Review Article
Male sexual health and dysfunction

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Premature Ejaculation and Endocrine Disorders: A Literature Review

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Premature ejaculation (PE) is the most common male sexual dysfunction, with 30% of men experiencing PE worldwide. According to the generally accepted classification, there are two types of PE: lifetime PE and acquired PE. Various biological and psychological causes are known to be involved in the etiology of PE. However, due to the incomplete definition and etiopathogenesis of PE, there is no effective treatment. Although clinical and animal studies indicate that hormones play a role in controlling the ejaculation process, the precise endocrine mechanisms are unclear. In addition, little is known about the role of endocrine disorders in PE etiology. However, there is evidence that diabetes mellitus (DM), obesity, metabolic syndrome (MetS), thyroid gland disorders, pituitary gland disorders, and vitamin D deficiency affect the prevalence of PE. Moreover, it has been reported that the prevalence of PE decreases with treatment of these endocrine disorders. In this review, the relationship between PE and DM, MetS, obesity, vitamin D deficiency, and thyroid and pituitary gland disorders is summarized.

Keywords: Diabetes mellitus; Hyperthyroidism; Metabolic syndrome; Premature ejaculation; Vitamin D

INTRODUCTION

Premature ejaculation (PE) is a phenomenon that occurs when a man's ejaculation occurs earlier than he or his partner intended during sexual activity. PE affects about 30% of men worldwide, but some reviews have stated that this number could be as high as 75% [1]. For this reason, PE is accepted as the most common sexual disorder in men [2]. In some cases, PE is not a cause for concern. However, it can cause significant distress and can have negative consequences between partners [3].

Because PE is subjective, it is difficult to conclusively define. However, many authors and several scientific societies have provided different definitions of PE, as they classify PE according to different situations, such as pathogenesis and time of onset [4]. While Masters and Johnson defined PE as a condition in which "the man cannot adequately control ejaculation to satisfy his female partner for more than 50% of sexual intercourse, provided that he is not anorgasmic," Strassberg et al [5] defines PE as "the state of the man ejaculating in 2 minutes or less in at least 50% of his attempts to have sexual intercourse because he has little control over ejaculation". The American Urological Association describes PE as "ejaculation that occurs before or after sexual intercourse, that occurs earlier than desired,

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and causes distress to one or both partners" [6]. The American Psychiatric Association defines PE as "recurrent or persistent ejaculation before or shortly after sexual intercourse and with minimal sexual stimulation despite the person's unwillingness" [7]. The World Health Organization (WHO) defines PE as "the occurrence of ejaculation before or shortly after the onset of sexual intercourse, or the inability to delay ejaculation (DE) enough to enjoy lovemaking, which is manifested by ejaculation that occurs in the absence of sufficient erection during sexual intercourse: [7]. However, these definitions have been criticized for being conceptual and ambiguous, rather than evidence-based [8]. The International Society for Sexual Medicine (ISSM) has made recommendations to develop a precise scientific definition of PE. According to these recommendations, lifetime PE (LPE) or primary PE was defined as "ejaculation that always or almost always occurs before vaginal penetration or within about 1 minute of the first sexual experience." Acquired PE (APE) or secondary PE has been defined as "a clinically significant and disturbing reduction in ejaculation time, and an inability to DE, usually in about 3 minutes or less" [9].

Schapiro [10] was the first to describe primary PE (PPE or lifelong PE), which affects men without erectile or desire difficulties and who have never achieved ejaculation control, and secondary PE (SPE or APE), which affects older men and is associated with erection difficulties. Cooper [11] defined three types of PE: PPE (Type 1), which occurs in adolescence and is characterized by normal erection and anxiety neurosis; acute onset PE (Type 2), which is associated with generalized anxiety and often with erectile failure; and insidious onset PE (Type 3), which is associated with low libido and erectile insufficiency. Anxiety was less prominent and often reactive to the development of Type 3 PE. Godpodinoff [12] described two main types of PE: (1) PPE that is present from the first sexual experience, and (2) SPE that develops over the years, after an initial satisfactory sexual performance. Godpodinoff stated that PPE is relatively homogeneous, while SPE can be divided into two subtypes, as those developing with organic and psychopathological elements. When PPE is classified in this way, appropriate treatment plans can be formulated. The simplest way to classify PE is to establish whether the symptoms occurred when the man first became sexually active (PPE) or after normal ejaculation control (SPE). Waldinger and Schweitzer [13] suggested that there is a third subtype of PE, called subjective PE, in which there are men who complain of PE but have normal ejaculation time.

ETIOLOGY OF PREMATURE EJACULATION

Although PE is considered the most common sexual dysfunction (SD) in men, its etiology remains unclear. However, psychogenic and biogenic factors have traditionally been held responsible for the etiology of PE [14]. Psychogenic factors include depression, anxiety, stress, guilt, unrealistic expectations about sexual performance, history of sexual repression, lack of trust/poor body image in general, sexual abuse, relationship problems, and early experience [1]. While PE was previously considered to be only a psychological problem, subsequent studies showed that PE may be affected by various somatic, genetic and/or neurobiological disorders [15]. Some genetic studies have shown that polymorphisms in serotonin transporters are associated with PE [16,17]. In addition, PE is associated with various factors such as chronic prostatitis, erectile dysfunction (ED), metabolic syndrome (MetS), and thyroid dysfunction [18-22]. Because PE has been shown to be affected by so many factors, it is difficult to fully understand and classify PE.

While it is known that the male reproductive system is largely hormonally regulated, the involvement of the endocrine system in the intravaginal ejaculatory delay time (IELT) and ejaculation process is not yet fully understood [23]. Studies have shown that pituitary (oxytocin and prolactin [PRL]), adrenal, thyroidal, and gonadal hormones can control ejaculation at various levels, and that ejaculation problems are experienced in endocrine disorders [7,24-26]. Therefore, PE may be a result of endocrine diseases. Based on a comprehensive review of the literature, this review will discuss the relationship between endocrine diseases and PE.

TESTOSTERONE AND PREMATURE EJACULATION

Hormones play a central role in ejaculation control, and therefore, any pathology in hormone levels may directly or indirectly affect ejaculation control. Testosterone is one of the most important hormones involved in ejaculation control. However, there are conflicting

data regarding the relationship between testosterone levels and PE. In one of the first studies on this subject, Cohen [27] reported that PE patients had low serum testosterone levels. More recently, Tahtali [28] reported that men with SPE have lower testosterone levels than healthy controls. In contrast, Corona et al [29] reported that PE patients between the ages of 25 and 39 had high total testosterone (TT) and free testosterone (FT) levels. Further, that study reported that men with LPE between the ages of 25 and 39 have higher FT levels than men with APE. In a later publication, Corona et al [30] reported that higher testosterone levels were associated with PE, and lower testosterone levels were associated with DE. Similarly, Mohseni et al [31] found that serum FT and follicle stimulating hormone (FSH) levels were higher in PE patients compared to controls, but there were no significant differences in serum TT and luteinizing hormone (LH) levels between PE patients and controls.

Canat et al [32] reported no significant difference in serum TT, FT, and FSH levels between PE patients and controls. In accordance with that study, Abu El-Hamd and Farah [33] reported no difference in serum TT, FT, FSH, LH, and PRL levels between PE patients and controls. Another study also reported no difference between PE patients and controls with regards to TT levels [34]. Based on a comprehensive review of the aforementioned studies, it is clear that there are conflicting results regarding the relationship between testosterone and PE. Therefore, we believe that more comprehensive studies are needed to better elucidate the relationship between testosterone and PE.

DIABETES MELLITUS

As a result of the short and long-term effects caused by hyperglycemia, many medical, psychological, and SD complications can develop in patients with diabetes mellitus (DM) [35]. These complications can be prevented or delayed with effective treatment and blood sugar control. SD in men is one of the lesser-known complications of DM. SD in diabetic men may present as ED, ejaculation problems, and libido disorders. All three of these types of SD can significantly affect the quality of life of diabetic patients [36]. It has been reported that the prevalence of SD is gradually increasing in diabetic patients [37]. However, the prevalence of PE has not been fully determined, due to the lack of a clear evidence-based definition of PE [7]. Studies investigating the relationship between PE and DM have been conducted separately on type 1 DM (T1DM), type 2 DM (T2DM), and preDM (Table 1).

In the study by El Sakka [38] including 676 male T2DM patients, the prevalence of PE was 32.4% in patients younger than 50 years old and 67.6% in patients over 50 years old. That study reported that patients who had diabetes for more than 10 years were 2.7 times more likely to have PE than men who had diabetes less than 5 years ($p<0.05$). In addition, the authors observed that diabetic patients with glycated hemoglobin (HbA1c) >7% were 10 times more likely to have PE than patients with HbA1c <7%. As a result of their study, El-Sakka concluded that long diabetes duration, the presence of cardiovascular disease, poor glycemic control, and the presence of ED are associated with an increased risk of PE in diabetic men [38]. In another study including 300 diabetic men, Owiredu et al [36] reported a prevalence of PE of 56.6%. In addition, testosterone levels were negatively correlated with fasting blood glucose (FBS), HbA1c, short IELT, weight, and waist circumference (WC). Majzoub et al [39] reported that of 488 patients with T2DM, 115 (23.6%) had ED and 294 (60.2%) had PE. The authors of that study observed that patients with T2DM had a significantly higher prevalence of PE and ED than the control group ($p<0.001$). In addition, the authors found that all PE types were higher in patients with T2DM, and that mean IELT was significantly lower in patients with T2DM (3.6±2.7) than controls (4.3±2.8) ($p=0.014$) [39]. In a study conducted to evaluate the prevalence of PE in Italy, 569 of 2,658 men with PE had LPE, 1,855 had APE, and 234 were not identified. In that same study, it was determined that diabetes treatment led to a decrease in PE prevalence [40]. Differences in PE rates in patients with T2DM may be due to variations in the studied populations or to the way PE was defined in each study [39]. The link between PE and T2DM is still unclear. However, psychogenic factors and organic causes, especially diabetic autonomic neuropathy, play a role in the proportionality of the incidence of PE with the duration and severity of DM [41].

To our knowledge, only one study has investigated the relationship between T1DM and PE. Results of that study showed that the prevalence of PE in young patients with T1DM was not different from that of age-matched controls [42]. However, it has been reported

Table 1. Studies investigating the relationship between T1DM, T2DM, PreDM, and PE in men

Study	Year	Definition of PE	Disorder	PE prevalence	Results
El-Sakka [38]	2003	The persistent or recurrent inability to voluntarily delay ejaculation either upon or shortly after penetration or with minimal sexual stimulation.	T2DM	50 years old ↓ 32.4% 50 years old ↑ 67.6%	Long diabetes duration, poor glycemic control, and the presence of ED increased risk of PE
Corona et al [45]	2004	PE was defined as ejaculation within 1 minute of vaginal intromission (as reported by the patient)	PreDM, T2DM	28.4%	There was no relationship between PE and FBS.
Basile Fasolo et al [40]	2005	DMS-IV	T2DM	21.2%	Decreased PE in those treated for T2DM
Owiredu et al [36]	2011	GRISS	T2DM	56.6%	Testosterone levels were negatively correlated with FBS, HbA1C, short IELT, weight, and WC.
Bellastella et al [42]	2015	PEDT	T1DM	24%	PE prevalence in T1DM same as control. PEDT score was strongly associated with LBGI
Majzoub et al [39]	2016	AIPE	T2DM	60.2%	LPE and APE were higher, and mean IELT was lower, in patients with T2DM compared to controls.
Salama et al [21]	2017	PEDT	PreDM	35.2%	Higher PEDT, higher FBS
Bolat et al [46]	2017	PEDT	PreDM	-	PEDT score higher, IELT score lower in PE

PE: premature ejaculation, T2DM: type 2 diabetes mellitus, ED: erectile dysfunction, PreDM: prediabetes mellitus, FBS: fasting blood sugar, DMS-IV: Diagnostic and Statistical Manual of Mental Disorders-IV, GRISS: Golombok Rust Inventory of Sexual Satisfaction, HbA1c: glycated hemoglobin, IELT: intravaginal ejaculatory delay time, WC: waist circumference, T1DM: type 1 diabetes mellitus, PEDT: premature ejaculation diagnostic tool, LBGI: low blood glucose indexes, AIPE: Arabic Index for Premature Ejaculation, LPE: lifetime pemature ejaculation, APE: acquired premature ejaculation, -: not available.

that the premature ejaculation diagnostic tool (PEDT) score is strongly associated with low blood glucose indexes (LBGI). This suggests that glycemic control, especially hypoglycemia, plays a role in the ejaculatory process. The relationship between hypoglycemia and PE may be related to inhibition of serotoninergic neuronal activity or activation of the adrenergic system [43,44].

After some studies showed a possible biological link between glycemic metabolism and ejaculation control, more studies were conducted with the goal of evaluating the prevalence of PE among men with preDM. Corona et al [45] defined PE as ejaculation within 1 minute after vaginal penetration, and evaluated some biochemical parameters associated with PE. However, despite detecting lower FBS in patients with PE compared to controls, they did not determine any relationship between the two. Conversely, in a recent case-control study involving 100 men with APE, the mean FBS of APE patients was higher than that of controls, but FBS did not correlate with PEDT score in multivariate analysis [46]. Further, the relationship between PE and MetS was investigated in a cohort of 300 men with various urological disorders [21]. Among the healthy controls without MetS in that study, there was a significantly higher proportion of men with PE (33.3%) with an FBS level greater than 110 mg/dL than men without PE (5.5%).

Although the causal relationship between PE and DM has been investigated, there remains a lack of understanding regarding the etiology of PE, and there is no defined relationship due to the multi-systemic and polyetiological nature of DM. Possible causal relationships between PE and DM include neurological, neurotransmitter-induced, and psychological dysfunctions [47]. Diabetic neuropathy is a well-known microvascular complication of DM that can affect neural control of ejaculation through sensory, focal/multifocal, and autonomic neuropathies [48]. It has been reported that there is a disruption in nitric oxide (NO) metabolism in DM as a result of insulin resistance [49]. NO is a key regulatory molecule with metabolic, vascular, and cellular effects [50]. NO has been shown to alleviate PE in an experimental animal study [51]. Hyposensitivity of the serotonin neurotransmitter receptor 5-HT2C has also been reported in the etiopathogenesis of PE [52]. Recent experimental animal studies have shown that

5-HT2C receptors play a role in glucose homeostasis [53]. 5-HT2C receptor agonists have been reported to improve glucose tolerance and insulin sensitivity in obese and diabetic mice [53]. It has been reported that DM patients with PE have lower levels of thyroid stimulating hormone (TSH) and PRL, which are also responsible for PE etiology, than healthy controls [54].

OBESITY AND METABOLIC SYNDROME

Risk factors for obesity include lack of physical activity, aging, and benign prostatic hypertrophy [55,56]. A recent study reported that MetS, particularly central obesity, plays a role in male SD [55]. Further studies revealed that MetS is an independent risk factor for ED [57]. MetS may affect ejaculatory dysfunctions, particularly the onset of PE, as it not only induces ED, but also alters serotonergic function and affects psychological changes, such as depression [58,59]. The results of some studies investigating the relationship between MetS and PE are presented in Table 2.

Gao et al [60] reported that men with complaints of APE have higher body mass index (BMI) than those that do not. Further, Bolat et al [46] revealed that the prevalence of MetS in patients with PE (51%) was significantly higher than in controls (24%). In addition, it has been shown that men with complaints of PE have higher WC and serum triglyceride (TG) levels than controls. Men with WC >102 cm and serum TG levels ≥150 mg/dL had lower IELT scores and a higher prevalence of PE [46]. Jeh et al [61] reported that pa-

Table 2. Studies investigating the relationship between MetS and PE in men

Study	Year	Definition of PE	Definition of MetS	PE prevalence	Results
Corona et al [63]	2006	PE was defined as ejaculation within 1 minute of vaginal intromission (as reported by the patient).	NCEP-ATP-III	22.7%	MetS is associated with a higher prevalence of hypogonadism in patients with SD.
Gökçe and Ekmekcioglu [64]	2010	PE was defined as ejaculation in <1 minute during more than half of the sexual attempts.	Unspecified	-	The prevalence of obesity in the PE group is lower than the control group.
Lotti et al [62]	2013	PEDT	IDF & AHA/NHLBI	22.2% with MetS 14.4% without MetS	MetS is associated with hypogonadism, poor sperm morphology, ED, somatization, depression.
Gao et al [60]	2013	According to the outcomes of questionnaires, men who were not satisfied with their time to ejaculation were accepted as having the complaint of PE.	WHO	25.80%	Higher age, BMI score, smoking rate, a lower frequency of sexual intercourse, IELT, and exercise rate in PE.
Salama et al [21]	2017	PEDT	NCEP-ATP-III	35.2%	WC and FBS were significantly associated with the presence of PE.
Bolat et al [46]	2017	PEDT	NCEP-ATP-III	51%	Men with WC >102 cm and serum TG levels ≥150 mg/dL had lower IELT scores and higher PE prevalence.
Cakir et al [66]	2018	PEDT	Unspecified	-	Men with PE had lower BMI, TG levels, WC, and HDL-C levels.
Jeh et al [61]	2019	ISSM	NCEP-ATP-III	7.2%	Men with MetS had a 2.2-fold higher risk of APE.
Lu et al [67]	2020	PEDT	NCEP-ATP-III	-	WC, visceral fat ratio, fat mass, FBS, and hs-CRP levels in the APE group were significantly higher than in the control group.

MetS: metabolic syndrome, PE: premature ejaculation, NCEP-ATP-III: National Cholesterol Education Program-Adult Treatment Panel III, SD: sexual dysfunction, PEDT: premature ejaculation diagnostic tool, IDF & AHA/NHLBI: International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood, ED: erectile dysfunction, WHO: World Health Organization, BMI: body mass index, IELT: intravaginal ejaculatory delay time, WC: waist circumference, FBS: fasting blood sugar, TG: triglyceride, HDL-C: higher high-density lipoprotein-cholesterol, ISSM: International Society for Sexual Medicine, APE: acquired pemature ejaculation, hs-CRP: high sensitivity C-reactive protein, -: not available.

tients with MetS had a 2.2-fold higher risk of APE than controls. In addition, that same study reported that as the number of MetS components increased, the Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD) scores and ejaculation anxiety scores gradually decreased. Salama et al [21] found that the prevalence of PE among patients with MetS (35.2%) was significantly higher (p<0.001) than in controls (7.6%). That study also revealed that both WC and FBS were significantly associated with the presence of PE. Interestingly, WC was significantly lower in men with MetS without PE compared to those with PE (p=0.047) and the difference was more significant when compared with controls without PE (p<0.001). FBS values were significantly higher in patients with PE associated with MetS compared to controls (p=0.019), which confirms data from other studies showing that there is an increase in PE prevalence in patients with DM [36,38]. Lotti et al [62] determined the prevalence of PE as 22.2% in those with MetS and 14.4% in those without MetS (p=0.283). In their study evaluating 236 MetS patients and 567 controls, Corona et al [63] reported a higher prevalence of PE among MetS patients (22.7% *vs.* 3% controls). On the contrary, Gökçe and Ekmekcioglu [64] reported that PE patients were leaner than healthy controls, and that the number of PE patients decreased as BMI increased. Amato et al [65] developed a new sex-specific metabolic index, the visceral adiposity index (VAI), which is calculated from WC, BMI, TG, and high-density lipoprotein values. In their study using VAI, Cakir et al [66] reported that the prevalence of obesity in the PE group was lower than that of the control group. The authors of that study also suggested that VAI is a useful index for assessing and calculating the risk of PE, and the relationship between adiposity and PE may be due to the increase in peripheral aromatization of androgens. The difference in the prevalence of PE in patients with MetS in the last two studies [64,66] may be due to regional and cultural differences. The differing prevalence of PE in patients with MetS may be due to the use of different definitions of PE, variations in the number of patients in each study, and the large inconsistency in the prevalence of hyperglycemia in these studies. In a recent study, Lu et al [67] investigated the relationship between MetS and APE in 500 men with APE and 500 men without APE. They observed that neck circumference, WC, visceral fat ratio, fat mass, FBS, and high sensitivity C-reactive protein (hs-CRP) levels in the APE group were significantly higher than those of the control group. They also found that the APE population had a higher prevalence of MetS (35.6% controls *vs.* 49.4% MetS, p=0.000) and that both the prevalence and severity of PE increased significantly as the number of MetS components increased. In their multivariate analysis, Lu et al [67] reported that both MetS and hs-CRP are independent risk factors for APE.

The underlying mechanism in the causality relationship between MetS and PE has not been fully elucidated. However, evidence has shown that there is a bidirectional relationship between depression, one of the known causes of PE, and MetS [58,59]. Rosmond et al [68] reported that abnormal production of the serotonergic receptor 5-HT2A gene, which is the primary organic cause of PE, can lead to obesity. Obesity is known to be associated with chronic low-grade inflammation [69]. Prostatic infections have been reported to be associated with the prevalence of PE [70], and treatment of prostatitis improves IELT scores [71]. Therefore, it is possible that MetS-induced tissue inflammation, such as prostatitis, may contribute to PE.

THYROID DISORDERS

The thyroid is a hormonally active gland that is part of the hypothalamic-pituitary-thyroid axis and secretes thyroxine (T4) and triiodothyronine (T3), which act on metabolism. Receptors that mediate the activity of thyroid hormones are found in almost all cells in the body. Indeed, hyperthyroidism, which is an excess of thyroid hormones, causes a hypermetabolic state characterized by tachycardia, tremors, anxiety, diarrhea, and sympathetic overactivity resulting in weight loss. Conversely, in hypothyroidism, there is a slowdown in physical and mental activity resulting in fatigue, decreased cardiac output, constipation, and weight gain. Although both hypothyroidism and hyperthyroidism affect almost all systems in the organism, the effects of these hormones on sexual function have been elucidated in less detail. The long-held false belief that the genital organs do not respond to thyroid hormone is responsible for this. However, studies have identified the presence of thyroid hormone receptors in both male and female genitalia, including the testis, corpora cavernosa, ovary, and vagina [72]. Therefore, it has been revealed that thyroid hormones can also be effective in the functioning

of the genital organs, and studies on thyroid hormones and sexual activity have been accelerated. The results of some studies investigating the relationship between thyroid disorders and PE are presented in Table 3.

Two to four months after treatment of hypothyroidism and normalization of thyroid hormone levels, one study showed that there is a reduction in the proportion of hypothyroidic men with ED (64.3% during treatment to 21.4% after treatment, p<0.05), hypoactive sexual dysfunction (HSD) (64.3% during treatment to 35.7% after treatment, p<0.05), and DE (64% during treatment to 28.6% after treatment, p<0.05). However, this study included only 14 patients, which is an important limitation [73].

Numerous studies have identified a link between hyperthyroidism and ejaculatory dysfunction. In the study of Carani et al [73], PE was detected in half of the patients with hyperthyroidism. After the treatment of hyperthyroidism, with normalization of thyroid hormone levels for 2 to 4 months, the prevalence of PE decreased from 50% to 15%, which is similar to the levels in the general population (14%). In their study including 755 men, Corona et al [74] observed that the prevalence of PE was significantly higher in patients with TSH less than 0.2 mU/L compared to the rest of the study group (57.1% *vs.* 26.5%). Interestingly, Corona et al [74] found that patients with TSH less than 0.2 mU/L that also had ED had higher rates of PE. Thus, they suggested that hyperthyroidism is associated with PE independently of ED. Cihan et al [75] examined the prevalence of PE in hyperthyroidic men from a different perspective. In their single-center prospective observational study, they detected PE in 72% of 49 men with untreated hyperthyroidism, and observed a direct correlation between IELT and TSH levels (r=0.37, p=0.04). After patients were treated med-

Table 3. Studies investigating the relationship between thyroid disorders and PE in men

Study	Year	Definition of PE	Disorder	PE prevalence	Results
Corona et al [45]	2004	PE was defined as ejaculation within 1 minute of vaginal intromission (as reported by the patient).	Hyperthyroidism	TSH ↓ 0.2 mU/L 57.1% TSH ↑ 0.2 mU/L 26.5%	TSH <0.2 mU/L and ED had higher rates of PE. Hyperthyroidism is associated with PE independent of ED.
Carani et al [73]	2005	DMS-IV	Hypothyroidism, hyperthyroidism	Hypothyroidism 7.1% Hyperthyroidism 50%	The prevalence of PE decreased from 50% to 15% after 2–4 months of treatment.
Waldinger et al [78]	2005	IELT ≤1 minute	Hyperthyroidism	-	There is no relationship between LPE and hypo- or hyperthyroidism.
Cihan et al [75]	2009	DMS-IV	Hyperthyroidism	72%	Correlation between IELT and TSH levels. Increase the IELT and decrease in the incidence of PE to 25% after treatment.
Cihan et al [76]	2009	Animal study	Hyperthyroidism	-	Hyperthyroid rat ejaculation time is shorter than control and returns to normal after treatment.
Corona et al [30]	2011	PE was defined as ejaculation within 1 minute of vaginal intromission (as reported by the patient).	Hyperthyroidism	42.4%	TSH level affected the ejaculation time independent of age, testosterone, or prolactin level, and the increase in TSH caused an increase in IELT levels.
Oztürk et al [77]	2012	Unspecified	Hyperthyroidism	-	Hyperprolactinemia was detected in 19 participants (17.8%) and TSH was below normal in 9 patients (8.4%) in the PE group. Mean serum prolactin and free T4 concentrations were found to be significantly higher in the PE group.
Canat et al [32]	2017	PEDT	Hyperthyroidism	-	TSH levels lower in PE men.

PE: premature ejaculation, TSH: thyroid stimulating hormone, ED: erectile dysfunction, DMS-IV: Diagnostic and Statistical Manual of Mental Disorders-IV, IELT: intravaginal ejaculatory delay time, LPE: lifetime pemature ejaculation, PEDT: premature ejaculation diagnostic tool, -: not available.

ically or surgically, the IELT increased from 75.8 to 123 seconds (p=0.004) and there was a decrease in the incidence of PE (to 25%.) In addition, Cihan et al [75] found significant increases in sexual desire, orgasmic function, erectile function, and general satisfaction domain scores in patients who were treated either medially or surgically (p=0.04, p=0.04, p=0.03, p=0.03, respectively). Cihan et al [76] then used a rat model to further investigate the relationship between hyperthyroidism and PE. That study utilized the ejaculation model, in which seminal vesicle pressure and bulbospongiosus muscle contraction was evaluated in response to para-chloroamphetamine. The ejaculation delay time after para-chloroamphetamine injection was significantly shorted in the hyperthyroid rat group compared to the recovered, sham operated, and control groups (202 *vs.* 480, 465, 444 seconds, respectively, p<0.001 for all). The ejaculation delay time of the hyperthyroid rats treated with para-chloramphetamine was similar to that of the controls. According to these results, hyperthyroidism can cause PE, and PE can be reversed by treating the hyperthyroidism.

Oztürk et al [77] conducted a case-control study involving 107 men with PE and 94 healthy controls. They found that free T4 levels were significantly increased in the PE group compared to controls. In a retrospective analysis of 2,652 patients, the prevalence of PE in patients with overt hyperthyroidism was found to be 42.4%. This ratio was significantly higher than the general male cohort of the clinic (hazard ratio=2.98, p<0.05). In that study, it was observed that TSH level affected the ejaculation time independent of age, testosterone, or PRL level (r=0.047, p=0.019). Moreover, that study reported that an increase in TSH level caused an increase in IELT levels [30]. In another case-control study by Canat et al [32] involving 63 men with PE and 39 controls, TSH levels were reported to be significantly lower in men with PE (p=0.017), but there were no significant changes in free T3 or free T4 levels (p>0.05). In addition, in a study involving 620 men with LPE, no relationship was observed between PE and hypo- and hyperthyroidism [78]. For this reason, it is suggested that hyperthyroidism can only increase the risk of developing APE. When the results of all of these studies are evaluated together, it can be concluded that there is a relationship between PE and thyroid disease. However, since thyroid disorders are not the only cause of PE, these studies report variable results [79].

PITUITARY GLAND DISORDERS

Testosterone production is driven by the hypothalamic-pituitary-gonadal (HPG) axis. Hypothalamic gonadotropin releasing hormone stimulates the secretion of LH and FSH from the pituitary gland. LH regulates testosterone secretion by Leydig cells while FSH supports spermatogenesis. Testosterone deficiency can be asymptomatic or cause SD such as decreased libido and ED. Hypogonadism is a clinical condition that causes low serum testosterone levels due to dysfunction of the HPG axis. The relationship of testosterone levels to PE has been discussed before. Although the relationship between hypogonadism and PE has not been fully elucidated, it has been suggested that patients with PE are associated with hypogonadotropic hypogonadism (HH) [27]. Whether or not there are symptoms of hypothalamic or pituitary disease, hypogonadism is common in sexually mature men. The results of some studies investigating the relationship between pituitary disease and PE are presented in Table 4.

Cohen [27] reported a relationship between PE and idiopathic HH in men with SD. Laumann et al [80] reported that the prevalence of PE in men with HH is 21%. They also suggested that it is possible that a large number of men suffer from hormonal inadequacy. Klinefelter syndrome (KS) is the most common sex chromosomal disorder causing male hypogonadism and infertility [81,82]. Corona et al [83] reported that patients with KS also have severe ED, HSD, PE, and DE. Other recent studies have shown that KS patients have significantly lower libido and PE rates compared to controls [84]. However, another study reported that there was no significant difference between KS patients and controls in terms of the incidence of PE (11.3% *vs.* 8.3%, respectively) and DE (6.4% *vs.* 5.0%, respectively) [85].

In a study investigating the relationship between PRL levels and SD, it was observed that 2,265 (89.5%) of the SD patients had ED, 929 (36.7%) had HSD, 658 (26.0%) had PE, and 165 (6.5%) had DE. Of the patients with PE, 241 (36.6%) were APE and 417 (63.4%) were LPE. The authors detected hyperprolactinemia (PRL >720 mU/L or 35 ng/mL) in 1.4% (n=35) of the SD patients. However, they reported that hyperprolactinemia, especially in patients with PRL levels in the lowest quartile, exhibited a higher prevalence of MetS, arteriogenic ED, PE, and anxiety [86]. Similarly, Oztürk

Table 4. Studies investigating the relationship between pituitary gland disorders and PE in men

Study	Year	Definition of PE	Disorder	PE prevalence	Results
Cohen [27]	1997	DMS-III-R	Hypogonadism	-	Plasma testosterone, free testosterone, LH, and FSH levels were decreased in PE.
Laumann et al [80]	1999	DMS-IV	Hypogonadism	21%	Large number of men suffering from hormonal inadequacy.
Corona et al [86]	2009	PE was defined as ejaculation within 1 minute of vaginal intromission (as reported by the patient).	Hypoprolactinemia	26%	Hyperprolactinemic patients exhibited a higher prevalence of MetS, arteriogenic ED, PE, and anxiety.
Corona et al [83]	2010	PE was defined as ejaculation within 1 minute of vaginal intromission (as reported by the patient).	KS	9.5%	Patients with KS have severe ED, HSD, PE, and DE.
El Bardisi et al [84]	2017	AIPE	KS	22.6%	There is a significantly lower libido and PE in KS.
Ferlin et al [85]	2018	PEDT	KS	11.3%	KS subjects had significantly fewer areas of sexual desire, sexual intercourse satisfaction, overall satisfaction, and erectile function, compared to controls. There was no difference in the incidence of PE and DE between KS patients and controls.

PE: premature ejaculation, DMS: Diagnostic and Statistical Manual of Mental Disorders, LH: luteinizing hormone, FSH: follicle stimulating hormone, ED: erectile dysfunction, KS: Klinefelter syndrome, HSD: hypoactive sexual dysfunction, DE: delayed ejaculation, AIPE: Arabic Index for Premature Ejaculation, PEDT: premature ejaculation diagnostic tool, KS: klinefelter syndrome, -: not available.

et al [77] reported that mean serum PRL levels were significantly higher in PE patients than in healthy controls. In addition, that same study reported that 19 of the PE patients (17.8%) had hyperprolactinemia and hypotestosteronemia. In their study including 1,249 patients with SD, El-Sakka et al [87] reported a significant relationship between hyperprolactinemia and PE. In contrast, Canat et al [32] reported that patients with PE had lower PRL than healthy controls. However, other published studies have shown that the serum PRL levels of PE patients were not different from controls [31,33].

VITAMIN D DEFICIENCY

Vitamin D is a steroid hormone produced in the skin that is converted to vitamin D3 through exposure to sunlight [88]. Studies suggest that vitamin D deficiency is associated with endocrinological disorders, autoimmune diseases, infectious diseases, and neurocognitive disorders (other than those in the musculoskeletal system) [89]. Other studies have investigated the relationship between vitamin D and PE, and the results of those studies are presented in Table 5. Mirzahosseini et al [90] reported that the administration of 2.5 mg of vitamin D3 during the critical hormonal imprint period (neonatal period) completely prevented ejaculation in male rats due to the overlap of sex steroid receptors.

Abd El Aal et al [91] investigated vitamin D deficiency in a sample of 40 men with LPE and 40 healthy controls. They detected vitamin D deficiency in 16 (20%) of the participants, all of whom had LPE. In addition, vitamin D was observed to be significantly lower in the group with LPE compared to controls (35.75 *vs.* 58.92 ng/mL, $p<0.001$, respectively). That study found a correlation between vitamin D levels and IELT ($r^2=0.349$; $p<0.001$) and PEDT ($r^2=0.425$; $p<0.001$). ROC analysis revealed that the best cut-off value of vitamin D to detect patients with LPE was 50.65 ng/mL (85% sensitivity and specificity). In logistic regression analysis, vitamin D was determined to be an important risk factor for LPE ($p<0.001$). Canat et al [92] investigated

Table 5. Studies investigating the relationship between vitamin D and PE in men

Study	Year	Definition of PE	Disorder	PE prevalence	Results
Mirzahosseini et al [90]	1996	Animal study	Vitamin D excess	-	Administration of 2.5 mg of vitamin D3 during the critical hormonal imprint period (neonatal period) completely prevented male rat ejaculation.
Abd El Aal et al [91]	2018	ISSM	Vitamin D deficiency	-	Vitamin D is lower in the group with LPE, there is a correlation between vitamin D levels and IELT and PEDT, vitamin D is an important risk factor for LPE.
Canat et al [92]	2019	Second Ad Hoc ISSM Committee and PEDT	Vitamin D deficiency	-	There was no significant relationship between vitamin D deficiency and APE.

PE: premature ejaculation, ISSM: International Society for Sexual Medicine, LPE: lifetime pemature ejaculation, IELT: intravaginal ejaculatory delay time, PEDT: premature ejaculation diagnostic tool, APE: acquired pemature ejaculation, -: not available.

the relationship between vitamin D levels and APE, and determined the vitamin D level in the APE group as 12.0±4.5 ng/mL and in the control group as 18.2±7.4 ng/mL. They suggested that serum vitamin D levels should be investigated in the etiology of APE, although the sensitivity and specificity are relatively low in the relationship between vitamin D deficiency and APE (60.9% and 83.5%, respectively).

Different mechanisms have been proposed that may reveal the causal relationship between PE and vitamin D deficiency. Animal studies have revealed an association between anxiety, a cause of PE [93], and vitamin D deficiency [94,95]. Vitamin D stimulates the production of NO and NO synthase, which are important effectors of the sympathetic nervous system, which can affect ejaculation [96]. High levels of vitamin D activating enzymes and vitamin D receptors have been reported in the hypothalamus and substantia nigra [97]. Moreover, vitamin D has been reported to control serotonin synthesis [96]. Since vitamin D binds to androgen receptors when it rises above normal values [98], many studies have found a relationship between serum androgen and vitamin D levels [99,100].

CONCLUSIONS

Most studies to date have focused on the psychogenic factors of PE. However, after recent studies have reported that PE can be caused by organic reasons, research has turned to this area. Endocrine disorders are one of the most important organic causes of PE. Recently, both clinical and experimental animal studies have shown that especially DM, obesity, MetS, hyperthyroidism, and vitamin D deficiency are associated with PE. Moreover, treatment of these endocrine disorders leads to a decrease in the prevalence of PE. Therefore, when treating patients with SD, physicians should also consider endocrine disorders. However, it should be noted that the relationship between endocrine disorders and SD has not been fully elucidated. Larger studies are needed in order to demonstrate the relationship between hormonal irregularity and PE.

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Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: ERC. Data curation: ERC, BO. Formal analysis: ERC, BO. Funding acquisition: ERC, BO. Investigation: ERC, BO. Methodology: ERC, BO. Project administration: ERC, BO. Resources: ERC, BO. Software: ERC, BO. Supervision: ERC, BO. Validation: ERC, BO. Visualization: ERC, BO. Writing – original draft: ERC. Writing – review & editing: ERC, BO.

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