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ORIGINAL RESEARCH

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The impact of vitamin B12 treatment on ejaculatory functions in men: symptomatic relief and improved outcomes

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Abstract

Background: To investigate whether intramuscular vitamin B12 treatment has an effect on ejaculaory functions in male patients with vitamin B12 deficiency. **Methods**: Male patients diagnosed with vitamin B12 deficiency in the internal medicine outpatient clinic of our hospital between October 2024 and March 2025 and started to receive intramuscular vitamin B12 treatment were included in study. The scores obtained from the self-estimated intravaginal ejaculation latency time (IELT), premature ejaculation diagnostic tool (PEDT), and premature ejaculation profile (PEP) questionnaires, reflecting the ejaculatory status of these patients before treatment, were recorded. After 3 months of treatment, these scores were re-recorded via phone calls, and scores recorded before and after treatment were compared. **Results**: The study included 54 patients. The mean age of the patients was 43.46 $\pm$ 13.3 years, the mean pretreatment IELT was 2.4 $\pm$ 1.4 min, and the mean pre-treatment PEDT score was 11.5 $\pm$ 4.6. In both the whole patient group and the premature ejaculation (PE) group, a statistically significant difference was observed in the items of perceived control over ejaculation, satisfaction with sexual intercourse, and interpersonal difficulty related to ejaculation from the PEP questionnaire forms completed after treatment, with no significant change found in the item of personal distress related to ejaculation. In terms of IELT and PEDT, no differences were observed in the whole patient group after treatment, whereas a statistically significant improvement was observed in the PE group. **Conclusions**: Intramuscular vitamin B12 may delay ejaculation times and improve sexual satisfaction levels in male patients based on the responses given by the patients to the questions in the survey forms. **Clinical Trial Registration**: The study was retrospectively registered with ClinicalTrials.gov as: NCT07036497.

Keywords

Premature ejaculation; Intravaginal ejaculatory latancy time; Premature ejaculation diagnostic tool; Vitamin B12; Premature ejaculation profile

El impacto del tratamiento con vitamina B12 en las funciones eyaculatorias del hombre: alivio sintomático y mejora de los resultados

Resumen

Antecedentes: Investigar si el tratamiento intramuscular con B12 tiene un efecto sobre la eyaculación en pacientes varones con deficiencia de B12. **Métodos**: Se incluyeron en el estudio pacientes varones a los que se diagnosticó deficiencia de vitamina B12 en la consulta externa de medicina interna entre octubre de 2024 y marzo de 2025 y que iniciaron tratamiento intramuscular con B12. Se registraron las puntuaciones obtenidas en los cuestionarios de tiempo de latencia de la eyaculación intravaginal autoestimado (IELT), herramienta de diagnóstico de la eyaculación precoz (PEDT) y perfil de eyaculación precoz (PEP), que reflejaban el estado eyaculatorio de estos pacientes antes del tratamiento. Tras 3 meses de tratamiento, se volvieron a registrar estas puntuaciones mediante llamada telefónica. Se compararon las puntuaciones registradas antes y después del tratamiento. **Resultados**: En el estudio participaron 54 pacientes. La media de edad de los pacientes era de 43.46 $\pm$ 13.3 años, la media de IELT antes del tratamiento era de 2.4 $\pm$ 1.4 min y la media de puntuación PEDT antes del tratamiento era de 11.5 $\pm$ 4.6. En el grupo de pacientes completo y en el grupo de pacientes antes del tratamiento se registraron las puntuaciones antes y después del tratamiento. Tanto en el grupo de pacientes completos como en el grupo de eyaculación precoz (EP), se observó una diferencia estadísticamente significativa en los ítems de control percibido sobre la eyaculación, satisfacción con las relaciones sexuales y dificultad interpersonal relacionada con la eyaculación del formulario del cuestionario PEP después del tratamiento, no se encontraron cambios significativos en el ítem de angustia personal relacionada con la eyaculación. En términos de IELT y PEDT, no se observaron diferencias en todo el grupo de pacientes después del tratamiento, mientras que se observó una mejora estadísticamente significativa en el grupo de PE. **Conclusiones**: La vitamina B12 intramuscular puede mejorar los tiempos de eyaculación y los niveles de satisfacción en los cuestionarios de los pacientes varones. **Registro del Ensayo Clínico**: El estudio se registró de forma retrospectiva en ClinicalTrials.gov como: NCT07036497.

Palabras Clave

Eyaculación precoz; Tiempo de latencia eyaculatoria intravaginal; Herramienta de diagnóstico de la eyaculación precoz; Vitamina B12; Perfil de eyaculación precoz

1. Introduction

Premature ejaculation (PE), which is one of the most common ejaculatory disorders, is defined as orgasm and ejaculation with minimal sexual stimulation before, during, or shortly after penetration and before the person's desire, causing significant distress or interpersonal difficulties [1, 2]. Its prevalence rate is 20–30% annually and rates may vary between countries [1, 3]. In a national database study conducted on 2593 volunteers in Turkey in 2011, PE was detected in 512 (20%) patients [4]. PE not only affects the patient's sexuality, but also significantly and adversely impairs the satisfaction level and sexual life of patient's partner [5, 6].

Proposed mechanisms involved in the pathophysiology of PE include anxiety, penile hypersensitivity, and 5-hydroxy tryptamine receptor dysfunction [7, 8]. Treatment of PE encompasses a variety of approaches, including pharmacological interventions, psychological therapies, and behavioral techniques. Selective serotonin reuptake inhibitors are commonly prescribed drugs that can further delay the onset of ejaculation by increasing serotonin levels [9, 10]. Topical anesthetic creams can also be used to reduce penile sensitivity. Psychological therapies, such as cognitive behavioral therapy, aim to address the underlying psychological factors that contribute to PE.

Recent studies have emphasized the contribution of nutritional deficiencies to PE. Vitamin B12 (cyanocobalamin) is involved in serotonin metabolism as a cofactor in the methylation of homocysteine to methionine. Vitamin B12 is also used as the most important methyl donor in the production of serotonin from tryptophan [11]. Studies have found a correlation between low levels of vitamin B12 and PE, suggesting that vitamin B12 may play a role in ejaculatory control [9, 12].

In our study, we aimed to investigate the effects of vitamin B12 treatment on ejaculatory control in men. Specifically, we hypothesized that intramuscular vitamin B12 delays premature ejaculation in male patients and leads to favourable improvements in their sexual life as revealed by responses given in premature ejaculation assessment forms.

2. Materials and methods

The study was conducted prospectively by obtaining informed consent forms from the patients. Ethics committee approval, dated 18 September 2024 and decision number 2024-15/6, was obtained from the University of Health Sciences Bursa City Hospital Ethics Committee for the study (clinical trial registration number: NCT07036497).

Male patients aged 18–70 years who were admitted to the internal medicine outpatient clinic of the University of Health Sciences Bursa City Hospital between October 2024 and March 2025 with nonspecific gastrointestinal complaints or to investigate the etiology of anemia in patients and who were started on intramuscular treatment with vitamin B12 due to vitamin B12 deficiency were included in the study. Detailed genital and physical examinations were performed. The body weights and heights of the male patients were also recorded and body mass indices (BMIs) was calculated for each patient.

Vitamin B12 deficient male patients aged 18–70 years with normal erectile function engaging in monogamous and hetero-

sexual intercourse for six months without any history of antidepressant treatment, alcohol use, smoking, underlying anatomical or endocrine disorder (malignancy, diabetes, thyroid disease) that may cause PE, urogenital and/or pelvic surgery, treatment with psychotropic drugs, hormone therapy, and use of ejaculation delaying condoms and topical agents were included in the study.

Patients under 18 years of age, those with missing data, and cases that could not be reached by telephone for the completion of follow-up questionnaire forms after vitamin B12 treatment were excluded from the study.

These patients were asked to complete the self-estimated intravaginal ejaculation latency time (IELT), premature ejaculation diagnostic tool (PEDT) (<9: no PE, 9–10: borderline PE, >10: PE) [13], premature ejaculation profile (PEP) questionnaire [14], international index of erectile function questionnaire questionnaire forms (IIEF-5) [15] and Beck Depression Inventory (BDI) (0–9: no depression, 10–16: mild to moderate depression, 17–29: moderate to severe depression and 30–63: severe depression), rated as indicated regardless of their PE status. The PEP measure consists of four single items (for questions 1 and 2: 0: very poor, 1: poor, 2: fair, 3: good, 4: very good, and for questions 3 and 4: 0: not at all, 1: a little, 2: moderately, 4: quite a lot, 5: extremely) rated as indicated and the mean of the four measures (PEP index score) was calculated for subjects and their female partners with and without premature ejaculation complaints [16]. Patients with normal erectile function who scored ≥22 points on the IIEF-5 according to the study criteria and showed no depressive symptoms according to the 21-question BDI (<9) scores were included in the study.

The presence of PE was assessed according to the European Association of Urology (EAU) guideline with PEDT, a five-item questionnaire assessing control, frequency, minimal stimulation, distress and interpersonal difficulty [7]. A score of 9 or less excludes PE. To improve diagnostic specificity, we combined PEDT with the self-estimated IELT being defined as the time interval between the start of vaginal penetration and the start of intravaginal ejaculation; an IELT of <2 min confirms the PE diagnosis according to EAU guideline [7].

Vitamin B12 treatment was started according to the indication of the internal medicine specialist, regardless of the PE status of the patients. Serum vitamin B12 levels below 300 ng/L were considered vitamin B12 deficiency. Patients were prescribed intramuscular vitamin B12 at a dose of 1000 mcg administered initially once a week for 4 weeks, then once a month [17]. At the 3rd month after treatment, patients were called by phone, and IELT, PEDT, and PEP scores were re-evaluated.

Total scores of PEDT, PEP forms, and self-estimated IELT were calculated before and after treatment. Pre- and post-treatment scores were compared. In addition, patients were divided into those with IELT less than 2 min (PE group) and PEDT <9, PEDT: 9 and 10, PEDT >10. These subgroups were analysed separately.

Statistical analyses were performed using SPSS software version 15.0 (IBM Corp., Armonk, NY, USA). Demographics and baseline characteristics are reported as frequencies (n) and percentages (%) for categorical variables, and as the mean ± SD for continuous variables. Kolmogorov-Smirnov test was used to test normality distribution. G-Power version 3.1.9.7 (Universitat KIEL, Kiel, SH, Germany) was used to determine the minimum number of patients to be included in the study. Differences between the groups were tested for significance by independent samples *t*-test, and paired *t*-test, as appropriate. Correlation analyses between baseline vitamin B12 levels and IELT, PEDT, and PEP scores were performed using Spearman's rank correlation test. The differences and correlations were considered significant at $p < 0.05$.

3. Results

Based on the results of the power analysis (two-way correlation, type-1 error rate (α) = 0.05, power of the study (1β) = 0.80, and effect size = 0.52) (n: 50), an adequate number of patients was included in this study. According to the results, 54 patients were included in the study. The mean age of the patients was 43.46 ± 13.3 years and the mean BMI was 28.3 ± 6.2 kg/m^2. The mean IIEF-5 score was 23.8 ± 2.3; the mean BDI score was 3.7 ± 2.4; the mean IELT was 2.4 ± 1.4 min; and the mean PEDT score was 11.5 ± 4.6 (Table 1). Twenty-two patients (PE group) had IELT less than 2 min. The patients were also grouped according to their PEDT scores as follows: PEDT: <9 (n = 16); PEDT: 9–10 (n = 6), and PEDT: >10 (n = 32). Biochemical analyses of peripheral blood samples of the patients were also performed before treatment (Table 1). The distributions of baseline vitamin B12 levels and IELT and PEDT scores are shown in **Supplementary material**.

TABLE 1. Baseline data of study participants.

Parameters	Mean ± SD	Min–max
Age (yr)	43.46 ± 13.3	21.0–69.0
BMI (kg/m^2)	28.3 ± 6.2	18.0–38.9
IELT (min)	2.4 ± 1.4	0.3–5.0
PEDT score	11.5 ± 4.6	3.0–20.0
IIEF-5	23.8 ± 2.3	22.0–25.0
BDI	3.7 ± 2.4	0–8.0
Vitamin B12 (ng/L)	174.4 ± 23.7	100.0–234.0
Folat (ng/mL)	10.4–4.9	2.5–20.0

BMI: Body mass index; IELT: Intravaginal ejaculatory latency time; PEDT: Premature ejaculation diagnostic tool; IIEF-5: International index of erectile function; BDI: Beck depression inventory; Min–max: Minimum–maximum.

The final diagnosis of 54 patients was vitamin B12 deficiency due to inadequate intake in 25 (46.2%), pernicious anemia in 15 (27.7%), vitamin B12 deficiency due to drug use in 10 (18.5%), and inflammatory bowel disease in 4 (7.4%) patients. Patients presented with fatigue (n = 15: 27.7%), headache (n = 10: 18.5%), weight loss (n = 8: 14.8%), impaired balance (n = 7: 12.9%), muscle weakness (n = 7: 12.9%), and with other symptoms (n = 7: 12.9%).

We performed correlation analyses to evaluate the relationship between baseline vitamin B12 levels and pre-treatment

IELT, PEDT, and PEP scores. No statistically significant correlations were found (all $p > 0.05$). A weak negative correlation was observed between vitamin B12 and PEDT ($r = -0.255$, $p = 0.063$), which did not reach statistical significance. The correlations are illustrated in Fig. 1.

3.1 PEP questionnaire

In both the whole patient group and the PE group, a statistically significant difference was observed in the items of perceived control over ejaculation, satisfaction with sexual intercourse, and interpersonal difficulty related to ejaculation based on the responses given to the questions in the PEP survey form applied after treatment. No significant change was found in the item of personal distress related to ejaculation (Table 2).

3.2 IELT and PEDT scores

There was no statistically significant difference in both IELT and PEDT scores in the whole patient group after treatment. When subgroup analysis was performed in patients with IELT <2 min, PEDT scores decreased significantly after treatment compared to pre-treatment ($p < 0.001$), while IELT increased significantly after treatment compared to pre-treatment ($p < 0.001$) (Table 3).

3.3 Results according to PEDT subgroups

In the subgroup of patients with pre-treatment PEDT scores less than 9, no changes were observed post-treatment in terms of IELT and PEP scores. However, in patients with pre-treatment PEDT scores less than 9 and between 9 and 10, PEDT scores significantly increased following treatment ($p < 0.001$ and $p = 0.001$). Similarly, in patients with pre-treatment PEDT scores greater than 10, a statistically significant improvement was seen in all post-treatment parameters (Table 4).

4. Discussion

To the best of our knowledge, this is the first study in the literature investigating the effects of vitamin B12 treatment on ejaculatory functions. Ejaculation is a complex event that occurs with the combined effects of emission and expulsion reflexes. Serotoninergic and dopaminergic neurotransmissions play an important role in this complex pathway in which both sympathetic and parasympathetic systems are involved. Serotonin (5-hydroxytryptamine) plays a role as an ejaculation inhibitor and shows its effects through 5-HT1a, 5-HT1b, and 5-HT2c receptors [10]. Therefore, selective serotonin reuptake inhibitors (SSRIs) are used in medical treatment. Our study is important in terms of showing the positive effects of vitamin B12 treatment, which plays a role as a methyl donor in the production of serotonin from tryptophan, on ejaculatory functions.

Vitamin B12 deficiency can be caused by malnutrition, malabsorptive disorders, and some comorbidities [17]. Vitamin B12 is mainly found in animal products and, therefore, those whose diets are poor in animal proteins are at risk of vitamin B12 deficiency. Malabsorption syndromes may be caused by conditions affecting the gastrointestinal tract, such as chronic antral gastritis, pernicious anaemia or post-gastrectomy dumping syndrome [12]. Long-term use of proton pump inhibitors and some other drugs may also interfere with vitamin B12 absorption. Symptoms of vitamin B12 deficiency can be very diverse and affect various systems of the body. Some common symptoms include weakness and fatigue, shortness of breath, and pale skin. Neurological symptoms such as numbness or tingling in the hands and feet, difficulty in maintaining postural balance, muscle weakness, memory problems, and mood disorders such as depression or anxiety are also common [17].

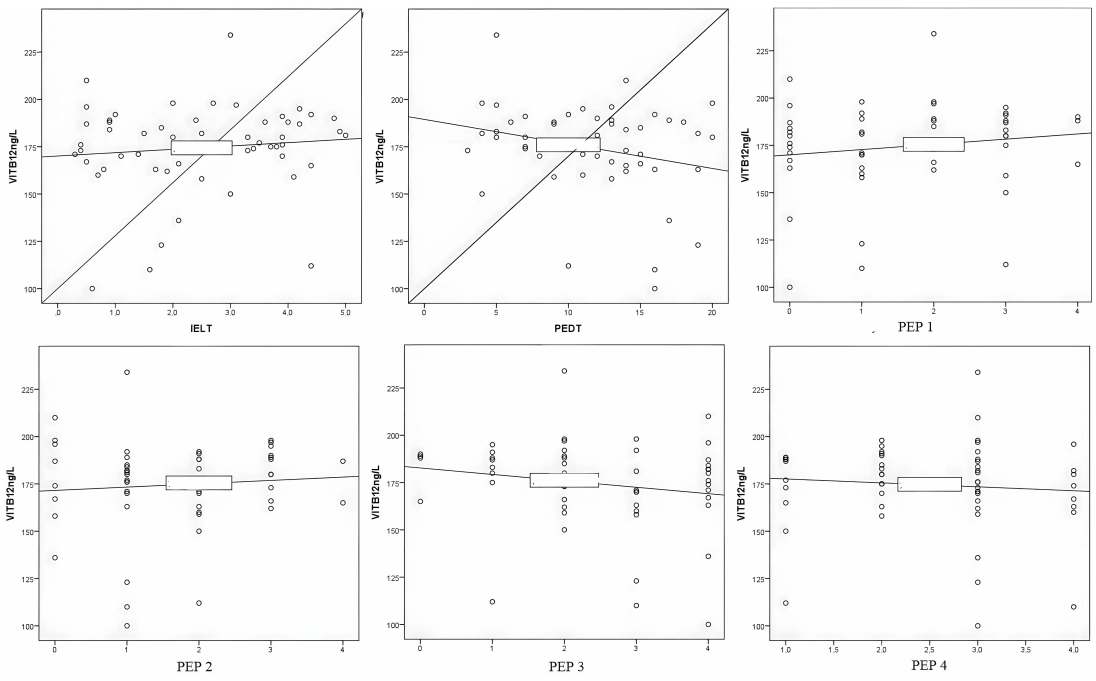

FIGURE 1. Correlations between Vitamin B12 levels and key parameters. IELT: intravaginal ejaculation latency time; PEDT: premature ejaculation diagnostic tool; PEP: premature ejaculation profile; VIT: vitamin.

TABLE 2. Pre- and post-treatment PEP responses.

	Pre-treatment (whole group) (n: 54)	Post-treatment (whole group) (n: 54)	*p* value	Pre-treatment (PE group) (n: 22)	Post-treatment (PE group) (n: 22)	*p* value
Perceived control over ejaculation (PEP 1) (Mean ± SD)	1.6 ± 1.2	1.8 ± 1.0	0.025	0.7 ± 0.7	1.4 ± 0.5	0.002
Satisfaction with sexual intercourse (PEP 2) (Mean ± SD)	1.6 ± 1.0	2.0 ± 0.8	0.005	1.2 ± 0.8	2.0 ± 0.8	0.002
Personal distress related to ejaculation (PEP 3) (Mean ± SD)	2.4 ± 1.2	2.2 ± 1.0	0.116	3.1 ± 1.0	2.5 ± 0.6	0.056
Interpersonal difficulty related to ejaculation (PEP 4) (Mean ± SD)	2.5 ± 0.9	2.1 ± 0.6	0.006	2.9 ± 0.9	2.2 ± 0.6	0.006

PEP: Premature ejaculation profile; SD: Standard deviation; PE: premature ejaculation.

TABLE 3. Pre- and post-treatment IELT and PEDT scores.

	Pre-treatment (whole group) (n: 54)	Post-treatment (whole group) (n: 54)	*p* value	Pre-treatment (PE group) (n: 22)	Post-treatment (PE group) (n: 22)	*p* value
IELT (Mean ± SD)	2.4 ± 1.4	2.5 ± 1.3	0.296	0.9 ± 0.5	1.1 ± 0.5	<0.001
PEDT (Mean ± SD)	11.5 ± 4.6	10.7 ± 5.2	0.472	14.8 ± 2.4	6.2 ± 2.6	<0.001

IELT: Intravaginal ejaculatory latency time; PEDT: Premature ejaculation diagnostic tool; SD: Standard deviation.

TABLE 4. Pre- and post-treatment values according to PEDT groups.

Parameters (Mean ± SD)	Pre-treatment PEDT <9 n: 16	Post-treatment PEDT <9 n: 16	*p* value	Pre-treatment PEDT 9–10 n: 6	Post-treatment PEDT 9–10 n: 6	*p* value	Pre-treatment PEDT >10 n: 32	Post-treatment PEDT >10 n: 32	*p* value
IELT	3.4 ± 0.5	3.4 ± 0.5	0.466	4.1 ± 0.2	3.8 ± 0.9	0.311	1.6 ± 1.3	1.8 ± 1.2	0.002
PEDT	5.8 ± 1.6	13.3 ± 3.6	<0.001	9.3 ± 0.5	16.0 ± 2.0	0.001	14.8 ± 2.7	8.3 ± 4.9	<0.001
PEP 1	1.9 ± 1.1	1.8 ± 1.1	0.164	3.0 ± 0.6	2.6 ± 1.3	0.363	1.1 ± 1.1	1.7 ± 0.9	0.001
PEP 2	1.7 ± 0.8	2.0 ± 0.8	0.261	2.3 ± 1.0	2.3 ± 0.5	1.000	1.4 ± 1.1	2.0 ± 0.9	0.009
PEP 3	2.1 ± 1.0	2.2 ± 1.1	0.718	1.3 ± 0.8	1.5 ± 1.2	0.741	2.7 ± 1.2	2.3 ± 0.9	0.032
PEP 4	2.4 ± 0.9	2.3 ± 0.6	0.580	2.0 ± 1.0	2.1 ± 0.4	0.695	2.6 ± 0.9	2.0 ± 0.7	0.001

PEDT: Premature ejaculation diagnostic tool; PEP: Premature ejaculation profile; PEP 1: PEP 1. Question (Perceived control over ejaculation); PEP 2: PEP 2. Question (Satisfaction with sexual intercourse); PEP 3: PEP 3. Question (Personal distress related to ejaculation); PEP 4: PEP 4. Question (Interpersonal difficulty related to ejaculation); SD: Standard deviation; IELT: intravaginal ejaculation latency time.

Vitamin B12 plays an indirect but crucial role in serotonin metabolism. It acts as a cofactor in the formation of S-adenosylmethionine (SAM), a compound essential for synthesizing neurotransmitters like serotonin. SAM donates a methyl group which is required for the production of serotonin. Maintaining adequate SAM levels is dependent on sufficient vitamin B12 which in turn support proper serotonin synthesis. Therefore, vitamin B12 deficiency can disrupt serotonin synthesis. When vitamin B12 is lacking, the conversion of homocysteine to methionine is impaired, indirectly affecting serotonin production. Numerous studies investigating the effect of vitamin B12 deficiency on neurological and psychiatric diseases have been published [18]. However, the relation of vitamin B12 deficiency with PE has been investigated in a limited number of studies. In their study on patients with chronic gastritis, Gökçen *et al*. [12] divided the patients into 3 groups; as follows: Group 1: chronic gastritis and vitamin B12 deficiency group; Group 2: chronic gastritis patients with normal vitamin B12 levels, and Group 3: healthy volunteers. According to the results, the mean IELT and vitamin B12 levels were found to be statistically significantly lower in Group 1 compared to the other groups. Similarly, the mean PEDT scores in Group 1 were significantly higher than the other groups. Kadihasanoglu *et al*. [9] investigated 56 patients with erectile dysfunction (ED) and 53 controls and found significantly lower Vitamin B12 levels in the PE group compared to the control group. Canat *et al*. [19] investigated the relationship between acquired PE and blood vitamin B12 and folic acid levels. They found that while vitamin B12 levels were lower in the acquired PE group compared to the control group, the difference was not statistically significant.

The neurological and psychological consequences of vitamin B12 deficiency characterized with symptoms ranging from cognitive impairment and depression to peripheral neuropathy and psychosis are well documented [20, 21]. These manifestations underscore the importance of vitamin B12 in maintaining optimal brain function and mental well-being [11]. The impact of vitamin B12 on serotonin levels may explain, in part, the observed association between vitamin B12 deficiency and mood disorders. Studies have indicated that individuals with depression often have lower serum vitamin B12 levels compared to healthy controls, suggesting a potential role for vitamin B12 supplementation in the management of depressive symptoms [22]. However, it's important to acknowledge that B12 deficiency can arise from various factors, including inadequate dietary intake, malabsorption issues, postgastrectomy states, bacterial overgrowth, and long-term medication use [22].

In our study, a significant decrease in PEDT scores was observed in the entire study group, while the increase in IELT did not reach statistical significance which may be attributed to several factors, including the relatively small sample size, variability in individual responses to vitamin B12 treatment, or the influence of other underlying factors contributing to PE. However, subgroup analysis of patients with baseline IELT values below 2 min revealed a statistically significant increase in IELT following vitamin B12 treatment which suggests that vitamin B12 treatment may be particularly beneficial for individuals experiencing more severe PE.

The Premature Ejaculation Diagnostic Tool is a validated questionnaire specifically designed for the diagnosis and evaluation of PE [13, 23]. It provides a standardized and easily administered method to assess the severity of PE symptoms, making it a valuable tool for both clinical practice and research. In our study, the statistically significant decrease in PEDT scores following vitamin B12 supplementation suggests a potential improvement in perceived ejaculatory control among participants. Accordingly, Gökcen *et al*. [12] also reported a strong negative correlation between vitamin B12 levels and PEDT scores in patients with chronic gastritis. Kadıhasanoglu *et al*. [9] also found that PE patients had significantly higher PEDT scores compared to healthy controls. These consistent findings across multiple studies emphasize the utility of PEDT as an indicator of PE severity and responsiveness to interventions such as vitamin B12 supplementation.

While the PEDT provides a comprehensive assessment of PE symptoms, the PEP offers a more nuanced assessment of the individual's experience of PE. By examining different aspects of the patient's perception of ejaculatory control, sexual satisfaction, and distress, the PEP can provide valuable information about the subjective impact of PE on their overall well-being. In our study, significant improvements in responses to questions 1, 2, and 4 of the PEP questionnaire were observed after treatment, suggesting that vitamin B12 treatment may have a positive impact on various aspects of the patient's experience of PE. Further research is needed to fully elucidate the specific aspects of PEP that are most sensitive to changes in vitamin B12 levels and to explore the potential of PEP as a tool for monitoring treatment outcomes in individuals with PE and vitamin B12 deficiency.

In addition to serotonin metabolism, other micronutrients have also been implicated in ejaculatory function. Deficiencies in magnesium and zinc have been reported as risk factors for PE [24, 25]. These findings suggest that multiple trace elements may contribute to ejaculatory physiology. Of note, vitamin B12 contains cobalt as its central metal ion. Reduced cobalt levels may therefore mirror reduced vitamin B12 status rather than acting independently [26]. Although cobalt supplementation has been shown to increase testosterone levels in animal models [27], human studies suggest little direct association between cobalt itself and sexual function [28]. Thus, the improvements observed in our study are more plausibly attributed to vitamin B12 supplementation rather than cobalt *per se*.

In our study, the primary objective was to evaluate the effect of the intervention. Therefore, the longitudinal comparisons of pre- and post-treatment scores for PEP 1, PEP 2, PEP 3, and PEP 4 are the most relevant findings for interpreting the intervention's efficacy. While our baseline characteristics (cross-sectional data) are essential for describing the study population and ensuring reproducibility, they do not directly speak to the change induced by the intervention. Therefore, we emphasize that the primary interpretation of our study's success rests on the statistically significant improvements observed in the longitudinal "before and after" treatment comparisons for relevant parameters.

One of the limitations of our study is that it was performed with a small number of patients. Second, our study relied

on self-reported rather than stopwatch measured ejaculatory latency; but it should be noted that self-reported and stopwatch measured ejaculatory latencies have been shown to be interchangeable [29, 30]. Third, functional biomarkers such as methylmalonic acid and homocysteine, widely accepted diagnostic criteria vitamin B12 deficiency, were not routinely measured which limited the potential to provide a more comprehensive diagnosis, especially in cases where serum vitamin B12 levels were borderline or where functional deficiency needed confirmation. Future studies incorporating these biomarkers would allow for a more detailed assessment of vitamin B12 deficiency. As another limitation, post-treatment serum vitamin B12 levels were not monitored; whereas the focus of our study was to evaluate the clinical effects of vitamin B12 supplementation on ejaculatory functions. The specific causes of vitamin B12 deficiency (such as malnutrition or gastrointestinal conditions) in the participants were not extensively investigated or recorded. Therefore, our study may not fully reflect the diversity of etiological factors leading to vitamin B12 deficiency. Lastly, the improvement of general physical symptoms associated with vitamin B12 deficiency, such as fatigue, malaise, non-specific gastrointestinal complaints, or anemia, was not systematically evaluated, and their potential confounding effects on ejaculatory functions were not examined using multivariate analyses. However, given our study's exclusion criteria and the known biological effects of vitamin B12 on serotonin metabolism, we believe that the observed improvements can largely be attributed to vitamin B12 supplementation. Future research could address these limitations to delve deeper into the relationship between vitamin B12 deficiency and sexual health.

5. Conclusions

In conclusion, our study demonstrates that vitamin B12 treatment leads to a statistically significant improvement in perceived ejaculatory control, as evidenced by decreased PEDT scores, particularly in the subgroup of men with baseline IELT under 2 minutes. Increases in IELT were observed and were only statistically significant in the aforementioned subgroup. These findings suggest a potential benefit of vitamin B12 treatment for men experiencing PE, especially those with more severe symptoms.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

OE and AHT—designed the research study. NK—performed the research. OS, UA, SG—provided help and advice on data extraction. SA, AE—analyzed the data. VC, EO and SO—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study follows the principles of the Declaration of Helsinki; and it was approved by the Ethics Committee of the University of Health Sciences, Bursa City Hospital, Bursa (Meeting/Decision No. 2024-15/6). All participants provided informed consent for participation.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://files.intandro.com/files/article/1980925966656913408/attachment/Supplementary%20material.docx.

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