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Original Research

Association between serum vitamin D levels and acquired premature ejaculation

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Abstract

Background and objective: Premature ejaculation is one of the most common and complex sexual diseases among men. Although there are four defined subtypes of premature ejaculation, the most common subtype is acquired premature ejaculation. This study investigated the association between serum vitamin D levels and acquired premature ejaculation. **Material and methods**: This retrospective cross-sectional study included 94 patients with a complaint of acquired premature ejaculation (the study group) and 92 patients without a complaint of premature ejaculation (the control group) between June 2018 and March 2020. Patients' demographic characteristics, laboratory results, intravaginal ejaculatory latency time, Turkish validated premature ejaculation diagnostic tool (PEDT), International Index of Erectile Function-5 (IIEF-5) and Beck Depression scores were statistically compared between groups. **Results**: The patients' mean age was 49.10 $\pm$ 14.85 years. There were differences between the two groups regarding serum vitamin D levels, dehydroepiandrosterone sulfate, total testosterone, and follicle-stimulating hormone levels. Upon comparing the questionnaire scores, the PEDT, intravaginal ejaculatory latency time, and Beck depression scores were clinically significant between groups. The cut-off value for serum vitamin D levels was 8.37 ng/mL, with a sensitivity of 93% and specificity of 92%. **Conclusion**: We revealed that serum vitamin D and follicle-stimulating hormone levels were independent risk factors according to the multivariate analysis. Measurement of serum vitamin D levels in patients with acquired premature ejaculation may be useful for treatment.

Keywords: Premature ejaculation; Serum vitamin D; Sexual dysfunction; Acquired premature ejaculation

1. Introduction

Premature ejaculation (PE) is a common and complex sexual disease among men that may impair their quality of life due to increased difficulties maintaining a relationship, decreased self-esteem, and inadequate self-confidence [1]. The estimated prevalence of PE is approximately 30–40% in previous studies [2]. Although previous studies involving PE patients have described various PE subtypes, the International Society for Sexual Medicine (ISSM) defined lifelong PE as male sexual dysfunction characterised by ejaculation that always or nearly always occurs before or within about 1 minute of vaginal penetration from the first sexual experience and acquired PE as a clinically significant and bothersome reduction in latency time (often about 3 minutes or less), the inability to delay ejaculation during all or nearly all vaginal penetrations; additionally, there are negative personal consequences, such as feeling distressed, bothered, frustrated, and/or avoiding sexual intimacy [3].

The aetiology of PE is still not clear, but many factors are considered to play a role [4]. Lifelong PE is often associated with neurological diseases of both the central and peripheral nervous systems; notably, pathologies involving neurotransmitters such as serotonin are considered an underlying pathophysiology [5]. Acquired PE (aPE) is more common than lifelong PE, but the prevalence of aPE is still unknown [6]. Multiple reported factors have been proposed to possibly cause aPE, including early experience, sexual conditioning, frequency of sexual activity, anxiety, erectile dysfunction, hyperthyroidism, chronic prostatitis, metabolic syndrome, and Parkinson's disease [7–12].

Vitamin D (vit D) belongs to the steroid hormone family and plays a vital role in the body's calcium metabolism [13]. Several studies have reported that vitamin D receptors (VDR) are expressed in all tissues of the body, regulating cellular differentiation and function [14–16]. After vit D binding to the VDR, it is translocated to the nucleus, where it affects transcription and stimulates both genomic and non-genomic genes [17].

There are limited studies in the literature concerning the association between serum vit D levels and PE. As such, the association between vit D and PE is still controversial. The role of vit D in the body is well known from previous studies; thus, we consider vit D's potential numerous roles in the underlying pathophysiology of aPE. We investigated the association between serum vit D levels and the clinical characteristics of aPE.

2. Material and methods

This cross-sectional retrospective study was performed between June 2018 and March 2020 in Bakircay

Table 1. Patients' demographic and laboratory characteristics according to group.

	Group 1 (acquired PE)	Group 2 (without PE)	*p* value
Age, *mean*, *year*	39.47 ± 12.27	41.95 ± 15.55	0.481
Height, *mean*, *cm*	173.52 ± 7.18	172.37 ± 6.07	0.123
Body mass index, kg/m^2	27.14 ± 4.03	28.90 ± 4.88	0.018
Alcohol assumption, *n*, *%*	2 (2.1%)	1 (1.1%)	0.583
Smoking, *mean*, *p/y*	6.51 ± 11.77	10.83 ± 17.25	0.378
Diabetes mellitus, *n*, *%*	5 (5.3%)	16 (17.4%)	0.009
Hypertension, *n*, *%*	1 (1.1%)	32 (34.8%)	<0.001
Systolic blood pressure, *mean*, *mmHg*	119.57 ± 10.25	125.65 ± 13.14	0.003
Diastolic blood pressure, *mean*, *mmHg*	75.11 ± 6.34	77.50 ± 7.79	0.049
Glucose, *mean*, *mg/dL*	98.18 ± 25.54	122.53 ± 74.17	<0.001
Glycated glucose, *mean*, *%*	5.61 ± 1.02	6.25 ± 1.70	0.001
Serum vitamin D, *mean*, *ng/mL*	17.86 ± 7.24	21.33 ± 9.21	0.006
AST, *mean*, *IU/L*	20.84 ± 9.49	21.76 ± 9.54	0.520
ALT, *mean*, *IU/L*	25.39 ± 18.66	20.82 ± 7.11	0.223
CRP, *mean*, *mg/L*	2.79 ± 3.16	0.52 ± 1.41	<0.001
Total cholesterol, *mean*, *mg/dL*	178.06 ± 41.16	207.89 ± 44.16	<0.001
Triglyceride, *mean*, *mg/dL*	157.44 ± 85.42	159.59 ± 92.57	0.999
HDL, *mean*, *mg/dL*	42.35 ± 9.56	48.86 ± 10.92	<0.001
LDL, *mean*, *mg/dL*	106.61 ± 32.56	127.62 ± 37.45	<0.001
Total testosterone, *mean*, *ng/mL*	4.61 ± 1.79	5.34 ± 2.25	0.031
Oestradiol, *mean*, *pg/mL*	36.38 ± 11.87	38.50 ± 12.50	0.233
FSH, *mean*, *mIU/mL*	5.21 ± 4.49	7.34 ± 3.80	<0.001
LH, *mean*, *mIU/mL*	6.06 ± 2.80	6.37 ± 2.91	0.413
Prolactin, *mean*, *pg/mL*	13.39 ± 9.05	11.66 ± 6.78	0.095
TSH, *mean*, *uU/mL*	1.86 ± 0.87	1.86 ± 1.29	0.398
WBC, *mean*, $\times 10^3/uL$	7.57 ± 2.00	7.57 ± 1.45	0.417
Haemoglobin, *mean*, *g/dL*	15.13 ± 0.93	14.74 ± 1.38	0.077

University Cigli Training and Research Hospital, Urology department. Patients admitted with a complaint of aPE were enrolled in the study. After local committee permission for patient admittance (local ethical number: 242/223; date: 01.04.2021), the patients' demographic characteristics, laboratory results, intravaginal ejaculatory latency time (IELT), Turkish validated international premature ejaculation diagnostic tool (PEDT) [18], International Index of Erectile Function-5 (IIEF-5) [19] and Beck Depression Inventory [20] scores were recorded. In order to evaluate the premature ejaculation status of patients, Turkish validated PEDT test, and erectile functions of patients, the Turkish validated IIEF-5 questionnaires were used. After a detailed history and physical examination, blood samples were obtained from the antecubital vein between 08:00 and 10:00 AM, following fasting for at least 8 hours. Serum glucose, glycated haemoglobin, lipid profile, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone, prolactin, oestradiol, C-reactive protein (CRP), white blood cell, neutrophile, lymphocyte, hemogram, and serum vit D levels were recorded for further statistical analysis.

Serum vit D levels were analysed using a chemiluminescence assay (the ADVIA Centaur XP®, Siemens Inc., Munich, Germany). The intra-assay coefficients of variation were 11.9% at a vit D concentration of 13.6 ng/mL; 9.9% at a vit D concentration of 17.2 ng/mL; 7.2% at a vit D concentration of 28.2 ng/mL; 6.1% at a vit D concentration of 46.1 ng/mL; 6.0% at a vit D concentration of 73.2 ng/mL; and 4.2% at a vit D concentration of 114.1 ng/mL. The test's reference range was 4.2–150 ng/mL (10.5–375 nmol/L). The test's accuracy was 0.99 (ID - LC/MS/MS) + 0.53 ng/mL (r = 0.96), and its detection limit was 3.20 ng/mL (8.0 nmol/L).

Patients with chronic prostatitis, urinary tract infections, psychiatric diseases, using medications that interfere with sexual functions and serum vit D levels, endocrinologic diseases, neurologic diseases, malignancies, chronic kidney failure, metabolic syndrome, cardiac diseases, a history of pelvic surgery, pelvic radiation therapy and irregular sex life were excluded from the study. After exclusion criteria, patients were divided into two groups. The first "study" group included patients with aPE, while the second "control" group included patients with no complaint of PE. In the control group, patients were randomly selected and

Table 2. Comparison of questionary scores of patients according to the groups.

	Group 1	Group 2	*p* value
International index of erectile dysfunction-5 score, *mean* ± *std dev.*	16.24 ± 5.94	17.15 ± 6.00	0.284
Premature ejaculation profile score, *mean* ± *std dev.*	17.98 ± 3.37	1.36 ± 1.11	<0.001
Intra vaginal ejaculatory time, *second, mean* ± *std dev.*	94.11 ± 73.73	576.08 ± 192.93	<0.001
Beck depression score, *mean* ± *std dev.*	11.04 ± 4.00	1.98 ± 1.28	<0.001

included those who had no complaint of any type of premature ejaculation.

All statistical analyses were conducted using the SPSS Statistics 26.0 (IBM Inc., Chicago, IL, USA) package program. Categorical variables were described by frequencies and percentages, and continuous variables were described using means and standard deviations. The Kolmogorov-Smirnov test was used to evaluate the normality of the distributions. Spearman's correlation analysis was applied to measure correlation. The Mann-Whitney U test was applied to compare groups. Multivariate analysis was performed after adjusting for age, smoking, diabetes mellitus, depression and hypertension as confounding factors. A *p*-value of less than 0.05 was omitted the criteria for statistical significance.

3. Results

The mean age of the patients was 49.10 ± 14.85 years. The first group included 94 patients with aPE (the study group); the second group was the control group and included 92 patients without aPE complaint. Table 1 summarises the patients' demographic and laboratory characteristics according to groups. Statistical significance was observed between groups in terms of serum vit D levels, age, presence of diabetes and hypertensive disease, serum glucose, HbA1c, insulin, C-peptide, dehydroepiandrosterone sulfate, gamma-glutamyltransferase (GGT), CRP, albumin, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total testosterone and FSH. When questionnaire scores were compared, the PEDT, IELT, and Beck depression scores were clinically significant between groups. Table 2 summarises the questionnaire score comparison between the groups. The Spearman correlation test revealed a positive observed correlation between serum vit D levels and oestradiol (*p*: 0.022; r: 0.168), prolactin (*p*: 0.022; r: 0.168), and IELT (*p*: 0.010; r: 0.189). Additionally, a negative correlation was observed between serum vit D levels and CRP (*p*: 0.027; r: –0.162), the PEP score (*p*: 0.010; r: –0.189), and the Beck depression score (*p*: 0.004; r: –0.213).

The serum vit D level cut-off value was set at 8.37 ng/mL, with a sensitivity of 93% and specificity of 92% by receiver operating characteristic (ROC) analysis (Fig. 1). Table 3 summarises the univariate and multivariate analysis results. Serum vit D and FSH levels were observed as independent risk factors according to the multivariate analysis results.

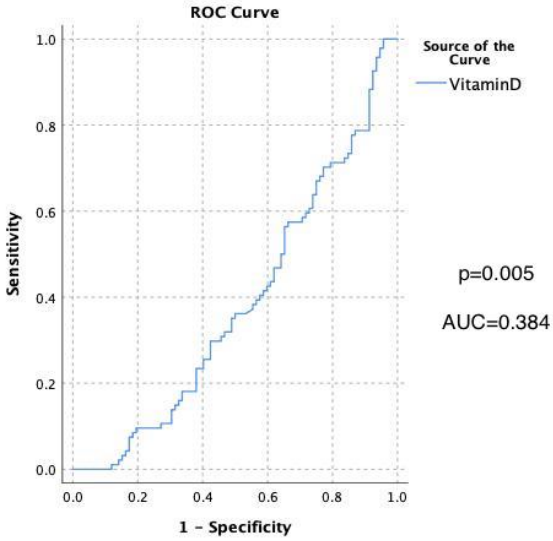

Fig. 1. ROC analysis result of serum vitamin D levels.

4. Discussion

In this retrospective, cross-sectional study, we revealed that low serum vit D levels negatively affect acquired PE. Decreased serum vit D levels were also associated with low serum testosterone and FSH levels, which may be the potential underlying pathophysiology of acquired PE through the affection of multiple ejaculation pathways.

Due to the differences in the definition of PE, previous studies investigating the aetiology of PE differ from each other; thus, the aetiology of PE is still controversial. Most reported causes of the underlying pathophysiology of PE are psychological disorders, endocrinological disorders, infectious diseases (e.g., chronic prostatitis), cardiac disorders, neurological diseases, genetic disorders, early sexual experiences, and an irregular sex life [21].

Recent studies revealed that vit D has many roles in the body via VDRs in the endocrine, cardiovascular, nervous, and immune systems, as well as some cancer pathogenesis, besides its role in calcium metabolism and the musculoskeletal system [22]. There is increasing evidence of the relationship between serum vit D and sexual dysfunction, especially erectile dysfunction [23–25]. Limited studies have investigated the relationship between serum vit D and PE. A study by Canat, which included 97 patients with aPE

Table 3. Univariate and multivariate analysis results.

	Univariate analysis		Multivariate analysis	
	p value	OR	*p* value	OR
Vitamin D	0.004*	0.05	0.003*	1.07
DHEAS	0.002*	0.53	0.055	0.99
Total testosterone	0.006*	0.05	0.051	1.21
FSH	<0.001*	0.31	0.009*	1.15
Prolactin	0.041*	0.82	0.056	0.93
PEP score	<0.001*	1.00	0.994	0.01
IELT	<0.001*	0.95	0.992	1.00

Dependent variables: age, smoking, diabetes mellitus, depression and hypertension. * *p* value less than 0.05.

and 67 healthy men, reported decreased serum vit D levels associated with aPE. The vit D cut-off level for aPE patients was 16 ng/mL, with a sensitivity of 60.9% and specificity of 83.5%. As a result, they supported that low serum vit D may be an underlying etiological factor for acquired PE [26]. Another study, which included 40 patients with lifelong PE and 40 healthy men, reported that serum vit D levels might be a potential risk factor for PE. The authors reported that serum vit D levels correlated with IELT and PEDT. Serum vit D levels were an independent risk factor for patients with lifelong PE. Our results on the vit D effect on aPE are similar to those of previous studies. The vit D cut-off levels were 50.65 ng/mL, with a sensitivity and specificity of 85%. Our cut-off level was 8.37 ng/mL, which was lower than the results of previous studies. We consider that these differences may be associated with seasonal and ethnic variations in serum vit D levels.

One of the pathologies considered to be related to premature ejaculation is anxiety and depression. Depression is one of the most common health problems all around the World, and previous studies reported the relation between decreased serum vit D and depression [27,28]. The association between PE and depression is well-known in the literature. According to the meta-analysis results, which included 18,035 patients, the PE risk (OR: 1.63, 95% CI: 1.42–1.87) increased in patients with depression [29]. Our results were similar to this meta-analysis: patients with PE had statistically higher Beck depression inventory scores than patients without PE. Low serum vit D levels may contribute to increased depression scores in patients with acquired PE.

Studies investigating the relationship between serum testosterone levels and serum vit D reported that low serum vit D levels were associated with low serum testosterone levels [30–32]. Pilz revealed in his study that vit D supplementation increases serum testosterone levels in patients with hypogonadism [33]. In a study including 100 healthy and 100 patients with low testosterone levels, Lerchbaum reported that vit D supplementation did not increase serum testosterone level. However, after 12 weeks of oral supplementation with vit D, they observed increasing sex hormone-binding globulin levels [34]. Several studies reported that vit D was positively associated with total and bioavailable T levels [35,36]. The association between serotonin and premature ejaculation is a well-known object. Current literature indicates that serotonergic neurons act on post-synaptic neuronal receptors where they primarily exert an inhibitory effect on ejaculation [37]. A recent animal study on the relationship between serotonin and serum testosterone levels revealed that low serum testosterone levels might increase serum serotonin levels. Furthermore, the authors reported that 5-HT concentration does not seem to be related to androgens plasmatic concentration since it is not dependent on castration or testosterone administration [38]. Another critical neurotransmitter for sexual behaviour and ejaculation regulation is dopamine. Dopamine is released from the medial preoptic area from the brain. A previous animal study investigating serum testosterone and gonadotropins revealed that low serum testosterone levels were associated with low dopamine release from the medial preoptic area, resulting in impaired sexual behaviour [39]. This study observed a decrease in serum testosterone and FSH levels in patients with low serum vit D levels. We consider that low serum vit D may cause aPE by decreasing serum testosterone levels, which may be the underlying pathophysiology of PE. We could not measure serum serotonin and dopamine levels, both of which play neurotransmitter roles and generally related to lifelong PE in the regulation of the ejaculation mechanism in central nervous system; as such, we could not compare serum testosterone with serotonin and dopamine levels. The association between serum testosterone, dopamine and serotonin levels is still controversial in current literature.

Previous studies have also reported that inflammation may be another underlying cause of PE [40]. More recently, the role of vit D in the immune system as a modulator was reported in several studies. Vit D regulates the proliferation, differentiation, and function of immune cells [41]. Another study revealed that serum vit D has a potential effect on regulating inflammation by inhibiting the expression of inflammatory cytokines in monocytes, including interleukins-1, interleukins-6, interleukins-8, and interleukins-12, and tumour necrosis factor-α [42,43], which may be related to chronic prostatitis as the underlying pathophysiology of PE. The current study considered that low serum vit D might result in increased inflammation through the expression of inflammatory cytokines in prostatic tissue.

We revealed in this study that low serum vit D may cause PE via multiple risk factors. PE may occur due to depression, inflammation, low serum testosterone, and FSH level. All these factors may be related to low serum vit D levels because of the various role of vit D. In our study, patients with low serum vit D levels had all risk factors for acquired PE.

This study also has some limitations. First, due to the retrospective design of the study, we could not randomise the patients. Second, because of the same reason, we could not evaluate the effect of vit D treatment in patients with aPE. Third, although ISSM defined the PE types, study designs in the literature varied, and the definition of PE differed. We used the ISSM definition for PE and excluded patients with natural variable PE and premature-like ejaculatory dysfunction. As a result, we reached a relatively small study population. The last limitation of this study was the seasonal differences in serum vit D levels: we ignored seasonal differences in serum vit D, which may affect serum vit D levels.

5. Conclusions

This study revealed that low serum vit D levels were associated with acquired PE. Serum vit D levels should be considered a risk factor in evaluating patients with the complaint of aPE. Based on our study results, low serum vit D levels could be related to aPE due to increasing prostatic inflammation, anxiety and/or depression, and decreasing serum testosterone and FSH levels. Vit D supplementation as a treatment option in these patients may improve complaints; however, this is still controversial in the recent literature. Through the supporting results of future studies, satisfactory results can be obtained for the treatment of serum vit D levels in patients with PE.

Author contributions

Study design: MOH, Data collection; MOH, AC, Statistical analysis: MOH, Manuscript writing: MOH, AC, YI, Manuscript editing: MOH, AC, YI.

Ethics approval and consent to participate

This cross-sectional retrospective study was performed between June 2018 and March 2020 in Bakircay University Cigli Training and Research Hospital, Urology department. The study protocol was reviewed and approved by local committee (local ethical number: 242/223; date: 01.04.2021). Patients admitted with a complaint of aPE were enrolled in the study. All participants gave their informed consent for inclusion before they participated in the study.

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Conflict of interest

The authors declare no conflict of interest.

References

[1] Montorsi F. Prevalence of premature ejaculation: a global and regional perspective. The Journal of Sexual Medicine. 2005; 2: 96–102.

[2] Jannini EA, Lenzi A. Epidemiology of premature ejaculation. Current Opinion in Urology. 2005; 15: 399–403.

[3] Serefoglu EC, McMahon CG, Waldinger MD, Althof SE, Shindel A, Adaikan G, *et al*. An Evidence-Based Unified Definition of Lifelong and Acquired Premature Ejaculation: Report of the second International Society for Sexual Medicine Ad Hoc Committee for the Definition of Premature Ejaculation. The Journal of Sexual Medicine. 2014; 11: 1423–1441.

[4] Giuliano F, Clément P. Physiology of ejaculation: emphasis on serotonergic control. European Urology. 2005; 48: 408–417.

[5] Waldinger MD. Pathophysiology of Lifelong Premature Ejaculation. Premature Ejaculation. 2013; 50: 71–80.

[6] Jannini EA, Lenzi A. Pathophysiology of Acquired Premature Ejaculation. Premature Ejaculation. 2013; 5: 81–97.

[7] Hartmann U, Schedlowski M, Krüger THC. Cognitive and partner-related factors in rapid ejaculation: differences between dysfunctional and functional men. World Journal of Urology. 2005; 23: 93–101.

[8] Carani C, Isidori AM, Granata A, Carosa E, Maggi M, Lenzi A, *et al*. Multicenter study on the prevalence of sexual symptoms in male hypo-and hyperthyroid patients. The Journal of Clinical Endocrinology & Metabolism. 2005; 90: 6472–6479.

[9] Screponi E, Carosa E, Di Stasi SM, Pepe M, Carruba G, Jannini EA. Prevalence of chronic prostatitis in men with premature ejaculation. Urology. 2001; 58: 198–202.

[10] Jeh SU, Yoon S, Choi JH, Do J, Seo DH, Lee SW, *et al*. Metabolic syndrome is an independent risk factor for acquired premature ejaculation. The World Journal of Men's Health. 2018; 17: e1573.

[11] Bronner G, Israeli-Korn S, Hassin-Baer S, Yahalom G. Acquired premature ejaculation in Parkinson's disease and possible mechanisms. International Journal of Impotence Research. 2018; 30: 153–157.

[12] Majzoub A, El-Hamd M, Saleh R. Premature ejaculation: an update on definition and pathophysiology. Asian Journal of Andrology. 2019; 21: 425.

[13] Canguven O, Al Malki AH. Vitamin D and Male Erectile Function: An Updated. The World Journal of Men's Health. 2021; 39: 31–37.

[14] Talib RA, Khalafalla K, Cangüven Ö. The role of vitamin D supplementation on erectile function. Turkish Journal of Urology. 2017; 43: 105–111.

[15] Haussler MR, Haussler CA, Whitfield GK, Hsieh J, Thompson PD, Barthel TK, *et al*. The nuclear vitamin D receptor controls the expression of genes encoding factors which feed the "Fountain of Youth" to mediate healthful aging. The Journal of Steroid Biochemistry and Molecular Biology. 2010; 121: 88–97.

[16] Deeb KK, Trump DL, Johnson CS. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. Nature Reviews. Cancer. 2007; 7: 684–700.

[17] Nagpal S, Na S, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. Endocrine Reviews. 2005; 26: 662–687.

[18] Serefoglu EC, Cimen HI, Ozdemir AT, Symonds T, Berktas M, Balbay MD. Turkish validation of the premature ejaculation diagnostic tool and its association with intravaginal ejaculatory latency time. International Journal of Impotence Research. 2009; 21: 139–144.

[19] Turunç T, Deveci S, Güvel S, Peşkircioğlu L. Uluslararası cinsel işlev indeksinin 5 soruluk versiyonunun (IIEF-5) Türkçe geçerlilik çalışmasının değerlendirilmesi. Türk Üroloji Dergisi/Turkish Journal of Urology. 2007; 33: 45–49.

[20] Canel-Çınarbaş D, Cui Y, Lauridsen E. Cross-Cultural Validation of the Beck Depression Inventory–II across U.S. and Turk-

ish Samples. Measurement and Evaluation in Counseling and Development. 2011; 44: 77–91.
[21] Pereira-Lourenço M, e Brito DV, Pereira BJ. Premature Ejaculation: From Physiology to Treatment. Journal of Family & Reproductive Health. 2019; 13: 120.
[22] Pludowski P, Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB, *et al*. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. Autoimmunity Reviews. 2013; 12: 976–989.
[23] 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. International Journal of Endocrinology. 2018; 2018: 1–8.
[24] Lerchbaum E, Pilz S, Trummer C, Schwetz V, Pachernegg O, Heijboer AC, *et al*. Vitamin D and Testosterone in Healthy Men: a Randomized Controlled Trial. The Journal of Clinical Endocrinology and Metabolism. 2017; 102: 4292–4302.
[25] Crafa A, Cannarella R, Condorelli RA, La Vignera S, Calogero AE. Is There an Association Between Vitamin D Deficiency and Erectile Dysfunction? A Systematic Review and Meta-Analysis. Nutrients. 2020; 12: 1411.
[26] Canat L, Degirmentepe RB, Atalay HA, Çakir SS, Alkan I, Çulha MG, *et al*. Low serum vitamin D is associated with an increased likelihood of acquired premature ejaculation. International Brazilian Journal of Urology. 2019; 45: 621–628.
[27] Geng C, Shaikh AS, Han W, Chen D, Guo Y, Jiang P. Vitamin D and depression: mechanisms, determination and application. Asia Pacific Journal of Clinical Nutrition. 2019; 28: 689.
[28] Milaneschi Y, Hoogendijk W, Lips P, Heijboer AC, Schoevers R, van Hemert AM, *et al*. Low vitamin D and depression-Study and meta-analysis, April 2013. Molecular Psychiatry. 2013.
[29] Xia Y, Li J, Shan G, Qian H, Wang T, Wu W, *et al*. Relationship between premature ejaculation and depression. Medicine. 2016; 95: e4620.
[30] D'Andrea S, Martorella A, Coccia F, Castellini C, Minaldi E, Totaro M, *et al*. Relationship of Vitamin D status with testosterone levels: a systematic review and meta-analysis. Endocrine. 2020; 72: 49–61.
[31] Chen C, Zhai H, Cheng J, Weng P, Chen Y, Li Q, *et al*. Causal Link between Vitamin D and Total Testosterone in Men: a Mendelian Randomization Analysis. The Journal of Clinical Endocrinology & Metabolism. 2019; 104: 3148–3156.
[32] Trummer C, Pilz S, Schwetz V, Obermayer-Pietsch B, Lerchbaum E. Vitamin D, PCOS and androgens in men: a systematic review. Endocrine Connections. 2018; 7: R95–R113.
[33] Pilz S, Frisch S, Koertke H, Kuhn J, Dreier J, Obermayer-Pietsch B, *et al*. Effect of vitamin D supplementation on testosterone levels in men. Hormone and Metabolic Research. 2011; 43: 223–225.
[34] Lerchbaum E, Trummer C, Theiler-Schwetz V, Kollmann M, Wölfler M, Heijboer AC, *et al*. Effects of vitamin D supplementation on androgens in men with low testosterone levels: a randomized controlled trial. European Journal of Nutrition. 2019; 58: 3135–3146.
[35] Rafiq R, van Schoor NM, Sohl E, Zillikens MC, Oosterwerff MM, Schaap L, *et al*. Associations of vitamin D status and vitamin D-related polymorphisms with sex hormones in older men. The Journal of Steroid Biochemistry and Molecular Biology. 2016; 164: 11–17.
[36] Wang N, Han B, Li Q, Chen Y, Chen Y, Xia F, *et al*. Vitamin D is associated with testosterone and hypogonadism in Chinese men: Results from a cross-sectional SPECT-China study. Reproductive Biology and Endocrinology. 2015; 13: 74.
[37] Motofei IG, Rowland DL. Neurophysiology of the ejaculatory process: developing perspectives. BJU International. 2005; 96: 1333–1338.
[38] Gillman N, Gillman M. Premature ejaculation: Aetiology and treatment strategies. Medical Sciences. 2019; 7: 102.
[39] Hull EM, Du J, Lorrain DS, Matuszewich L. Testosterone, preoptic dopamine, and copulation in male rats. Brain Research Bulletin. 1997; 44: 327–333.
[40] Culha MG, Tuken M, Gonultas S, Cakir OO, Serefoglu EC. Frequency of etiological factors among patients with acquired premature ejaculation: prospective, observational, single-center study. International Journal of Impotence Research. 2020; 32: 352–357.
[41] Hewison M, Freeman L, Hughes SV, Evans KN, Bland R, Eliopoulos AG, *et al*. Differential regulation of vitamin D receptor and its ligand in human monocyte-derived dendritic cells. Journal of Immunology. 2003; 170: 5382–5390.
[42] Almerighi C, Sinistro A, Cavazza A, Ciaprini C, Rocchi G, Bergamini A. 1α,25-Dihydroxyvitamin D3 inhibits CD40L-induced pro-inflammatory and immunomodulatory activity in Human Monocytes. Cytokine. 2009; 45: 190–197.
[43] D'Ambrosio D, Cippitelli M, Cocciolo MG, Mazzeo D, Di Lucia P, Lang R, *et al*. Inhibition of IL-12 production by 1, 25-dihydroxyvitamin D3. Involvement of NF-kappaB downregulation in transcriptional repression of the p40 gene. The Journal of Clinical Investigation. 1998; 101: 252–262.