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REVIEW

Male Sexual Function

Premature ejaculation: an update on definition and pathophysiology

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Premature ejaculation (PE) is the most common male sexual dysfunction, which represents a diagnostic as well as a therapeutic challenge for physicians. However, no universally accepted definition is currently available for PE. As a result, physicians continue to diagnose patients with PE according to major guidelines set by the professional societies. These guidelines either recommend the use of validated questionnaires or patient-reported outcomes. Recent efforts directed toward classifying PE may help provide a better understanding of the prevalence and risk factors of this disorder. While the exact etiology of PE has not been clearly elucidated, several risk factors have been strongly reported in the literature. Clearly, to understand the revised definition of PE, its etiology and pathophysiology is necessary to improve the clinical management of this medical condition and form the basis of future research in this regard. In this review, we highlight the past and current definitions of PE and present an appraisal on the classifications and theories suggested for the etiopathogenesis of PE.

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INTRODUCTION

Premature ejaculation (PE) is the most common sexual dysfunction in men, with the prevalence rate reaching up to 75%.[1] Currently, assessment of patients with PE relies mainly on the use of validated questionnaires. Five validated questionnaires have been developed and published to date, including Index of PE,[2] PE Profile,[3] PE Diagnostic Tool,[4] Arabic PE Questionnaire,[5] and Chinese PE Questionnaire.[6]

Other methods for the assessment of PE include patient-reported outcome measures (the ability to control ejaculation and the extent of sexual satisfaction of the patient and his partner) and stopwatch measures of intravaginal ejaculatory latency time (IELT). Despite the wide utility of the stopwatch measure of IELT in clinical trials and observational studies of PE, it has not been recommended for use in routine clinical management of PE.[7] That is because stopwatch measures have the disadvantage of being intrusive and potentially disruptive of sexual pleasure or spontaneity.

Identification of and inquiry into PE both in the clinical and research settings have been hindered by the lack of a universally accepted definition of the condition. An understanding of the normal physiology of ejaculation is important before embarking on the complex etiologic factors of this exasperating sexual dysfunction. In this review, we discuss the definitions, classifications, and etiopathogenesis of PE.

PHYSIOLOGY OF EJACULATION

Normal antegrade ejaculation is a highly coordinated physiological process comprising emission and expulsion phases, which are under the control of the autonomic and somatic nervous systems, respectively (**Table 1**). Orgasm, a feature perhaps unique to humans, is a cerebral process that occurs, in normal conditions, alongside the expulsion of semen.[8]

Emission

Emission is the first phase of ejaculation characterized by the passage of seminal fluid from the prostate, seminal vesicles, and vas deferens into the posterior urethra. It occurs concomitant with the contraction of the internal urethral sphincter, which closes the bladder neck and prevents retrograde passage of semen into the bladder. Emission is solely dependent on contractions of the smooth muscles of the prostate, seminal vesicles, and vas deferens, and its initiation can be voluntarily controlled.[9] However, once the semen reaches the posterior urethra, ejaculation becomes inevitable.[10]

All organs participating in the emission phase receive dense autonomic innervations composed of sympathetic and parasympathetic axons that originate from the pelvic plexus (occasionally referred to as the inferior hypogastric plexus). In humans, the pelvic plexus is situated retroperitoneal in the sagittal plane on either side of the rectum and lies lateral and posterior to the seminal vesicles.[11] Its neural fibers are conveyed by both pelvic and hypogastric nerves as well as the caudal paravertebral sympathetic chain.[12] Sympathetic nerves play a predominant role in commanding emission by releasing norepinephrine although other chemical mediators such as acetylcholine, oxytocin, and nonadrenergic/noncholinergic (NANC) factors including adenosine triphosphate (ATP),[13] neuropeptide Y (NPY),[14] vasoactive intestinal peptide (VIP),[15] and nitric oxide (NO),[16] may be important mediators within sex glands.

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Table 1: Physiology of ejaculation

Characteristic	*Emission*	*Expulsion*	*Orgasm*
Nervous system	Sympathetic spinal cord reflex	Combined sympathetic and somatic	Cerebral process
Control	Voluntary control	Limited voluntary control	Involuntary control
Sensory input	Genital or cerebral erotic stimulation	Sensation resulting from distension of posterior urethra	Cerebral processing of pudendal nerve sensory stimuli
Motor output	Sequential contractions of accessory sexual glands	Rhythmic contractions of bulbocavernosus/pelvic floor muscles	Contraction of urethral bulb Smooth muscle contraction of accessory sexual organs

Stimuli from genitalia, essentially those reflecting the degree of activation of the sensory receptors that are mainly located in the glans penis, are integrated at the spinal level and stimulate emission.[17] The emission phase of ejaculation is under considerable cerebral control and may be elicited following visual and physical erotic stimulations.[18]

Expulsion (antegrade ejaculation)

Expulsion is the second phase of ejaculation in which there is a passage of seminal fluid from the posterior urethra to the external urethral meatus. Expulsion is a spinal cord reflex that occurs as the ejaculatory process reaches a "point of no return." It depends on contractions of the pelvic floor muscles in addition to the bulbospongiosus and ischiocavernosus muscles. These contractions occur rhythmically at 0.8-s intervals. This phase is associated with the intense pleasure of orgasm and is analogous to the orgasmic phase in the female.[19]

The trigger of rhythmic pelvic striated muscle contractions responsible for the expulsion of semen is still not clearly identified. It has been proposed that the expulsion phase of ejaculation is a reflex response to the presence of semen in the bulbar urethra.[20] However, experimental and clinical data do not support this view, demonstrating that urethral stimulation by the ejaculate does not contribute to the regulation of striated muscle components of ejaculation.[19,21]

Orgasm

The human sexual response cycle consists of four distinct stages, desire, arousal, orgasm, and resolution, with the orgasmic stage being the shortest but most intense of the four.[22] Orgasm is one of the most pleasurable sensations known to humankind. Very little is known about the underlying physiological mechanisms that control orgasmic responses. Orgasm is a cerebral process that usually follows a series of peripheral physical events comprising contraction of accessory sexual organs and the urethral bulb together with the buildup and release of pressure in the distal urethra.[8] It can occur irrespective of the patency of the neurologic innervation of sex glands similar to what can be seen in patients after radical prostatectomy[23] or after lesions of the hypogastric plexus causing failure of seminal emission.[24] Furthermore, orgasmic sensations can be generated cerebrally without any input from genitals or without the occurrence of ejaculation.[25]

DEFINITION OF PE

The medical literature contains several definitions of PE. The disharmony regarding what constitutes PE has had a detrimental influence on basic and clinical research into the etiology and management of this condition. Aspects such as a patient's assessment of self-efficacy, extent of sexual satisfaction of patients or their partners, quantitative measures of intercourse, and the level of bother or distress noted are the principle areas that constitute most of the available definitions of PE (**Table 2**).

In the past, PE was defined as the inability to exert voluntary control over the ejaculatory reflex.[26] Hastings[27] defined PE as a condition in which a man reaches orgasm and ejaculates before he desires to do so. Cooper[28] defined PE as persistent occurrence of ejaculation and orgasm before or immediately after vaginal penetration during coitus and before the male wishes it. Masters and Johnson[29] defined PE as the inability of the male to control ejaculation to satisfy his female partner in more than 50% of coital episodes provided that she is not anorgasmic.

Strassberg *et al*.[30] defined a man as having PE if during at least 50% of his attempts at intercourse he had little voluntary control over ejaculation and ejaculated within 2 min or less after intromission. The previous definitions acknowledge that PE may have aspects of both control and latency. The International Classification of Diseases, 10th edition (ICD10) issued by the World Health Organization (WHO)[31] introduced a quantified cutoff point as it described PE as "the inability to delay ejaculation sufficiently to enjoy lovemaking, which is manifested by either an occurrence of ejaculation before or very soon after the beginning of intercourse or ejaculation occurring in the absence of sufficient erection to make intercourse possible."

IELT is the time between the start of vaginal intromission and the start of intravaginal ejaculation. This quantitative measure was used to aid in defining PE with considerable variance in the reported latencies. However, the definition of PE based on vaginal latency excludes passive homosexual men who may have PE. Further, the fact that the latter group of men with PE do not require penile stimulation excludes penile sensitivity as a simple cause of PE and supports the notion that it is a much more complex issue.

Some authors defined PE as occurring when male orgasm occurs within 1 min of vaginal penetration,[32–34] while others reported an average duration of intercourse of 4–7 min, suggesting that ejaculation before 4 min after intromission should be considered premature.[35] Although IELT covers only one parameter of PE, namely "short time interval between penetration and ejaculation," and ignores other patient-reported outcomes (PROs) such as "lack of control over ejaculation" and "distress experienced by one or both partners," it was welcomed by the research community as it provided a tool to objectively assess the efficacy of pharmacological or surgical interventions.[36] A definition of PE was proposed, based on pathological IELT with loss of voluntary control and distress or relational disturbances.[37] In this regard, two different forms of PE were defined: "objective PE" (which can be "severe" when ejaculation occurs before penetration or with an IELT ≤15 s, "moderate" with an IELT ≤1 min, or "mild" with an IELT ≤2 min) and "subjective or relational PE" (when the loss of voluntary control is experienced with distress by the male or both partners).

The growing amount of basic research exploring the prevalence of PE triggered scientific committees/authorities to update their definitions of the condition.[22,38,39] In 2013, DSM-V[40] defined PE as "a male sexual dysfunction characterized by a persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately 1 min following vaginal penetration and before the individual wishes it. The symptom must have been present

Table 2: Definitions of premature ejaculation adopted by scientific committees/authorities

Scientific committees/authorities	*Definition*
DSM-V (2013)	Persistent or recurrent pattern of ejaculation Within approximately 1 min following vaginal penetration Before the individual wishes it Duration: 6 months Experienced on almost all or all (approximately 75%–100%) occasions of sexual activity Cause clinically significant distress in the individual Not explained by a nonsexual mental disorder/severe relationship distress/other significant stressors/substance/medication/another medical condition
ISSM (2014)	Always or nearly always occurs prior to or within about 1 min of vaginal penetration Lifelong PE: from the first sexual experience Acquired PE: clinically significant and bothersome reduction in latency time, often to about 3 min or less Negative personal consequences
EAU (2004)	Inability to control ejaculation for a "sufficient" length of time before vaginal penetration
AUA (2004)	Ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either 1 partner or both partners

PE: premature ejaculation; DSM-V: diagnostic and statistical manual of mental disorders – fifth edition; ISSM: International Society for Sexual Medicine; EAU: European Association of Urology; AUA: American Urological Association

for at least 6 months and must be experienced on almost all or all (approximately 75%–100%) occasions of sexual activity (in identified situational contexts or, if generalized, in all contexts). The symptoms cause clinically significant distress in the individual and the sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition."

Furthermore, the ISSM recently updated its definition of PE to define it as a male sexual dysfunction characterized by ejaculation that always or nearly always occurs before or within about 1 min of vaginal penetration from the first sexual experience (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to about 3 min or less (acquired PE); the inability to delay ejaculation on all or nearly all vaginal penetrations; negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.[41]

EPIDEMIOLOGY OF PE

A wide variation exists in the epidemiology of PE in different parts of the world. The prevalence of PE among sexually active men ranged from 20% to 75% in different studies.[1,42,43] Most epidemiological studies exploring the prevalence of PE have been criticized as either relying on patient self-report or poorly validated definitions of PE, suggesting their reported rates to be inaccurate. Further, the variation in the epidemiology of PE, noted in international reports, may be related to differences in the type of reported prevalence, study methodology, assessment tools, ethnic groups, and age distribution.

TYPES OF PE

Schapiro[44] was the first to describe two types of PE: primary PE (PPE, or lifelong PE), which affects men who had never attained ejaculatory control, but had no erectile or desire difficulties, and secondary PE (SPE, or acquired PE), which affects elderly men and is associated with erectile difficulties. Cooper[28] described three types of PE: PPE (Type 1) that occurs from adolescence and is characterized by normal erection and associated anxiety neurosis; acute-onset PE (Type 2) that is usually associated with erectile insufficiency and a more generalized anxiety; and insidious onset PE (Type 3) that is associated with erectile insufficiency and low libido. Anxiety was less prominent and often reactive to the development of the condition.

Godpodinoff[45] classified PE into two main types: PPE, when the condition is consistently present from the first coital experience, and SPE, when satisfactory sexual performance, often for many years, preceded its onset. He indicated that PPE is relatively homogenous, while SPE can be subdivided into two subtypes, one with demonstrable organic, and the other with psychopathological elements (*e.g.*, disturbed relationships and high level of anxiety). This classification appeared to be helpful in formulating appropriate treatment plans.

The simplest way to classify PE is to consider whether symptoms begin when a male first becomes sexually active (PPE, lifelong), or occur after a period of normal ejaculatory control (SPE, acquired). PE can be absolute (irrespective of partners or context, permanent) or relative (to a partner and/or context, situational). Ejaculation may take place before penetration (ante portas) or suddenly during coitus (intra moenia). It can occur in the absence (simple) or presence (complicated) of other sexual symptoms that can be caused by or result from PE.[37]

A newer classification of PE has been proposed by DSM-V and ICD-11. It distinguishes four PE categories: lifelong PE, acquired PE, natural variable PE, and premature-like ejaculatory dysfunction. According to this new classification, there are different pathophysiologies of and treatment options for PE depending on the underlying PE syndrome (**Table 3**).[46–48]

ETIOPATHOGENESIS OF PE

The etiology of PE has been traditionally divided into psychogenic and biogenic factors[48] (**Table 4**). Psychogenic factors include psychodynamic theories, early experience, sexual conditioning, anxiety, and technique and frequency of sexual activity. Biogenic factors include penile hypersensitivity, hyperexcitable ejaculatory reflex, hyperarousability, endocrinopathy, genetic predisposition, and 5-hydroxytryptamine (5-HT) receptor dysfunction (neurobiological theory).[49–51] Urologic causes, including chronic prostatitis, have also been implicated.[52]

Psychological factors

PE has generally been considered a psychosexual disorder with a psychogenic etiology.[53] The main causes of psychogenic PE can be divided into three groups each belonging to a different phase of time: (i) immediate factors (performance anxiety), (ii) antecedent life events from recent history, and (iii) developmental vulnerabilities from childhood and adolescence.[54]

Anxiety

Anxiety is considered as the primary agent in precipitating rapid ejaculation. However, anxiety is not specific; it is used to characterize at least three different mental phenomena. Anxiety may refer to: (1)

Table 3: Classification of premature ejaculation

Attribute	*Lifelong PE*	*Acquired PE*	*Natural variable PE*	*Premature-like ejaculatory dysfunction*
IELT	Very short (<1–1.5 min)	Short (<1.5–2 min)	Normal (3–8 min)	Normal or long (3–30 min)
Symptoms	Consistent	New onset of PE secondary to a known cause; history of normal ejaculation earlier	Inconsistent	Subjective perception of PE despite normal ejaculation
Etiology	Neurobiological and genetic	Medical and/or psychological	Normal variation	Psychological
Treatment	Medication with/without counseling	Medication with/without psychotherapy	Psycho-education	Psychotherapy
Prevalence	Low	Low	High	High

PE: premature ejaculation; IELT: intravaginal ejaculatory latency time

Table 4: Etiology of premature ejaculation

Psychological factors	*Biogenic factors*
Anxiety	Genetic factors: polymorphisms of the *5-HTTLPR* gene
Technique of sex: lack of awareness of techniques effective in ejaculatory control	5-hydroxytryptamine receptor dysfunction: 5-HT2C receptor hyposensitivity and/or 5-HT1A receptor hypersensitivity
Early sexual experience: haste, nervous experience	Penile sensitivity: increased
Frequency of sexual activity: less frequent sexual behavior	Endocrinal causes: diabetes, hyperthyroidism, low vitamin B12 levels
Arousability: high	Urologic conditions: prostatitis
Psychoanalytic theories: deep seated hateredness, personality disorders	Neurogenic diseases: MS, peripheral neuropathies, and medullary expansion processes
	Drug induced: amphetamine, cocaine, and dopaminergic drugs
	Chronic renal insufficiency
	Low seminal magnesium levels
	Increased serum leptin levels
	Varicocele
	Sexual dysfunction: ED and decreased libido

PE: premature ejaculation; *5-HTTLPR*: serotonin-transporter-linked promoter region; 5-HT2C: 5-hydroxytryptamine 2C; 5-HT1A: 5-hydroxytryptamine 1A; MS: multiple sclerosis; ED: erectile dysfunction

a phobic response, like being fearful (*i.e.*, afraid of the dark, wet, unseen vagina); (2) an affect, the end result of conflict resolution where two contradictory urges are at play (*i.e.*, the man is angry at his partner, but feels guilty about directly expressing his hostility); or (3) anticipatory anxiety commonly referred to as performance anxiety where preoccupation with sexual failures and poor performance leads to deteriorating sexual function and avoidance of future sexual interactions.[55]

A number of investigators suggested that PE can be caused by high levels of anxiety.[49,56–58] Kaplan[57] found that increased anxiety activates the sympathetic nervous system responsible for the emission phase of ejaculation. Kockott *et al*.[59] found that men with PE could be subdivided into high- and low-anxiety groups. High-anxiety men showed more sex avoidance behavior and only ejaculated rapidly during intercourse. Low-anxiety men ejaculated rapidly during both intercourse and masturbation and showed significantly less sex avoidance.

No difference was found in sex-related anxiety between a non-PE control group and men with PE.[30] Men with high levels of anxiety were distracted during sexual activity by thoughts that prevented them from monitoring their level of arousal or premonitory sensations of ejaculation proposing lack of sexual awareness as a cause of PE.[60] Neither of these studies measured anxiety in relation to interpersonal sexual activity, despite the fact that PE is usually defined with respect to ejaculation during sexual intercourse, nor did they use objective psychological measures of anxiety to validate the subjective self-reports of PE.[61]

It has been suggested that performance anxiety *per se* does not generally cause the initial episode of rapid ejaculation.[55] However, performance anxiety was thought to be important in maintaining the dysfunction. By the time patients present for treatment, the initial precipitating event is often obscured because of the intensity of performance anxiety. With each failure, performance anxiety heightens, further worsening sexual performance resulting in sexual avoidance behaviors.

Sex technique

Zilbergeld[58] argued that ejaculatory control is a result of consciously or unconsciously learning to use techniques that are effective in delaying ejaculation. Men with good ejaculatory control reported changes in their behavior during sexual activity to delay ejaculation. These changes included relaxing pelvic muscles, slowing the tempo, and changing the depth or type of thrusting. However, the author did not report any quantifiable data and did not use a control group consisting of men with poor ejaculatory control.[61]

Early sexual experience

Masters and Johnson[10,29] suggested that early conditioning was an important cause of PPE. Men whose early sexual experiences are characterized by haste and nervousness, for example, making love in the backseat of an automobile or during an encounter with a prostitute, became conditioned to ejaculate rapidly. Only two or three "trials" of rushed intercourse were thought to be necessary before a pattern of PE is established. However, none of the researchers compared the sexual histories of men with PE with a non-PE control group. Thus, it is not known whether these early conditioning experiences are unique to men with PE.

Frequency of sexual activity

There are conflicting data regarding an association between the amount of sexual activity and PE, with some studies showing that PE is associated with less frequent sexual activity[45,49,62] and others finding no such relationship.[63] The mechanism underlying such a relationship has yet to be specified. Frequent sexual activity may lead to increased awareness of sensations premonitory to ejaculation, increased ejaculatory threshold, decreased anxiety, and decreased penile sensitivity.

Arousability

A common statement by men with PE is that they ejaculate rapidly because they become aroused more quickly than other men. A study by

Spiess *et al*.[62] called this interpretation into question. Compared with controls, men with PE (I) did not become aroused more quickly, (II) did not show greater sexual arousal, and (III) did not become sexually aroused in a greater number of sexual situations. Again, arousal was measured in the laboratory, and therefore, the results cannot be related to interpersonal situations.

Psychoanalytic theories

Kaplan[57] suggested that PE is related to an unconscious, deep-seated hatred of women. By ejaculating quickly, the man both symbolically soils the woman and robs her of her sexual pleasure. This theory does not explain PE in homosexual men. In addition, it assumes that vaginal intercourse is the primary source of sexual pleasure for women. The same author suggested that most men who experience PE do not have personality disorders, thus reversing the earlier psychodynamic explanation.[64]

Biogenic factors

Genetic factors

Schapiro[44] noted that PE runs in families. Waldinger *et al*.[53] hypothesized that lifelong PE and IELT are genetically determined for some men. Supporting this hypothesis was the report of a high prevalence of lifelong PE among first-degree male relatives of Dutch men with lifelong PE. However, conclusive evidence for a hereditary component in PE was not established until twin studies revealed that genetic effects account for around 30% of the variance in PE.[65,66]

Polymorphisms of the serotonin transporter promoter region gene, of chromosome 17, which encodes the serotonin-transporter-linked promoter region (5-HTTLPR) have been investigated in many studies exploring the genetic basis of PE. The *5-HTTLPR* gene has two variant alleles: a short (S) and a long (L) allele. Ozbek *et al*.[67] and Luo *et al*.[68] found significant differences in allelic frequencies of the *5-HTTLPR* between PPE patients and controls, with the short allele being significantly more frequent in PPE patients. However, Janssen *et al*.[69] reported that significantly shorter IELTs were present in the long-allele carriers within PE patients. In addition, Safarinejad[70] reported that carriers of the long allele of the *5-HTTLPR* with PE were more inclined to respond to treatment with a selective serotonin reuptake inhibitor (SSRI) than carriers of the short allele.

A recent meta-analysis explored six case–control studies including 481 lifelong PE and 466 healthy controls. The authors detected significant associations between lifelong PE risk and *5-HTTLPR* polymorphisms and revealed that the long allele might protect individuals against lifelong PE risk.[71]

5-Hydroxytryptamine receptor dysfunction (neurobiological theory)

The neurobiological theory hypothesized that lifelong PE in humans may be attributed, in part, to decreased central serotonergic neurotransmission, 5-hydroxytryptamine 2C (5-HT2C) receptor hyposensitivity, and/or 5-hydroxytryptamine 1A (5-HT1A) receptor hypersensitivity. It hypothesized that men with a low 5-HT neurotransmission and/or 5-HT2C receptor hyposensitivity may have their ejaculatory threshold genetically set at a lower point and ejaculate quickly with minimal stimulation.[32,72] It has been suggested that the efficacy of SSRIs in inhibiting PE is probably due to an increase in synaptic 5-HT concentrations via blockade of the 5-HT transporter and activation of the 5-HT2C receptor, which then decreases the function of the 5-HT1A receptor or restores the balance between the two receptor functions (5-HT1A and 5-HT2C).[73,74]

Penile sensitivity

In fact, little is known about the intensity of the stimulus required to induce ejaculation, or the influence of the cerebral cortex on the ejaculatory reflex, although the peripheral neural pathway involved in ejaculation is fairly well understood.[75] The average number of dorsal penile nerves in patients with PPE was found to be higher than normal, which may have an impact on PPE via increased sensitivity and provide topographic data for the possible treatment of PPE.[76]

Men with PE ejaculate more quickly because their penises have a greater sensitivity to stimulation and thus quickly reach the critical level of stimulation required to ejaculate.[62,77] If the hypothesis connecting penile sensitivity and PE is correct, penile sensitivity should be related to ejaculatory latency at all ages. To date, no studies have compared the penile sensitivity of men of various ages with and without PE. If penile sensitivity is a cause of PE, men with PE would be expected to ejaculate more quickly than controls only in situations of direct stimulation to the penis.[61]

Recently, Guo *et al*.[78] reported that a dose-dependent association between penile vibratory threshold and PE exists. Therefore, the vibratory threshold can serve as a potential marker for predicting the severity of PE.

Endocrine factors

A study found no significant differences in the levels of sex hormones (luteinizing hormone and free and total testosterone) between men with and without PE.[79] In contrast, serum levels of total and free testosterone were found to be higher in young (25–40 years) patients with PE.[80] The authors, in the later study, suggested that testosterone plays an excitatory role in the control of the ejaculatory reflex.[80] Another study found that the serum levels of free testosterone and follicle-stimulating hormones were higher in patients with PE compared with normal men.[81]

Corona *et al*.[82] reported low prolactin levels among patients with PE. Low prolactin levels have also been observed in patients with high anxiety and guiltiness during masturbation, suggesting perturbations of the neurological pathway involving serotonin and its receptors. Canat *et al*.[83] found that there were no significant differences in serum levels of total testosterone, free testosterone, and follicle-stimulating hormones between patients with PE and controls. However, the later study reported lower levels of luteinizing hormone and prolactin in patients with PE.

Recently, serum levels of testosterone, gonadotropins, and prolactin were found to be undisturbed in patients with PE.[84]

The prevalence of PE was increased in noninsulin-dependent diabetic patients,[85,86] although the exact pathogenesis of PE in diabetic patients is not well known. It has been proposed that PE in diabetic patients may be secondary to psychogenic factors such as performance anxiety and depression or organic factors such as diabetic neuropathy, which may be implicated in the pathophysiology of PE due to the fact that potency and ejaculation depend on the integrity of the autonomic nervous system and its central and peripheral neurotransmitters.[85,87] Bellastella *et al*.[88] showed that the prevalence of PE in young male patients with Type 1 diabetes was similar to an age-matched control population and in diabetic patients with PE; higher glycemic variability in the hypoglycemic domain is significantly associated with the premature ejaculation diagnostic tool (PEDT) score.

It has been reported that most patients with thyroid hormone disorders (hyper- and hypothyroidism) experience some sexual dysfunctions such as PE, which can be reversed by normalizing thyroid hormone levels.[89] Excess thyroid hormones and PE were clinically interrelated conditions.[90] These results lead to the suggestion of hyperthyroidism as a novel and reversible etiological risk factor for PE. Although the exact pathogenesis of PE in patients with hyperthyroidism

is still obscured, it has been proposed that the relationship between hyperthyroidism and PE may be secondary to increased sympathetic activity, altered serotoninergic neurotransmission, or an altered paracrine system (estrogen-to-androgen ratio), which may lead to increased epididymal contractility.[89]

Urological diseases

PE may be secondary to urological diseases (*e.g.*, prostatovesiculitis).[91] Many studies found a high prevalence of chronic prostatitis in patients with PE.[92–94] Chronic prostatitis may play a role in the pathogenesis of some cases of PE, and a careful examination of the prostate is warranted before initiating therapy for PE.[95]

The exact pathophysiology linking prostatitis and PE is unknown. However, it has been proposed that prostatic inflammation may lead to altered sensation and modulation of the ejaculatory reflex through a neurophysiologic pathway.[37,96] Patients suffering from PE with chronic prostatitis could be successfully treated with the antibiotic ciprofloxacin.[97]

Neurological diseases

PE may be secondary to neurological diseases such as multiple sclerosis, peripheral neuropathies, and medullary expansion processes.[91] However, the data on neurological causes of PE are lacking and warrant research.

Drug-induced PE

Premature ejaculation may be iatrogenic and caused by drugs such as amphetamine, cocaine, and dopaminergic drugs.[91] However, the data on drug-induced PE are lacking and warrant research.

Chronic renal insufficiency

Ejaculatory disorders, mostly PE, are commonly experienced by patients with chronic renal insufficiency. While limited research exists to explain such an association, it can be linked to the complex endocrine, neurogenic, and psychogenic alterations that occur secondary to renal failure. As such, few investigators have proposed that renal transplantation can decrease the prevalence and severity of PE in this patient population.[98]

Low seminal plasma magnesium levels

Some studies found significantly lower seminal plasma magnesium levels in men with PE.[99] Decreased levels of magnesium result in an increase in thromboxane A2 levels, which leads to a rise in endothelial intracellular calcium and a decline in nitric oxide levels. These changes will ultimately result in cavernosal smooth muscle contraction, which might be a contributing factor to PE.[100,101]

Increased serum leptin levels

Leptin was discovered in 1994 as the product of the obese (*ob*) gene. Its primary role is to provide information on the amount of body fat to the hypothalamus, thereby modulating the CNS function that regulates food intake and energy balance.[102] Serum leptin levels in patients with PE were significantly higher than those in healthy controls and were negatively related to the IELT. In addition, the use of citalopram to treat PE resulted in the reduction of serum leptin levels.[103,104]

Varicoceles

An association was found between varicoceles and PE in patients consulting for sexual dysfunction.[105] The exact mechanism(s) linking varicoceles with PE appears to be complex and difficult to explain. However, a number of studies[106–108] have speculated that varicoceles may lead to intrapelvic congestion and prostatic inflammation, which could be the primum movens for the onset of PE, at least in some subjects. It has been reported that varicoceles are associated with an underlying systemic venous abnormality and with an increased diameter of the prostatic venous plexus in particular.

Gat *et al.*[109] demonstrated the presence of a venous blood reflux from the high pressure testicular venous drainage system to the low pressure prostatic drainage system through a direct communication represented by the deferential vein and the vesicular plexus. This communication between the testicular and the prostatic venous systems justifies the backflow of venous blood from the testis to the prostate leading to intrapelvic venous congestion and consequently symptoms of prostatitis. Patients with echographic evidence of high-grade varicocele had increased seminal interleukin-8 levels (a surrogate marker of nonbacterial prostatitis) and a higher prevalence of echographic signs of prostate inflammation.[110] In addition, there was an association between any degree of echographic varicocele and symptoms of prostatitis, as measured by the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) scoring.[111,112]

Other sexual dysfunctions

PE coexists in 30%–50% of patients complaining of erectile dysfunction (ED).[43,113,114] PE and ED may form a vicious cycle, where a man trying to control his ejaculation instinctively reduces his level of excitation (which may lead to erectile loss), or where a man trying to achieve an erection basically attempts to do so by increasing his excitation and arousal (which can lead to PE). Furthermore, ED may be superimposed with PPE by efforts to minimize sexual excitement. PE and ED may further be linked by the fact that lack of ejaculatory control may generate reactive ED, due to anxiety arising from poor sexual performance.[115]

Althof *et al.*[7] showed that men with ED may require higher levels of manual stimulation to achieve an erection or intentionally "rush" intercourse to prevent early detumescence of erection, resulting in PE. This may be associated with high levels of performance anxiety related to their ED, which serves to increase PE. Hypoactive sexual desire may lead to PE due to an unconscious desire to abbreviate unwanted penetration. Diminished sexual desire may also be a consequence of chronic frustrating PE. Low sexual desire may be due to the lack of sexual arousal present in some cases of ED.[115]

CONCLUSIONS

Premature ejaculation is a complex medical condition that is incompletely characterized despite the recently witnessed advances in the study of men's health. The ambiguity surrounding an agreed-upon definition for PE has hindered our understanding of its true worldwide prevalence rates. However, the recently developed evidence-based definitions by international societies aim to provide a solid platform for further research into this complex condition.

Further, the recent classification of PE into four distinct subtypes allows for a better delineation of the disorder and helps in our understanding of the pathoetiologic processes surrounding its occurrence. As a result, research efforts have started to unravel the interplay between the central and peripheral nervous systems that occurs during ejaculation and how derangement in neurotransmission may lead to persistently early ejaculations. Understanding the various psychologic and biologic factors that have been recognized in the etiopathogenesis of PE will help clinicians to effectively treat it.

AUTHOR CONTRIBUTIONS

MAE contributed to data search and drafting the manuscript. AM contributed to drafting and reviewing the manuscript. RS contributed

to critically revising the manuscript. All authors read and approved the final manuscript and agreed with the order of presentation of the authors.

COMPETING INTERESTS

All authors declared no competing interests.

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