level was low in almost all the participants and even that higher than the other group was in the insufficient class that could be the reason for these opposing results. Therefore, future randomized clinical trials are required to determine the causal relationship between vitamin D and PFD. Since in case this association is proven, then the incidence and health/economic burden of this disorder can be reduced by easy and simple supplementation.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

The study protocol was approved by the Ethics Committee of Babol University of Medical Sciences (Code: MUBABOL.REC.1393.19).

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