Urologia Internationalis

Research Article

Urol Int 2021;105:514–519
DOI: 10.1159/000514056

Received: October 12, 2020
Accepted: December 22, 2020
Published online: March 31, 2021

Whether Adding Vitamin D to Tadalafil 5 mg Treatment Is Useful in Patients with Erectile Dysfunction and Vitamin D Deficiency?

Aykut Demirci[a] Murat Çakan[b] Murat Topçuoğlu[c]

[a]Urology Department, Aksaray University Training and Research Hospital, Aksaray, Turkey; [b]Urology Department, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey; [c]Urology Department, Alaaddin Keykubat University Alanya Training and Research Hospital, Antalya, Turkey

Keywords
Vitamin D · Erectile dysfunction · Tadalafil · Impotence · Sexual dysfunction

Abstract
Introduction: Numerous factors such as endothelial disease and hormonal disorder cause the development of erectile dysfunction (ED). However, the relationship between vitamin D deficiency (VDD) and ED is unclear. Moreover, the benefit of vitamin D replacement on ED patients with VDD is uncertain. As far as we know, there is no study yet in the literature regarding the addition of vitamin D to phosphodiesterase type 5 inhibitors in the treatment of ED patients with VDD. In this study, we investigated whether adding vitamin D to daily tadalafil treatment would be beneficial in ED patients with VDD. ***Methods:*** A total of 111 patients with VDD accompanying ED were retrospectively evaluated between January 2016 and December 2019. Patients were divided into 2 groups according to the treatment they received. Group 1 ($n = 58$) was treated with daily oral tadalafil 5 mg, while group 2 ($n = 53$) received oral tadalafil 5 mg and 4,000 IU vitamin D3. Total International Index of Erectile Function-15 (IIEF-15) scores and vitamin D levels of the groups were compared at the end of the study. ***Results:*** The mean vitamin D level was increased statistically significant in group 2, but no difference was seen in group 1 ($p < 0.001$ and $p > 0.05$, respectively). There was a significant increase in median erectile function, orgasmic function, sexual desire, sexual satisfaction, and overall satisfaction scores in both groups ($p < 0.001$). However, the increase in median erectile function and sexual desire scores was significantly higher in group 2 compared to group 1 at the end of the study ($p = 0.01$ and $p < 0.001$, respectively). ***Conclusion:*** We found that adding vitamin D to 5 mg oral daily tadalafil treatment may have an additional positive effect on erectile function and sexual desire in ED patients with VDD.

Introduction

Erectile dysfunction (ED) is an important sexual health problem in males between the ages of 40 and 70, with a rate of 52% and an annual incidence of 26/1,000 [1, 2]. Among organic causes, vascular ED is a dominant form mainly caused by endothelial dysfunction [3, 4].

karger@karger.com
www.karger.com/uin

Correspondence to:
Aykut DEMİRCİ, draykutdemirci@hotmail.com

Table 1. Demographic characteristics of the ED patients

	ED patients (N = 111)	Group 1 (n = 58)	Group 2 (n = 53)	p values
Age*	44.48±11.63	44.05±11.45	44.94±11.92	0.68
CCI**	0 (1)	0 (1)	0 (2)	0.19
BMI, kg/m^2*	24.25±1.92	24.01±1.73	24.51±2.09	0.08
Smoking, *n* (%)				
Yes	37 (33.3)	16 (43.2)	21 (56.8)	0.17
No	74 (66.7)	42 (56.8)	32 (43.2)	
Alcohol use, *n* (%)				
Yes	4 (3.6)	1 (25)	3 (75)	0.34
No	107 (96.4)	57 (53.3)	50 (46.7)	
Diabetes mellitus, *n* (%)				
Yes	20 (21.9)	7 (35)	13 (65)	0.08
No	91 (78.1)	51 (56)	40 (44)	
Hypertension, *n* (%)				
Yes	6 (5.4)	2 (33.3)	4 (66.7)	0.42
No	105 (94.6)	56 (53.3)	49 (46.7)	
Dyslipidemia, *n* (%)				
Yes	5 (4.5)	2 (40)	3 (60)	0.67
No	106 (95.5)	56 (52.8)	50 (47.2)	
Glucose, mg/dL*	114.23±48.18	104.72±30.35	124.36±60.50	0.57
Total cholesterol, mg/dL*	157.07±31.05	158.2±27.6	155.7±34.6	0.37
HDL cholesterol, mg/dL*	44.47±9.53	42±8.6	45.8±10.3	0.22
LDL cholesterol, mg/dL*	88.25±31	90.17±30	86.15±32.2	0.26
Triglycerides, mg/dL*	121.67±45.3	124.4±51.7	118.64±37.2	0.95
Testosterone, ng/mL*	4.23±1.35	4.17±1.45	4.29±1.25	0.29

Group 1, patients receiving oral tadalafil 5 mg/day; group 2, patients receiving oral tadalafil 5 mg/day + 4,000 IU/day vitamin D3; ED, erectile dysfunction; CCI, Charlson Comorbidity Index; BMI, body mass index; IQR, interquartile range; SD, standard deviation. * Mean ± SD. ** Median (IQR).

Vitamin D plays an important role in endothelial system health by providing blood pressure regulation through suppression of renin and also with direct effects such as anti-oxidative and anti-inflammatory [5–8]. It also plays an important role in providing an intact penis anatomy and histology and in the synthesis of nitric oxide, which is necessary in physiology of erection [6, 9, 10]. In addition, it is hypothesized that vitamin D may have an effect on the improvement of erectile function (EF) by its affinity on testosterone receptors [11].

Because vitamin D deficiency (VDD) has been shown to disrupt endothelial functions, theoretically it may cause ED also [12]. Although there are some studies which reported a positive relationship between vitamin D level and the International Index of Erectile Function (IIEF-5) score, this relationship is not clear [13, 14]. Moreover, whether vitamin D replacement therapy is useful in patients with ED and VDD is also uncertain [13].

Phosphodiesterase type 5 inhibitors (PDE5i) are used as first-line treatment in ED [3]. However, approximately 30% of ED patients are unresponsive to PDE5i treatment [15]. It was shown that ED patients who did not respond to oral sildenafil citrate had lower vitamin D levels and EF score [16]. Therefore, it may be beneficial adding the vitamin D to PDE5i treatment to increase its effect in patients with ED and VDD. However, there is no study in the literature on this subject. In this study, we investigated whether adding vitamin D to the daily 5 mg tadalafil in ED patients with VDD has a favorable effect on EF.

Materials and Methods

This retrospective study was approved by the local ethics committee. Written consent was obtained from all the patients, and the study was conducted in accord with the Helsinki Declaration. Between January 2016 and December 2019, 111 male patients with VDD (vitamin D <20 ng/mL) accompanying ED were included in our study. Fifty-

Table 2. Comparison of pre- and posttreatment values of the patients

	Group 1 (n = 58)			Group 2 (n = 53)			p values		
	pretreatment values	first month	third month	pretreatment values	first month	third month	pretreatment values	first month	third month
EF*	14 (10)	21.5 (11)[a]	22 (10)[a]	11 (12)	21 (9)[c]	24 (7)[c, d]	0.28	1	**0.01**
SD*	6 (4)	8 (2)[a]	8 (2)[a]	7 (3)	9 (1)[c]	9 (2)[c]	0.09	**0.02**	**<0.001**
OF*	5 (4)	8 (2)[a]	8 (1)[a]	5 (3)	8 (1)[c]	8 (1)[c]	0.94	0.91	0.98
SS*	6 (3)	10.5 (4)[a]	11 (4)[a]	6 (3)	9 (3)[c]	9 (3)[c]	0.55	0.84	0.75
OS*	5 (3)	8 (2)[a]	8 (2)[a]	5 (3)	8 (1)[c]	8 (1)[c]	0.96	0.40	0.50
Vit-D, ng/mL**	14.48±2.78	14.77±2.60[b]	16.21±3.58[b]	13.96±3.42	30.81±4.22[c]	34.94±4.49[c, d]	0.38	**<0.001**	**<0.001**

EF, erectile function; SD, sexual desire; OF, orgasmic function; SS, sexual satisfaction; OS, overall satisfaction; group 1, patients receiving oral tadalafil 5 mg/day; group 2, patients receiving oral tadalafil 5 mg/day + 4,000 IU/day vitamin D3; IQR, interquartile range; SD, standard deviation. * Median (IQR). ** Mean ± SD. Bold text indicates a statistically significant difference ($p < 0.05$). [a] $p < 0.001$ versus pretreatment values in group 1. [b] $p > 0.05$ versus pretreatment values in group 1. [c] $p < 0.001$ versus pretreatment values in group 2. [d] $p < 0.001$ versus first-month values in group 2.

eight patients were assigned as the control group who received tadalafil 5 mg only (group 1), and 53 of the patients were determined as the case group who received oral daily tadalafil 5 mg and 4,000 IU vitamin D3 replacement (group 2). Age, Charlson Comorbidity Index (CCI) scores, body mass index (BMI), smoking and alcohol abuse, fasting blood glucose, HDL, LDL, total cholesterol, triglyceride, total testosterone, and vitamin D levels were recorded.

The IIEF scores (EF [questions 1, 2, 3, 4, 5, and 15], orgasmic function [OF] [questions 9 and 10], sexual desire [SD] [questions 11 and 12], sexual satisfaction [SS] [questions 6, 7, and 8], and overall satisfaction [OS] [questions 13 and 14]) and vitamin D level of the groups were compared before the treatment and at the first and also the third month of the treatment. Fasting blood samples of the patients were taken (8:00–10:00 a.m.) in the morning. 25-(OH) vitamin D levels were measured using the Cobas e 601 modular system (Roche Diagnostics) via the chemiluminescence microparticle immunoassay method.

Vitamin D level was not routinely checked in ED patients in our clinic. The patients included in the study groups were those whose vitamin D level was checked for the check-up program. It was measured only in patients who admitted to the routine check-up program. VDD (Vit D < 20 ng/mL) was detected in 128 of 367 (34%) ED patients whose vitamin D levels were checked. Among these, 111 patients who met the inclusion criteria were included in the study. Vitamin D replacement therapy was recommended in all patients with a vitamin D level of <20 ng/mL. Patients who had contraindications for PDE5i (such as myocardial revascularization, percutaneous coronary intervention, and history of stable angina pectoris), history of vitamin D usage, pelvic surgery, hypogonadism, and renal insufficiency, have previously received ED treatment, and those using drugs that may affect erectile function were excluded from the study.

Statistical Analysis

SPSS 20.0 (SPSS, Chicago, IL) program was used for statistical analysis. Continuous quantitative data were presented as mean ± SD, discrete quantitative data as median (interquartile range), and classifiable qualitative data as percentages (%). The Shapiro-Wilk test was used to evaluate the homogeneous distribution of the data. Student's t test was used when parametric test assumptions were met in 2 independent groups, and the Mann-Whitney U test was used otherwise. The χ^2 test was used to compare qualitative data. Fisher's exact test was used if the expected values were not met. The repeated measures ANOVA test was used when parametric test assumptions were met in >2 repeated measurements, and the Friedman test was used otherwise. A p value of < 0.05 was considered as statistically significant.

Results

Group 1 and group 2 were similar in terms of mean age, median Charlson Comorbidity Score, mean body mass index, mean fasting blood glucose, mean HDL, LDL, total cholesterol, triglyceride, total testosterone, vitamin D level, comorbid diseases such as diabetes mellitus, hypertension, and dyslipidemia, and also smoking and alcohol abuse ($p > 0.05$) (Table 1). In addition, it was found that the groups were similar in terms of pretreatment values of median EF, OF, SD, SS, and OS scores ($p > 0.05$) (Table 2).

In the first month of treatment, there was a statistically significant increase in median EF, OF, SD, SS, and OS scores in both groups ($p < 0.001$) (Table 2) (Fig. 1b–f). The mean vitamin D levels increase significantly in group 2 compared to the pretreatment values ($p < 0.001$) (Fig. 1a). The mean vitamin D level and median SD level were significantly higher in group 2 compared to group 1 ($p < 0.001$ and $p = 0.02$, respectively) (Table 2) (Fig. 1a, c).

In the third month of treatment, the median EF, OF, SD, SS, and OS scores were statistically higher compared to the pretreatment values in both groups ($p < 0.001$) (Table 2; Fig. 1b–f). Increase in the mean vitamin D level was significantly higher in group 2 according to the pretreat-

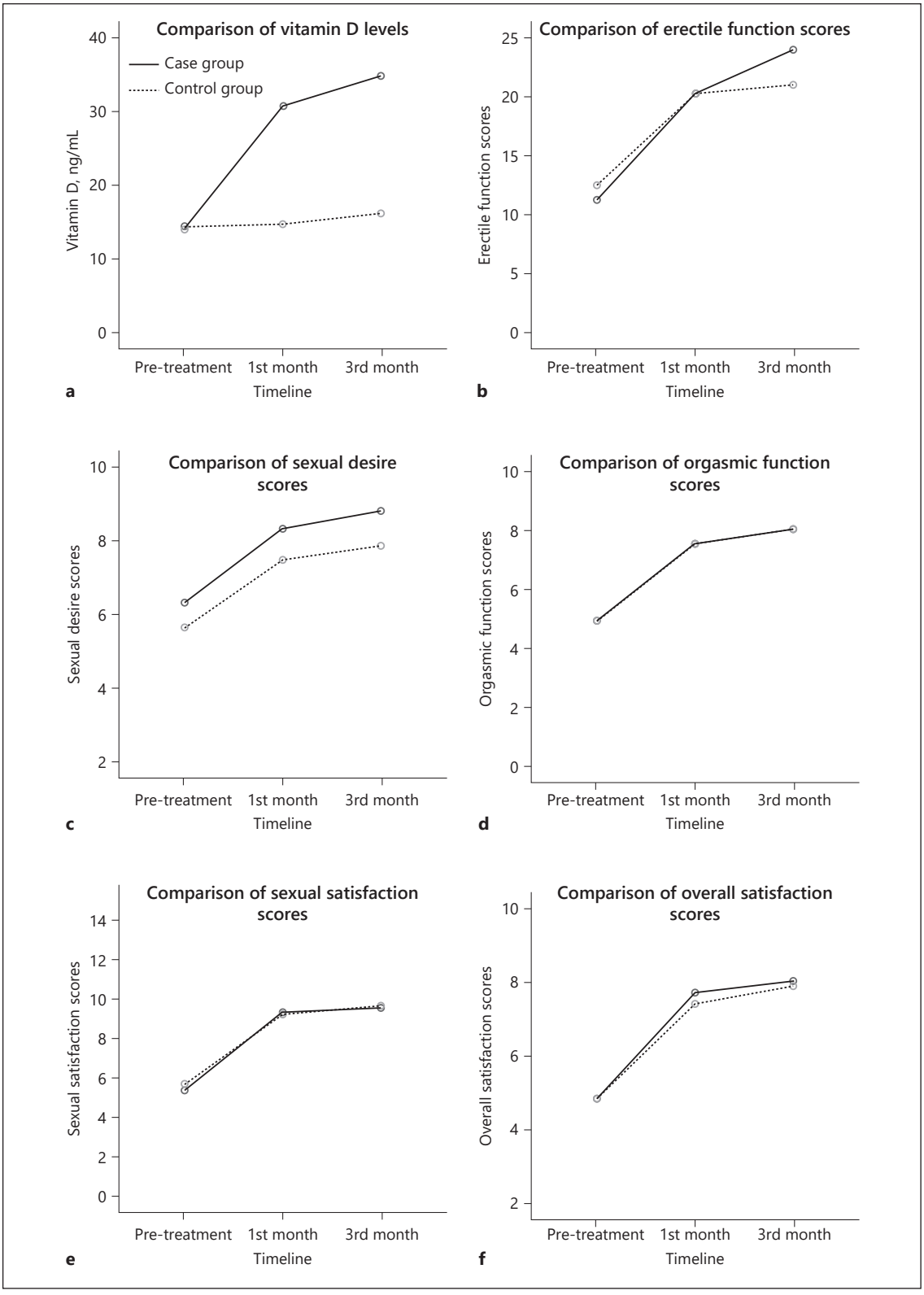

Fig. 1. a Comparison of vitamin D levels. **b** Comparison of erectile function scores. **c** Comparison of sexual desire scores. **d** Comparison of orgasmic function scores. **e** Comparison of sexual satisfaction scores. **f** Comparison of overall satisfaction scores.

ment values ($p < 0.001$) (Fig. 1a). The mean vitamin D levels and median EF and SD scores were significantly higher in group 2 compared to group 1 ($p < 0.001$, $p = 0.01$, and $p < 0.001$, respectively) (Table 2; Fig. 1a–c).

In group 1, there was no significant difference in EF, OF, SD, SS, and OS scores and vitamin D levels in the first and in the third month of treatment ($p > 0.05$) (Fig. 1a–f). The median OF, SD, SS, and OS scores in the first and the third month were similar in group 2 also ($p > 0.05$); however, mean vitamin D levels and median EF score in the third month of treatment were significantly higher than those in the first month of treatment ($p < 0.001$) (Fig. 1a, b). No significant side effect was observed in both groups.

Discussion

The etiopathogenesis of ED is unclear, and another issue that has been emphasized in recent years is VDD. VDD is also a common condition which was found in 38% of males in a study consisting of 926 males in our country [17]. However, despite numerous studies, the relationship between VDD and ED is not clear. In a meta-analysis including the results of 7 trials consisting of 4,132 patients, it was found that there was no evidence of strong relationship between vitamin D and ED [13]. However, it was indicated that the results should be evaluated carefully with more qualified studies.

Treatment of ED ranges from lifestyle modification to oral therapy with PDE5i, intracavernosal treatments, and, finally, penile prosthesis implantation. PDE5i are recommended as first-line treatment which is a highly effective oral treatment with low side effects [3]. It can be used on demand before sexual intercourse or daily. Tadalafil is one of the FDA-approved PDE5i and is preferred as its long half-life allows spontaneous intercourse. However, only 70% of the patients can respond to PDE5i [15]. Therefore, response of PDE5i which were given as initial treatment should be ensured at the maximum level. One of the precautions that must be taken may be adding vitamin D to the treatment in ED patients with VDD. The effects of vitamin D on many mechanisms such as endothelial system, nitric oxide release, and androgen receptors were shown in many studies preclinically and clinically [18].

In a cross-sectional study with 192 male patients, it was evaluated whether the response to 100 mg oral sildenafil was related to the level of blood vitamin D and it has been pointed out that maintaining the 25 (OH) vitamin D level in normal range is important for the success of oral therapy [16]. However, no study yet has been published in the literature regarding the addition of vitamin D to PDE5i treatment in ED patients with VDD.

We studied whether vitamin D replacement is beneficial to daily tadalafil 5 mg treatment in ED patients with VDD. In this study, unlike many similar studies, IIEF-15 was used instead of the IIEF-5 questionnaire to evaluate not only EF but also other parameters of sexual life such as libido, SS, and OF. The median EF, OF, SD, SS, and OS scores have increased statistically significantly compared to the pretreatment values for both groups. At the first month of study, only the SD value was found significantly higher in group 2 ($p = 0.02$), whereas both EF and SD values were found higher in group 2 at the third month ($p = 0.01$ and $p < 0.001$, respectively).

At this point, administration of vitamin D as monotherapy may be an option in patients with VDD accompanying ED. Unfortunately, there are few studies in the literature in this regard and the results are still uncertain. In a study by Cangüven et al. [19], 102 patients with VDD who were administered monthly single high-dose vitamin D treatment for 12 months were prospectively evaluated. It was shown that there was a significant increase in IIEF-5 scores with the improvement in vitamin D level. In line with these results, significant improvement in EF after vitamin D replacement therapy was reported in another longitudinal study [14]. However, in another study evaluating the effect of vitamin D supplementation in dialysis patients, there were no significant changes in sexual parameters following vitamin D supplementation [20].

Our study has some potential limitations. First, since treatment of ED was arranged according to EAU and AUA guidelines in our study, daily 5 mg tadalafil treatment was planned for all patients. Therefore, a patient group who received only vitamin D treatment could not be formed. Therefore, we could not determine the results of administering vitamin D as monotherapy in these patients. The second limitation of our study is the uncertainty in normal reference values and the conflict about the duration and dosage of vitamin D treatment [21]. Evaluating the studies in the literature, general recommendation is to maintain the level of 25 (OH) vitamin D above 20 ng/mL, and it is generally suggested that 1,000–4,000 IU should be used daily to reach the level of 30 ng/mL in case of VDD [22, 23]. We treated our patients with oral daily dosage of 4,000 IU vitamin D, which was frequently recommended in previous reports. Although there is no agreed duration of vitamin D treatment for the improvement of endothelial functions, we have determined a period of 12 weeks in order to see the results since usual follow-up periods ranged from 12 to 16 weeks in the

literature [24]. The retrospective design of the study, relatively short term of follow-up, and the small number of patients are the other limitations of our study.

Conclusion

The role of vitamin D treatment in patients with ED still remains as a controvertible topic in andrology. In this study, we showed that adding vitamin D to the daily tadalafil treatment in ED patients with VDD may lead to significant improvement on EF and SD scores. Thus, determination of serum vitamin D level can be useful for the management of ED patients, as vitamin D supplementation may be a low-cost, low-risk alternative, beside the potential to increase the efficacy of PDE5i. This potential will be useful for clinicians especially in the management of ED patients with VDD. However, further long-term prospective randomized studies with larger number of patients are needed.

Statement of Ethics

This retrospective study was approved by the local ethics committee. Written consent was obtained from all the patients, and the study was conducted in accord with the Helsinki Declaration.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There is no funding.

Author Contributions

Aykut Demirci: project development, manuscript writing, and data collection and analysis. Murat Çakan: supervision. Murat Topçuoğlu: translation of text.

References

1 Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, McKinlay JB. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. J Urol. 2000 Feb;163(2):460–3.
2 Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts male aging study. J Urol. 1994 Jan;151(1):54–61.
3 Hatzimouratidis K, Giuliano F, Moncada I. Male sexual dysfunction. European Association of Urology. 2018. Available from: https://uroweb.org/guideline/male-sexual-dysfunction/.
4 Randrup E, Baum N, Feibus A. Erectile dysfunction and cardiovascular disease. Postgrad Med. 2015 Mar;127(2):166–72.
5 Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest. 2002 Jul;110(2):229–38.
6 Andrukhova O, Slavic S, Zeitz U, Riesen SC, Heppelmann MS, Ambrisko TD, et al. Vitamin D is a regulator of endothelial nitric oxide synthase and arterial stiffness in mice. Mol Endocrinol. 2014 Jan;28(1):53–64.
7 Uberti F, Lattuada D, Morsanuto V, Nava U, Bolis G, Vacca G, et al. Vitamin D protects human endothelial cells from oxidative stress through the autophagic and survival pathways. J Clin Endocrinol Metab. 2014 Apr;99(4):1367–74.
8 Calton EK, Keane KN, Newsholme P, Soares MJ. The impact of vitamin D levels on inflammatory status: a systematic review of immune cell studies. PLoS One. 2015 Nov 3;10(11):e0141770.
9 Fernandes-Lima F, Gregório BM, Nascimento FAM, Costa WS, Gallo CBM, Sampaio FJB. Effects of Vitamin D restricted diet administered during perinatal and postnatal periods on the penis of Wistar rats. Biomed Res Int. 2018 Apr 23; 2018:6030646.
10 Molinari C, Uberti F, Grossini E, Vacca G, Carda S, Invernizzi M, et al. 1α,25-dihydroxycholecalciferol induces nitric oxide production in cultured endothelial cells. Cell Physiol Biochem. 2011;27(6):661–8.
11 Proal AD, Albert PJ, Marshall TG. Dysregulation of the vitamin D nuclear receptor may contribute to the higher prevalence of some autoimmune diseases in women. Ann N Y Acad Sci. 2009 Sep;1173:252–9.
12 Canguven O, Al Malki AH. Vitamin D and male erectile function: an updated review. World J Mens Health. 2021 Jan;39(1):31–37.
13 Wei Y, Chen P, Chen Q, Zhu H. Serum vitamin D levels and erectile dysfunction: a systematic review and meta-analysis. Andrologia. 2019 Apr;51(3):e13211.
14 Tirabassi G, Sudano M, Salvio G, Cutini M, Muscogiuri G, Corona G, et al. Vitamin D and male sexual function: a transversal and longitudinal study. Int J Endocrinol. 2018;2018: 3720813; Published 2018 Jan 8.
15 Curran MP, Keating GM. Tadalafil. Drugs. 2003; 63(20):2203–12; discussion 2213–4.
16 Mostafa T, Rashed LA, Sabry DA, Osman I, Nabil N, Kareem F, et al. Serum L-carnitine and vitamin D levels may be low among oral sildenafil citrate non-responders. Int J Impot Res. 2019;31(2):85–91.
17 Öğüş E, Sürer H, Kılınç ŞA, Fidancı V, Yılmaz G, Dindar N, et al. Evaluation of vitamin D levels by months, sex and age. Ankara Med J. 2015;15(1): 1–5.
18 Talib RA, Khalafalla K, Cangüven Ö. The role of vitamin D supplementation on erectile function. Turk J Urol. 2017 Jun;43(2):105–11.
19 Cangüven O, Talib RA, El Ansari W, Yassin DJ, Al Naimi A. Vitamin D treatment improves levels of sexual hormones, metabolic parameters and erectile function in middle-aged vitamin D deficient men. Aging Male. 2017 Mar;20(1):9–16.
20 Blumberg A, Wildbolz A, Descoeudres C, Hennes U, Dambacher MA, Fischer JA, et al. Influence of 1,25 dihydroxycholecalciferol on sexual dysfunction and related endocrine parameters in patients on maintenance hemodialysis. Clin Nephrol. 1980 May;13(5):208–14.
21 Grant WB. Vitamin D and health in the Mediterranean countries. Hormones. 2019 Mar; 18(1):23–35.
22 Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011 Jan;96(1):53–8.
23 Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Jul; 96(7):1911–30.
24 Kim D-H, Meza CA, Clarke H, Kim J-S, Hickner RC. Vitamin D and endothelial function. Nutrients. 2020 Feb 22;12(2):575.