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The role of vitamin D supplementation in lifelong premature ejaculation

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***Abstract*---**Background: Premature ejaculation (PE) is defined as persistent or recurrent ejaculation with minimal sexual stimulation before, upon, or shortly after penetration and before the person wishes it. Aim and objectives: The aim of this study was to measure the serum level of 25-hydroxyvitamin D (25 (OH) D) in lifelong premature ejaculation patients and evaluate the role of 25-hydroxyvitamin D (25 (OH) D) supplementation in these patients with low or in sufficient level of 25-hydroxyvitamin D (25 (OH) D). Subjects and methods: A total of 80 consecutive men who presented with lifelong PE. Results: The mean PEDT showed a statistically significant decrease after treatment. The mean IELT in the included cases before treatment with vitamin D is 31.14 ± 20.511 and the mean IELT in the included cases after treatment is 48.86 ± 26.432. The mean IELT showed a statistically significant increase after treatment. Conclusion: This study demonstrates that lower vitamin D levels are associated with the acquired PE. The result of our study showed that the role of serum vitamin D levels should be investigated in the etiology of acquired PE. Perhaps supplementation of vitamin D in men with acquired PE will ameliorate the sexual health of these patients.

***Keywords*---**premature ejaculation, sexual stimulation, treatment, vitamin D.

Introduction

Premature ejaculation (PE) is defined as persistent or recurrent ejaculation with minimal sexual stimulation before, upon, or shortly after penetration and before the person wishes it and always associated with marked distress and interpersonal difficulty.[1] it is the most common sexual dysfunction that may affect 20%-30% of men. [2] Godpodinoff defined two types as lifelong and acquired PE. [3] and two more types of PE have been suggested as naturel variable PE and premature-like ejaculatory dysfunction by Waldinger and Schweitzer. [4] International Society for Sexual Medicine (ISSM) Committee defined PE as a male sexual dysfunction characterized by 'ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration from the first sexual experiences (lifelong PE), or a clinically significant and bothersome reduction in latency time, often to about three minutes or less (acquired PE), and the inability to delay ejaculation on all or nearly all vaginal penetration and negative personal consequences, such as distress ,bother, frustration and\or the avoidance of sexual intimacy. [5]

The biological link between PE and vitamin D deficiency exhibits different mechanisms. Firstly, several animal studies reported that vitamin D deficiency resulted in anxiety-related behaviors. [6] Anxiety has also been reported as a cause of PE by multiple researches. [7] Second, activated vitamin D stimulates the production of nitric oxide (NO) and NO synthases. [8] NO and serotonergic system are important at the level of the sympathetic nervous system which can affect the ejaculation. [9] Third, when vitamin D increases above its normal range, it binds to the androgen receptor, displacing their native ligands. Therefore, several studies have determined that serum androgen levels and vitamin D levels are associated in men. [10] In recent study showed that vitamin D has significant association with LPE and correlates significantly with intravaginal ejaculatory latency time (IELT) and Premature Ejaculation Diagnostic Tool (PEDT). [11] The aim of this study was to measure the serum level of 25-hydroxyvitamin D (25 (OH) D) in lifelong premature ejaculation patients and evaluate the role of 25-hydroxyvitamin D (25 (OH) D) supplementation in these patients with low or in sufficient level of 25-hydroxyvitamin D (25 (OH) D).

Patients and Methods

A total of 80 consecutive men who presented with lifelong PE

Ethical consideration

An informed consent was taken from all participants before enrollment in the study after approval of the Medical Research Ethics Committee at Al-Azhar University.

Inclusion criteria

We included healthy potent Egyptian males with lifelong PE aged 20–60 years old with regular sexual activity.

Exclusion criteria

Patients with acquired PE, history of psychiatric or neurological disorders, pelvic/perineal trauma, liver or renal failures, chronic prostatitis, anatomical abnormalities, and chronic diseases which may affect the sexual functions, the participants who were taking selective serotonin reuptake inhibitors, alpha-blockers, phosphodiesterase inhibitors, anticholinergics, antipsychotics, and vitamin D supplementation and patients with erectile dysfunction. The entire patient assessed by international index of erectile function to exclude ED

Methods

All members of the study was subjected to the following

- History and examination: Smoking history, alcohol consumption, partner age, frequency of intercourse, associated comorbidities,level of education, working status, coital habits, duration of PE, morning stiffness, medical and sexual history and the self-reported IELT recorded by face-to-face interview. Aphysical examination performed in order to evaluate secondary sex characteristics, testes, penis, prostate, gynaecomastia and muscle mass.
- Procedure: All patients assessed by Premature Ejaculation Diagnostic Tool (PEDT), a five item questionnaire assessing control, frequency, minimal stimulation, distress and interpersonal difficulty. A score of 8or less excludes PE. Serum vitamin D measured in all cases by fluro illuminance immunoassay (VIDAS). Vitamin D deficiency diagnosed if the serum level of 25-hydroxyvitamin D [25(OH)D] was < 20 ng/ml, and vitamin D insufficiency as a 25(OH)D of 21–29 ng/ml. We had two groups: Patients with vitamin D deficiency or insufficiency level, Patients with normal level. Vitamin D supplements recommendations.

Cases with vitamin D deficiency recommend intake of 6000 IU daily or 50.000 IU/week. Cases with vitamin D insufficiency recommend intake of 800 IU daily(maintenance dose): Cases with vitamin D deficiency or insufficiency received oral Vitamin D tablets once daily for one month Then assessed again by PEDT. After 2 weeks of stopping treatment with Vitamin D(washing out period); patients received oral placebo tablets once daily for two weeks then assessed by PEDT. All participants instructed to record intravaginal ejaculatory latency time (IELT) using stopwatch which was held by the partner. The results of this study tabulated and analyzed by appropriate statistical methods.

Statistical analysis and data interpretation

Data were fed to the computer and analyzed using IBM SPSS software package version 26. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) and mean, standard deviation. Student t-test was used to compare 2 independent groups • Paired samples t-test was used to compare 2 independent groups Non-Parametric tests: Mann-Whitney U test was used to compare 2 independent groups. Wilcoxon signed rank test: was used to compare 2 dependent groups.

Results

Table 1
Demographic data of the subjects in the study

Items	Study cases n= 35	
	Number	Percent (%)
Age (Years)		
Mean ± SD	30.2 ± 2.89	
Median (Range)	30 (25- 35)	
BMI (Kg/m^2)		
Mean ± SD	24.36 ± 2.47	
Median (Range)	23.46 (21.51- 29.07)	
Residence		
Average weight	24	68.6
Overweight	11	31.4
Residence		
Urban	18	51.4
Rural	17	48.6

Categorical data expressed as Number (%)
Continuous data are expressed as mean ± SD median (Min-Max)

The mean age of the cases with low serum vitamin D levels is 30.2 ± 2.89 years and the median age was 30 years with range between 25 and 35 years. The mean BMI is 24.36 ± 2.47 Kg/m2 and the median BMI is 23.46 Kg/m2 with range between 21.51 and 29.07 Kg/m2. There were 24 cases (68.6%) with average body weight and 11 cases (31.4%) overweight. Table (1)

Table 2
Risk factors of the cases in the study

Items	Study cases n= 35	
	Number	Percent (%)
Smoking		
No	17	48.6
Yes	18	51.4
Dyslipidemia		
No	29	82.9
Yes	6	17.1

Categorical data expressed as Number (%)

Regarding the risk factors, there are 18 cases (51.4%) smokers and there are 6 cases (17.1%) with dyslipidemia. Table (2)

Table 3
Vitamin D status of the subjects in the study

Items	Study cases n= 35	
	Number	Percent (%)
Vitamin D level (ng/ml)		
Mean ± SD	20.94 ± 6.36	
Median (Range)	23 (9- 29)	
Vitamin D status		
Deficiency	13	37.1
Insufficiency	22	62.9

Categorical data expressed as Number (%)
Continuous data are expressed as mean ± SD median (Min-Max)

The mean serum vitamin D level is 20.94 ± 6.36 ng/ml and the median level is 23 ng/ml with range between 9 and 29 ng/ml. There are 13 cases (37.1%) with vitamin D deficiency and 22 cases (62.9%) with vitamin D insufficiency. **Table (**3**)**

Table 4
Analysis of PEDT and ILET before treatment and after vitamin D treatment

Items	Before treatment n= 35	After treatment n= 35	Test of significance
PEDT	15.14 ± 2.290	12.63 ± 2.390	t = 5.735 P< 0.001*
ILET	31.14 ± 20.511	48.86 ± 26.432	t = -5.208 P< 0.001*

P: probability.
Continuous data expressed as mean ± SD
t: Paired samples t-test
*: significant value < 0.05

The mean PEDT in the included cases before treatment with vitamin D is 15.14 ± 2.290 and the mean PEDT in the included cases after treatment is 12.63 ± 2.390. The mean PEDT showed a statistically significant decrease after treatment. The mean IELT in the included cases before treatment with vitamin D is 31.14 ± 20.511 and the mean IELT in the included cases after treatment is 48.86 ± 26.432. The mean IELT showed a statistically significant increase after treatment. Table (4)

Table 5
Analysis of PEDT and ILET after the washout and after placebo

Items	After washout n= 35	After placebo n= 35	Test of significance
PEDT	15.26 ± 2.33	14.59 ± 3.16	t = 1.728 P = 0.314
ILET	31.54 ± 19.94	33.18 ± 18.68	t = - 2.010 P= 0.136

P: probability.
Continuous data expressed as mean ± SD
t: Paired samples t-test
*: significant value < 0.05

The mean PEDT in the included cases after the washout was is 15.26 ± 2.33 and the mean PEDT in the included cases after placebo is 14.59 ± 3.16. The mean PEDT showed non-statistically significant decrease after treatment with placebo. The mean IELT in the included cases after washout 31.54 ± 19.94 and the mean IELT in the included cases after placebo is 33.18 ± 18.68. The mean IELT showed a non-statistically significant increase after treatment with placebo. Table (5)

Table 6
Analysis of the degree of improvement after treatment with vitamin D and placebo

Items	After vitamin D n=35	After placebo n=35	Test of significance
Improvement			
Improved	14 (40%)	5 (14.3%)	□2= 4.983 P< 0.001*
Not improved	21 (60%)	30 (85.7%)	

P: probability.
Categorical data expressed as Number (%)
□2: Chi-square test
*: significant value < 0.05

After treatment with vitamin D, 14 cases (40%) improved while after treatment with placebo, 5 cases (14.3%) improved. The degree of improvement after treatment with vitamin D was statistically significantly higher as compared with the treatment with placebo. Table (6)

Table 7
Analysis of the degree of improvement after treatment with vitamin D and placebo according to the vitamin D status

Items	Vitamin D deficiency n= 13	Vitamin D insufficiency n= 22	Test of significance
Improvement after vitamin D	6 (46.2%)	8 (36.4%)	□2= 3.542 P= 0.009*
Improvement after placebo	2 (15.4%)	3 (13.6%)	FET= 1.645 P= 0.138

P: probability.
Categorical data expressed as Number (%)
□2: Chi-square test
FET: Fisher's exact test
*: significant value < 0.05

After treatment with vitamin D, in the vitamin D deficiency group, 6 cases (46.2%) improved while in the vitamin D insufficiency, 8 cases (36.4%) improved after vitamin D treatment. The degree of improvement was statistically significantly higher in the vitamin D deficiency group. After treatment with placebo, in the vitamin D deficiency group, 2 cases (15.4%) improved while in the vitamin D insufficiency, 3 cases (13.6%) improved after placebo treatment. There was no statistically significant difference in the degree of improvement between the cases with vitamin D deficiency and vitamin D insufficiency after the placebo treatment. Table (7)

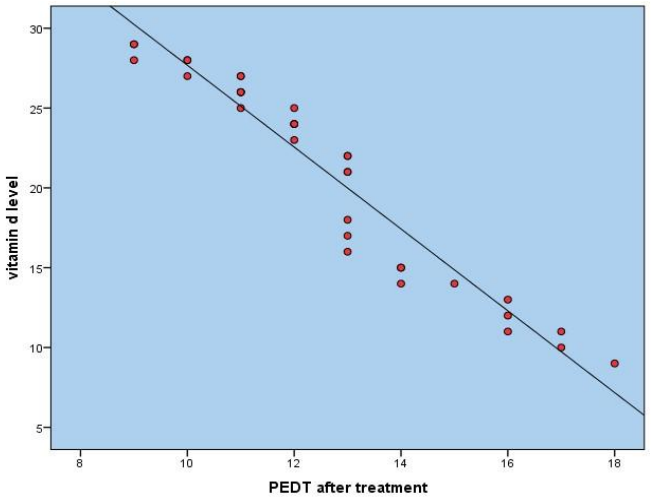

Figure 1. Correlation between vitamin D level with PEDT after treatment

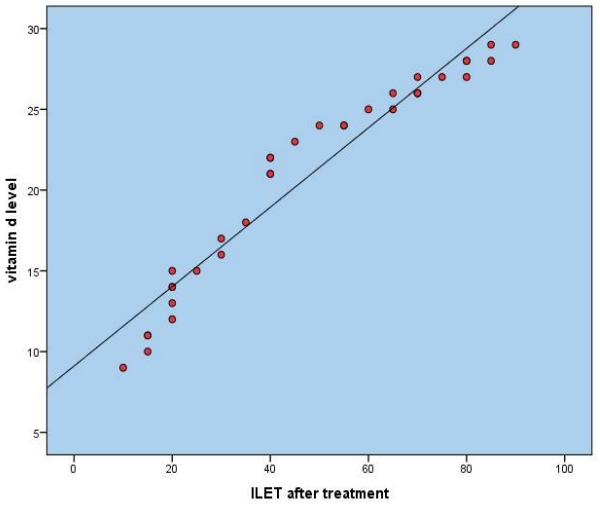

Figure 2. Correlation between vitamin D level with ILET after treatment

Discussion

Premature ejaculation is defined as short ejaculatory latency and lack of control upon ejaculation and described as one of the most common forms of sexual dysfunction in men. [12] Corona et al. [13] demonstrated that delayed ejaculation is associated with lower testosterone level whereas a higher level of testosterone characterizes PE. The data from the European Male Aging Study reported that vitamin D is positively associated with total testosterone (Lee et al., 2012). Wehr et al. [10] has also showed that androgen levels were associated with vitamin D levels in a large study population. The current study was conducted to measure the serum level of 25-hydroxyvitamin D (25 (OH) D) in lifelong premature ejaculation patients and evaluate the role of 25-hydroxyvitamin D (25 (OH) D) supplementation in these patients with low or in sufficient level of 25-hydroxyvitamin D (25 (OH) D).

To the best of our knowledge, this is the first study to assess the effect of vitamin D supplementation versus placebo in treatment of premature ejaculation. The current study initially included 80 married sexually active male patients who presented with lifelong PE. After assessment of serum vitamin D levels, there are 45 cases with normal levels and 35 cases wit low serum vitamin D levels (43.75%). Among these cases, there are 13 cases (37.1%) with vitamin D deficiency and 22 cases (62.9%) with vitamin D insufficiency. In the current study, after treatment with vitamin D, 14 cases (40%) improved while after treatment with placebo, 5 cases (14.3%) improved. The degree of improvement after treatment with vitamin D was statistically significantly higher as compared with the treatment with placebo. After treatment with vitamin D, in the vitamin D deficiency group, 6 cases (46.2%) improved while in the vitamin D insufficiency, 8 cases (36.4%) improved after vitamin D treatment. The degree of improvement was statistically significantly higher in the vitamin D deficiency group.

After treatment with placebo, in the vitamin D deficiency group, 2 cases (15.4%) improved while in the vitamin D insufficiency, 3 cases (13.6%) improved after

placebo treatment. There was no statistically significant difference in the degree of improvement between the cases with vitamin D deficiency and vitamin D insufficiency after the placebo treatment. Also, in the current study, there was weak statistically non-significant negative correlation between vitamin D and PEDT before and after treatment as the mean PEDT in the included cases before treatment with vitamin D was 15.14 ± 2.290 and the mean PEDT in the included cases after treatment decreased to 12.63 ± 2.390. There was weak statistically non-significant positive correlation between vitamin D and ILET before and after treatment as the mean IELT before treatment with vitamin D was 31.14 ± 20.511 and after treatment it increased to 48.86 ± 26.432.

This may be explained by studies have also reported that inflammation may be another underlying cause of PE.[14] 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. [15] 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 [16], 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.

Similar results were obtained by Din et al., [17] who conducted a study to compare serum level of vitamin D [25(OH)D] in patients with life-long premature ejaculation (LPE) versus healthy controls. They included 40 patients with PE and among them; there were 16 cases (40%) with low serum vitamin D level. Eleven (27. 5%) participants had vitamin D insufficiency while 5 (12.5%) participants had vitamin D deficiency. Din et al. investigated vitamin D deficiency in a sample of 40 men with LPE and 40 healthy controls. That study found a correlation between vitamin D levels and IELT ($r2=0.349$; $p<0.001$) and PEDT ($r2=0.425$; $p<0.001$) (Din et al., 2018). In the retrospective cross-sectional study by Horsanali et al., [18] that included 94 patients with a complaint of acquired premature ejaculation, the Spearman correlation test revealed a positive observed correlation between serum vit D levels and IELT (p: 0.010; r: 0.189). Additionally, a negative correlation was observed between serum vit D levels and the PEP score (p: 0.010; r: –0.189).

Our study has some limitations that must be considered. Its main limitation is the small number of participants, which means that larger studies are required to confirm our results. PEDT and lIET scoring systems, like other self-report inventories, are subjective in nature. The present study shows some strengths of the treatment. Firstly, the use of vitamin D for the treatment of PE was well accepted by all the patients (high compliance to the protocol). Moreover, the very low prevalence of adverse events contributed to the high compliance with the protocol. The variations in the results of the different studies could be explained due to variations of the sample size, geographic variations, and diet habits in the included cases

Conclusion

This study demonstrates that lower vitamin D levels are associated with the acquired PE. The result of our study showed that the role of serum vitamin D levels should be investigated in the etiology of acquired PE. Perhaps supplementation of vitamin D in men with acquired PE will ameliorate the sexual health of these patients.

Conflict of interest: no conflicts of interest.

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