

# Effect of Serum Vitamin B12 Levels on Premature Ejaculation

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## ABSTRACT

**Objective:** To assess the impact of vitamin B12 levels in the failure of the dapoxetine used in premature ejaculation (PE) treatment.

**Study Design:** Experimental study.

**Place and Duration of the Study:** Andrology Clinic, between May and December 2020.

**Methodology:** Patients with premature ejaculation complaints completed the Premature Ejaculation Diagnostic Tool (PEDT) questionnaire. Patients were also asked to fill in the Premature Ejaculation Profile (PEP) surveys. Intravaginal ejaculation latency time (IELT) were recorded based on the estimates of patients. Serum vitamin B12 levels were evaluated based on blood samples. All patients were advised to use dapoxetine 30 mg, 1-3 hours prior to intercourse. After four weeks, patients were asked to complete the PEP questionnaire again. IELT times were recorded.

**Results:** A total of 62 patients were included in the study. A total of 39 patients (62.90%) were satisfied with the treatment of the dapoxetine. In comparison to patients who benefited from dapoxetine treatment and those who did not, vitamin B12 levels of patients who did not benefit from dapoxetine were found to be significantly lower ( $p=0.005$ ).

**Conclusion:** Vitamin B12 deficiency can reduce the effectiveness of dapoxetine treatment in patients with PE. It is important to evaluate serum vitamin B12 levels for the evaluation of patients with PE.

**Key Words:** Premature ejaculation, Dapoxetine, Vitamin B12, Serotonin, Treatment.

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## INTRODUCTION

Premature ejaculation (PE) is the most widespread sexual dysfunction, observed at a rate of about 20-30% in men.<sup>1,2</sup> Recently defined by the International Association of Sexual Medicine, PE is "a male sexual dysfunction characterised by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations," starting from the first sexual intercourse (lifelong PE). The decrease in this duration from normal to less than 3 minutes is referred to as acquired PE.<sup>3</sup>

Dapoxetine is a selective serotonin reuptake inhibitor approved by the EMA for the treatment of PE.<sup>4</sup> This on-demand agent has been proven to improve the Quality of Life (QoL) for couples based on the assessment of randomised controlled, phase 3 clinical studies (N=6081).<sup>5</sup>

Moreover, the discontinuation rate of dapoxetine therapy is as high as unlabelled SSRIs, with confirmation of the effectiveness in improving intravaginal ejaculation latency (IELT) and safety.<sup>6</sup>

Nitric oxide (NO) and serotonergic neurotransmitters (5-hydroxytryptamine [5-HT]) play a crucial role in the central nervous system and are regulated by genetic factors.<sup>7</sup> It was found that 5-HT had an effect on sexual functions and hyposensitivity of the glans penis.<sup>8</sup> The central decrease in 5-HT levels plays an effective role in PE pathogenesis. Vitamin B12 is an effective factor in NO, homocysteine, and 5-HT metabolism.<sup>9</sup> Vitamin B12 affects 5-HT metabolism and has been shown to play an active role in lots of methylation reactions in the brain.<sup>10</sup> Kadihasanoglu *et al.* showed that low vitamin B12 levels could correlate with PE.<sup>11</sup>

Although vitamin B12 levels have been assessed for their relationship with PE, there is no study on the effects of vitamin B12 levels on the treatment of dapoxetine. This study aimed to evaluate the effect of vitamin B12 levels in the failure of the dapoxetine used in PE treatment.

## METHODOLOGY

This study was conducted on patients who were referred to the Urology Clinic, from May to December 2020 with a PE complaint. The study was approved by local ethical board. The study has

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been designed in accordance with the Helsinki Declaration, with written consents obtained from the participants.

The study included PE patients who have been regularly sexually active over the past 6 months, with no sexual dysfunction reported in their partners. Patients who used dapoxetine 30 mg at least twice a week and continued for 4 weeks were included. Patients with erectile dysfunction (international erectile function index - EF (IIEF-EF) <21) who had any organic causes for PE, such as diabetes mellitus, or hypertension were excluded. Additionally, patients with psychiatric disorders and those using any chronic drug within the last 3 months were also excluded from the study.

As part of the initial evaluation of patients, their detailed histories were obtained. Patients completed the Premature Ejaculation Diagnostic Tool (PEDT) questionnaire to confirm the PE diagnosis.<sup>12</sup> Patients with a PEDT score above 10 were included. Patients were also asked to fill in the Premature Ejaculation Profile (PEP) surveys. IELT times were recorded based on the estimates of patients. Previous studies have shown that there is no significant difference between estimated IELT and stopwatch IELT.<sup>13</sup> Therefore, in this study, the authors preferred to measure the estimated IELT of the patients. Serum vitamin B12 levels were evaluated based on blood samples taken from the median cubital vein between 9.00 a.m. and 11.00 a.m. All patients were advised to use dapoxetine 30 mg, 1-3 hours prior to intercourse. Patients were advised to engage in sexual intercourse for at least two days a week for 4 weeks. After four weeks, patients were asked to complete the PEP questionnaire again. IELT times were recorded. Side effects were recorded during the follow-up. Treatment satisfaction was assessed with Clinical Global Impression of Change (CGIC). Those with a CGIC score of "0" were considered unsuccessful (n=23), while those with a CGIC score of "1" and above were considered successful (n=39).

PEP is a 4-point survey designed to assess the key elements of PE (e.g., control, pain, inter-partner difficulty and sexual relationship satisfaction; each evaluated on five-point response scales). Turkish validity and reliability study was conducted by Serefoglu *et al.* in 2011.<sup>2</sup> The International Index of Erectile Function-Erectile Function (IIEF-EF) was used to evaluate the ED status. The IIEF-EF questionnaire consists of 15 questions, covering questions 1-5 and 15 of the IIEF.<sup>14</sup> The total score from the survey is 0-30. An IIEF-EF score of less than 21 is considered to be ED.

Vitamin B12 levels were measured in ng ml<sup>-1</sup> unit using Beckman Coulter DXI800 immunological tests (chemiluminescence).

SPSS 25.0 (IBM, NY, USA) was used for statistical analysis. Categorical variables were expressed as counts and percentages and continuous variables were expressed as mean and SD. The distribution of variables was evaluated with the Kolmogorov-Smirnov test. The independent sample t-test (for comparing dapoxetine responders and non-responders) and Pearson's

correlation test (Vit B12 levels and PEDT and IELT) were used. Significant p-value was determined as <0.05.

## RESULTS

A total of 62 patients were included in the study. The mean age of patients is 40.39±10.89 years, and the mean BMI is 27.44±10.89 kg/m<sup>2</sup>. Mean IELT was 32.42±50.65 seconds, PEDT score was 14.40±4.08, PEP score was 0.71±0.78, and IIEF-EF score was 22.55±5.39. In total, 5 patients experienced side effects related to dapoxetine use (3 had nausea and, 2 two dizziness) (Table I).

The patients' mean Vitamin B12 level is 346.64±165.63 ng/ml. Patients' mean IELT increased to 108.87±69.63 seconds as a result of a four-week treatment of dapoxetine (p <0.001). The PEP index score increased to 1.91±0.98 (p=0.003). A total of 39 patients (62.90%) were satisfied with the treatment of the dapoxetine and 23 reported no effects.

In comparison to patients who benefited from dapoxetine treatment and those who did not, it was found that the vitamin B12 levels of patients who did not benefit from dapoxetine were lower (p=0.005, Table II).

An examination of the relationship between vitamin B12 levels, the PEDT scores, and the IELT changes of patients showed no significant relationship with the initial PEDT scores and IELT (Table III).

**Table I: Demographic characteristics of patients.**

Demographic characteristics (n=62)	Mean±SD	Min-Max
Age	50.39±10.89	28-65
BMI	27.44±3.75	18.93-37.89
PEDT	14.40±4.08	10-22
IELT (sec)	84.44±52.13	0-120
IIEF-EF	20.55±5.39	21-30
Vitamin B12 (ng/ml)	346.64±165.63	101.10-1002

BMI: Body Mass Index, PEDT: Premature Ejaculation Diagnostic Tool, IELT: Intravaginal Ejaculation Latency Time, IIEF-EF: International Index of Erectile Function-Erectile Function.

**Table II: Comparison of patients with and without response to treatment.**

	CGIC = 0 (N = 23)	CGIC >1 (N=39)	p
Age	53.04±10.82	51.82±10.73	0.142
BMI	26.83±2.69	27.79±4.25	0.336
PEP Index	1.57±1.21	2.51±1.17	0.003
IELT	56.95±17.11	139.49±70.86	<0.001
Vit B12	270.88±91.73	391.32±183.42	0.005
IIEF-EF	19.48±5.88	21.18±5.05	0.233

Independent sample t-test was used. BMI: Body Mass Index, PEP: Premature Ejaculation Profile, IELT: Intravaginal Ejaculation Latency Time, IIEF-EF: International Index of Erectile Function-Erectile Function. Independent sample t-test was used.

**Table III: Correlation of vitamin B12 levels between PEDT and IELT.**

		PEDT	IELT
Vit B12	p	0.632	0.117
	r	-0.062	0.201

Pearson correlation test was used. PEDT: Premature Ejaculation Diagnostic Tool, IELT: Intravaginal Ejaculation Latency Time; Pearson correlation test was used.

## DISCUSSION

As a result of the prospective observational study, in patients with PE complaints, the treatment effectiveness of 30 mg dapoxetine decreases with the decrease of Vitamin B12 levels. In addition, a significant relationship is observed between IELT dura-

tions and the symptom scores with respect to Vitamin B12 levels.

The three separate stages of ejaculation are emission, expulsion, and orgasm. The tight connection of the nervous system plays an important role during the ejaculation of the man.<sup>15</sup> Serotonin (5-hydroxytryptamine [5-HT]), which is found in the many areas of the brain, plays an important role in various neuraxial levels.<sup>16</sup> In the literature, 5-HT1A, 5-HT1B, and 5-HT2C receptor subtypes on ejaculation have been identified to mediate the modulating activity of 5-HT. While activation of post-synaptic 5-HT2C or 5-HT1B receptors from 5-HT receptor subtypes prolongs ejaculation latency, pre-synaptic 5-HT1A activation, which inhibits 5-HT, shortens ejaculation time.<sup>17</sup>

In the control of ejaculation, some active neurons are formed, resulting from the complex interaction of central serotonergic and dopaminergic neurons. The development mechanism of PE remains unclear. SSRIs are widely used in PE treatment as a result of the psychopharmacological studies related to the pathways that control ejaculation.<sup>8</sup> SSRIs may prevent neuronal reuptake of serotonin and thus the strengthening of its activity. The discharge time is extended as the serotonergic neurotransmission is associated with the pathways that control ejaculation. Although the studies have been published with a 12-week follow-up period, the effect of dapoxetine reaches the desired level at the end of the 4<sup>th</sup> week.<sup>18</sup> The short duration of the study is stated in the limitation section. Again, in the same study, both dapoxetine 30 mg and dapoxetine 60 mg were found to be effective.

Vitamin B12 is a water-soluble vitamin involved in many metabolic processes.<sup>19</sup> Vitamin B12 acts as a cofactor in methionine synthesis from homocysteine. However, vitamin B12 plays an important role in the formation of S-adenosylmethionine. This pathway is involved in the synthesis of an intermediate for the production of serotonin, other monoamine neurotransmitters, and catecholamines.<sup>10</sup>

Vitamin B12 provides the methyl group for the conversion. With this transformation, a donor is formed for many methylation reactions in the brain. Vitamin B12 supplementation has been reported to produce an antidepressant-like effect due to interaction with noradrenergic receptors (alpha1 and alpha2) and serotonergic receptors (5-HT1A and 5-HT2A/2C). With this effect, it is thought that the effect caused by the use of SSRIs will be more. Despite the limited number of patients in the study, this study will shed light on future studies about Dapoxetine+vitamin B12 combination therapy.

Vitamin B12 is a cofactor involved in the synthesis of serotonin, which plays an important role in the inhibition of ejaculation. Focusing on its roles in the synthesis of methionine, the existence of a potential relationship between B-complex vitamins and depression. The basis of this connection may be the fact that methionine synthesis uses methyl folate and requires Vitamin B12 as a co-factor.<sup>20</sup>

As part of this study, the effectiveness of dapoxetine treatment, which is a short-acting SSRI, decreases with decreasing levels of vitamin B12. This raises the hypothesis that SSRI-group medication does not act as the pathways in the serotonin synthesis stage are affected.

There are certain limitations to this study. Firstly, it has been performed with a small sample size and short follow-up. Secondly, the non-use of the stopwatch method for IELT measurement. Thirdly, the folate level was not measured.

## CONCLUSION

Vitamin B12 deficiency can reduce the effectiveness of dapoxetine treatment in patients with PE. It is important to evaluate serum vitamin B12 levels for the evaluation of patients with PE and keep them in mind for the treatment plan. Larger studies are required to determine the effect of vitamin B12 on the pathophysiology of PE.

### ETHICAL APPROVAL:

Ethical approval of this study was obtained from the Ethics Committee of Izmir Atatürk University.

### PATIENTS' CONSENT:

Informed consents were taken from all patients included in the study.

### COMPETING INTEREST:

The authors declared no competing interest.

### AUTHORS' CONTRIBUTION:

AES: Project development, data collection, and manuscript writing.

MGC: Project development, manuscript writing, and supervision. All authors approved the final version of the manuscript to be published.

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