



# The correlation between premature ejaculation and a high incidence of erectile dysfunction and its research progress: a narrative review

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**Background and Objective:** Premature ejaculation (PE) and erectile dysfunction (ED) are two common sexual symptoms of male sexual dysfunction that can strongly affect men's mental health and quality of life, and they often coexist. This aim of this study was to explore the causes and relationships between PE and ED, with a focus on the progression of PE accompanied by high-frequency ED. A deeper understanding of the causes and treatments for PE combined with ED will help improve clinical diagnosis and treatment.

**Methods:** We conducted a literature review of the most relevant articles related to the outlined topic in the PubMed, Google Scholar, and Web of Science databases. We did not limit language, covering both English and non-English publications, and include Chinese and English papers published between January 1996 and March 2024.

**Key Content and Findings:** The incidence of PE and ED increases with age. Approximately one-third of patients who complain of ED suffer from PE. Similarly, in a large-scale survey in the Asia-Pacific region, more than 30% of patients with PE reported concurrent ED. Various research findings indicate a strong correlation between PE and ED. Some scholars speculate that there is a vicious cycle between PE and ED. Men who attempt to control ejaculation can reduce the level of arousal, leading to ED, whereas men who try to achieve an erection will attempt to increase the level of arousal, which can lead to PE. This cycle of mutual influence may lead to reciprocal aggravation and persistence of sexual dysfunction in both parties. Although some studies have explored the relationship between PE and ED, the specific determinants and underlying factors have not yet been clarified.

**Conclusions:** There is a close interrelationship between PE and ED, and a vicious cycle may exist between the two. This cycle of mutual influence may lead to the mutual aggravation and persistence of both sexual dysfunctions. However, the specific determining factors and potential factors underlying the correlation between the two have not been clearly identified and require further exploration.

**Keywords:** Premature ejaculation (PE); erectile dysfunction (ED); male sexual dysfunction; andrology

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## Introduction

Premature ejaculation (PE) and erectile dysfunction (ED) are common sexual dysfunction symptoms in men. PE is described mainly by rapid ejaculation, which is characterized by ejaculation occurring almost always before or within approximately 1 minute of vaginal penetration and the inability to delay ejaculation during vaginal penetration (1). Nearly 22.7–39% of men worldwide suffer from PE (2). The diagnosis of PE is mainly based on the patient's sexual and medical history (3). The Chinese Index of Premature Ejaculation (CIPE), Premature Ejaculation Diagnostic Tool (PEDT), Index of Premature Ejaculation (IPE), Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD), International Index of Erectile Function (IIEF), Premature Ejaculation Profile (PEP), and other scales are ideal tools for PE diagnosis (4–11) (*Table 1*). IIEF, Female Sexual Function Index (FSFI), Golombok-Rust Inventory of Sexual Satisfaction (GRISS), Sexual Life Quality Questionnaire (SLQQ), Arizona Sexual Experience Scale (ASEX), Structure Interview on Erectile Dysfunction (SIEDY), and other scales are ideal tools for ED diagnosis (12–17) (*Table 2*).

ED is usually the inability of the penis to achieve or maintain an erection hard sufficient for satisfactory intercourse during sexual intercourse. Many studies have shown that there is a close relationship between PE and ED. Some scholars have hypothesized that there is a vicious cycle between PE and ED (18). Men's attempts to control ejaculation reduce the level of excitement and lead to ED, whereas men's efforts to maintain an erect state will increase stimulation and arousal, which in turn may lead to PE. The two situations with each other and lead to a vicious cycle. Although many studies have explored the relationship between PE and ED, the cause and mechanism are still unknown. Therefore, this review aims to discuss the underlying causes of PE and ED and the correlations between them, as well as the causes and treatments of PE combined with ED, which will help improve the clinical diagnosis and treatment and provide better treatment strategies. We present this article in accordance with the Narrative Review reporting checklist (available at <https://tau.amegroups.com/article/view/10.21037/tau-24-204/rc>).

## Methods

We performed a literature review of the most relevant articles on the outlined topic in the PubMed, Google

Scholar, and Web of Science databases, and we limited the search to January 1996 to March 2024 to ensure that we captured the latest relevant research. The search keywords included “PE”, “ED”, “PE combined with ED”, “male sexual dysfunction”, and “relationship, treatment, and epidemiology in combination with ‘PE’ and ‘ED’”. We also manually reviewed the article's reference list to include other papers related to the topic. We did not limit language, covering both English and non-English publications, and include Chinese and English papers published between January 1996 and March 2024. To ensure broad coverage of our review, we also translated and analyzed some non-English literature. Our screening process consisted of two stages: title/abstract screening and full-text screening. In the title/abstract screening stage, two independent researchers conducted a preliminary screening of the title and abstract of each document to exclude documents that were not relevant to the research topic. During the full-text screening phase, two investigators independently evaluated the full text of each article and screened against predetermined inclusion and exclusion criteria (*Table 3*).

## Epidemiology of PE combined with ED

Epidemiological data show that the global average prevalence of ED is 14–48% (18). According to long-term data from the MMAS study, the incidence rate (new cases per 1,000 men per year) of ED is 26 (19), and approximately 5–20% of men suffer from moderate to severe ED (20). The incidence of age-related ED is significant, ranging from 2% for 18–30-year-old and 48% for those over 70 years old of age (21). It is estimated that the number of ED patients in 2025 will be approximately 322 million (22). IIEF is the most widely used tool for diagnosing the presence and severity of ED and determining the efficacy of treatment in controlled clinical trials (23).

PE and ED often coexist (11), with a prevalence rate approaching 20% (24). Patients with PE and ED share many comorbidities, such as diabetes (25), thyroid disease (26), and lower urinary tract symptoms (LUTSs) (27). In clinical practice, the simultaneous occurrence of PE and ED is very common, and 50% of patients with PE patients also report ED (28). Similarly, Cilio *et al.* analyzed data from 1258 Europeans from 2005 to 2021 and reported that 25.9% of patients who visited the ED also had unreported PE, and patients with ED combined with PE were younger, had fewer comorbidities and had less severe ED (29).

**Table 1** PE diagnosis and assessment tools

Tool	Content	Description	References
1. CIPE	Ejaculation time; control ability; degree of bother; frequency	CIPE is a comprehensive assessment based on multiple dimensions. The total score is 20 points, with 4–8 points indicating severe, 9–12 points indicating moderate, 13–16 points indicating mild, and 17–20 points indicating asymptomatic	(4)
2. PEDT	Ejaculation time; frequency of delayed ejaculation; satisfaction with ejaculation time; impact on sexual life; psychological distress	Consisting of 5 questions with a total score of 20 points, with 13–20 points indicating severe PE, 11–12 points indicating moderate PE, 9–10 points indicating mild PE, and 0–8 indicating no symptoms	(5)
3. IPE	Intravaginal ejaculation latency time; control over ejaculation; satisfaction with sex life; anxiety associated with ejaculation	Each assessment item usually uses a Likert scale from 1 to 5 or 1 to 7. The scores of each assessment item are summed to obtain a total score. The lower the total score, the more severe is the PE	(6)
4. MSHQ-EjD	The impact of ejaculation ease; control; satisfaction; ejaculation function on quality of life	The total score is 20 points, with 4–8 points indicating severe ejaculation disorder, 9–12 points indicating moderate ejaculation disorder, 13–16 points indicating mild ejaculation disorder, 17–20 points indicating no ejaculation disorder	(7)
5. IIEF	EF; ejaculation function; sexual satisfaction; SD; OS	Multidimensional questionnaire, including 15 questions, with 1–10 points indicating severe ED, 11–16 points indicating moderate, 17–21 points indicating mild to moderate ED, 22–25 points indicating mild ED, and 26–30 points indicating a normal status	(8)
6. PEP	Control over ejaculation; satisfaction with sexual intercourse; interpersonal difficulties; distress related to ejaculation	The rating scale is based on the patient's responses to a series of questionnaires. Each question has a rating system, usually a Likert scale from 1 to 5 or from 1 to 7	(9)
7. Mental health assessment tools (e.g., HADS, PHQ-9)	To assess mental health conditions, such as anxiety and depression, which are often associated with sexual dysfunction	HADS consists of 14 items with a total score ranging from 0 to 21 points; PHQ-9 consists of 9 items with a total score ranging from 0 to 27 points	(10,11)

PE, premature ejaculation; CIPE, Chinese Index of Premature Ejaculation; PEDT, Premature Ejaculation Diagnostic Tool; IPE, Index of Premature Ejaculation; MSHQ-EjD, Male Sexual Health Questionnaire for Ejaculatory Dysfunction; IIEF, International Index of Erectile Function; EF, erectile function; SD, sexual desire; OS, overall satisfaction; ED, erectile dysfunction; PEP, Premature Ejaculation Profile; HADS, Hospital Anxiety and Depression Scale; PHQ-9, Patient Health Questionnaire-9.

### Causes of PE combined with ED

There is a strong relationship between PE and ED, and these two sexual dysfunctions may cooccur. Despite being two separate sexual function problems, PE and ED can interact with each other, causing one problem to occur or exacerbating the other; they can also exist independently and be caused by different factors. A man may experience PE and ED at the same time, but the two problems are relatively independent and do not directly affect the other.

### The correlation between PE and ED

The Global Study of Sexual Attitudes and Behaviors (GSSAB), an international survey of various aspects of sex and relationships among adults aged 40–80 years in 29 countries around the world, revealed significant correlations between PE and ED in the regions that studied sex (30). Chin *et al.* (31) conducted a cross-sectional observational study on the coexistence of PE and ED. The prevalence of ED among 483 participants in the PE group was 30.2%,

**Table 2** Sexual dysfunction diagnosis and assessment tool

Tool	Content	Description	References
1. IIEF	EF; ejaculation function; sexual satisfaction; SD; OS	Multidimensional questionnaire including 15 questions, with 1–10 points indicating severe ED, 11–16 points indicating moderate ED, 17–21 points indicating mild to moderate ED, 22–25 points indicating mild ED, and 26–30 points indicating normal status	(12)
2. FSFI	Desire; arousal; lubrication; orgasm; satisfaction; pain	Used mainly to evaluate female sexual function, but can also be used indirectly to understand the sexual function problems of partners. It contains 19 questions. With a total score ranging from 2 to 36 points	(13)
3. GRISS	Sexual dysfunction; frequency of sexual intercourse; SD level; satisfaction, etc.	A multidimensional questionnaire for assessing sexual dysfunction in couples, divided into male and female versions	(14)
4. SLQQ	SD; arousal; orgasm; frequency of sexual intercourse; satisfaction, etc.	A assesses an individual's OS with their sex life across multiple dimensions, with a total score ranging from 7 to 35 points	(15)
5. ASEX	Sex drive; arousal; penile erection; ability to reach orgasm; orgasm satisfaction	A useful international tool to assess sexual dysfunction in people suffering from mental illness. Sexual dysfunction is defined as follows: (I) a total ASEX score of $\geq 19$ ; (II) any item with a score of $\geq 5$ ; or (III) any three items with a score of $\geq 412$	(16)
6. SIEDY	Includes three main domains: organic factors; psychological factors; relational factors	The only validated structured interview that is able to simultaneously identify and quantify pathogenic structures present in subjects with ED. The higher the score, the greater is the impact of the factors in this domain on ED	(17)

IIEF, International Index of Erectile Function; EF, erectile function; SD, sexual desire; OS, overall satisfaction; ED, erectile dysfunction; FSFI, Female Sexual Function Index; GRISS, Golombok-Rust Inventory of Sexual Satisfaction; SLQQ, Sexual Life Quality Questionnaire; ASEX, Arizona Sexual Experience Scale; SIEDY, Structure Interview on Erectile Dysfunction.

**Table 3** The search strategy summary

Items	Specification
Date of search	April 15, 2024
Databases and other sources searched	PubMed, Google Scholar, Web of Science
Search terms used	“PE”, “ED”, “PE combined with ED”, “male sexual dysfunction”, and “relationship, treatment, and epidemiology in combination with ‘PE’ and ‘ED’”
Timeframe	January 1996–March 2024
Inclusion and exclusion criteria	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>● Focusing on the relationship between PE and ED</li> <li>● Not limit language, covering both English and non-English publications, and include Chinese and English papers published between January 1996 and March 2024</li> <li>● Peer-reviewed, published literature including review papers</li> </ul> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> <li>● Main topic not related to PE and ED</li> <li>● Editorials, letters to the editors, and abstracts</li> <li>● Papers before 1996</li> </ul>
Selection process	In the title/abstract screening stage, two independent researchers conducted a preliminary screening of the title and abstract of each document to exclude documents that were not relevant to the research topic. During the full-text screening phase, two investigators independently evaluated the full text of each article and screened against predetermined inclusion and exclusion criteria

PE, premature ejaculation; ED, erectile dysfunction.

the prevalence of lifelong PE among 1,893 participants in the ED group was 4.1%, and the prevalence of acquired PE was 18.0%. In addition, Corona *et al.* (32) reported that the prevalence of ED in men with PE (31.9%) was higher than that in men without PE (11.8%), confirming the high prevalence of both PE and ED, indicating that both sexual symptoms are susceptible to each other. Chin *et al.* (31) also reported that the majority (77.8%) of patients with lifelong PE and ED and one-third of patients with acquired PE and ED reported ED after PE, suggesting that PE may contribute to ED to some extent.

The Global Sexual Attitudes and Behaviors Study assessed sexual disorders among 13,618 middle-aged and older men from 29 countries worldwide and reported that among men who reported PE (n=1,257), 62.2% had accompanying ED, correspondingly, having ED increases the chance of having PE 4–11 times (30). Among men complaining of ED (n=3,549), 22.0% had comorbid PE, which indicates that PE may be secondary to ED. These findings suggest that PE and ED are related and influence each other.

Some scholars have proposed the hypothesis of a vicious cycle between PE and ED (33). PE patients may try to reduce their sexual arousal to delay ejaculation (31) or attempt to control ejaculation through rapid erection, which may lead to ED; early erection subsidence after ejaculation in some PE patients may cause symptoms of ED (34). People with ED may require intense stimulation to achieve and maintain an erection (33). To complete sexual intercourse during a normal erection, ED patients may speed up the ejaculation process, which may lead to PE. In addition, psychosocial factors related to PE or ED affect both (33), and PE can lead to unsatisfactory sexual relationships, increase sexual stress and anxiety, and affect erectile function (EF). ED causes sexual anxiety and tension in patients, which in turn affects ejaculation control and the occurrence of PE.

Corona *et al.* (32) reported a direct relationship between the risk of PE and ED and symptoms of anxiety and depression. In addition, the risk of PE-related ED is also greater if the patient is not in a stable relationship (35). The presence of organic diseases such as diabetes, hypertension, and dyslipidemia shows the opposite trend. Therefore, PE related to ED may be more attributable to psychological factors than to organic factors (32).

PE can also be superimposed on ED when it develops as an adaptive mechanism that masks ED, and similarly, ED can also occur on top of PE when PE generates anxiety

due to poor sexual performance (33). In conclusion, ED and PE are not distinctly separate entities. Therefore, they should not be categorized into rigid diagnostic figures, but should be viewed from a dimensional perspective (32). Understanding this dimensional perspective might help sexual health care professionals provide the most appropriate therapeutic approach. Colonnello *et al.* (28) introduced another classification entity, loss of control of erection and ejaculation (LCEE), as a disorder that considers the two sexual symptoms to be closely related. Introducing LCEE is expected to reduce the risk of incorrect treatment strategies that do not consider the adverse effects of PE treatments on EF. This including avoiding treatments that might lead to penile hypoesthesia or female genital anesthesia due to transvaginal contamination from topical anesthetic (36). The IIEF includes five dimensions: EF, ejaculatory function (OF), sexual desire (SD), intercourse satisfaction (IS), and overall satisfaction (OS) (37). Use of the IIEF allows for a comprehensive assessment of EF and ejaculatory control, ensuring that both aspects are considered in patients presenting with symptoms of sexual dysfunction. Using the IIEF to assess EF and OF simultaneously is critical for diagnosing LCEE. Clinicians can more accurately identify and manage patients with LCEE, ensuring that treatment options comprehensively address both erectile and ejaculatory problems.

### *Mechanism of PE and ED*

The co-occurrence and relative independence of PE and ED means that PE and ED may be caused by different causes and have a certain degree of independence. The two can coexist but are not necessarily directly responsible for each other, meaning that improving PE will not necessarily automatically improve ED. PE and ED occur for a variety of reasons, with a focus on the following aspects.

### **Neuromodulation imbalances**

PE and ED may be related to regulatory imbalances between the central nervous system, the autonomic nervous system, and the neural pathways involved in erection and ejaculation. The most relevant causative factor is the pathology of the neurovascular bundles that control the complex mechanisms of the cavernous erectile response (38). EF is regulated by the relaxation and contraction functions of the smooth muscle cells (SMCs) of the corpus cavernosum. The smooth muscle and vascular endothelial cells in the corpus cavernosum undergo apoptosis, and

excessive collagen deposition can lead to fibrosis (39).

### **Blood flow issues**

Vascular dysfunction, arteriosclerosis, and insufficient blood supply may affect the quality and duration of erections. Vascular endothelial dysfunction is currently recognized as an important pathological mechanism of ED. Reduced nitric oxide production or sensitivity may contribute to ED. In vasogenic ED, endothelial dysfunction due to vascular disease reduces endothelial NO levels and sensitivity to this signaling molecule (40). There is evidence that the presence of ED also increases the risk of future cardiovascular disease (41). Hypercholesterolemia (HC)-induced ED is thought to be related to HC-induced oxidative stress damage to vascular endothelium and erectile tissue (42).

### **Physiological and psychological factors**

A cross-sectional study revealed that the severity of ED increases with prostate size, which may be related to the compression of blood flow caused by prostatic hypertrophy (43). And the compression of erectile nerves by prostatic hypertrophy (44). Age-related ED is attributed primarily to increased oxidative stress and endothelial dysfunction in the penis. Most men with depression have some degree of ED (45). In addition, a decrease in testosterone may also affect SD and EF. In the past, the relationship between urogenital infections and male sexual dysfunction has been largely overlooked (46). A previous study revealed that the prevalence of PE in men is correlated with the occurrence of chronic prostatitis. Liang *et al.* (47) reported a high prevalence of PE in patients with chronic prostatitis. Prostate examination should be considered during the evaluation of patients with PE. Excessive foreskin, penile curvature, and urethral stricture may also affect erection and ejaculation.

### **Iatrogenic factors: diseases, diagnosis, and treatment methods**

The side effects of drugs such as selective serotonin reuptake inhibitors (SSRIs) and 5-alpha reductase inhibitors can also lead to impaired sexual function (48). According to previous studies, the risk of ED is increased after transrectal ultrasound-guided prostate biopsy (49) and open urethroplasty. Pelvic surgery, radical prostatectomy (50), radical cystectomy and urethral diversion (51) may also have a negative impact on EF (19). The main cause of ED after radical prostatectomy is damage to the cavernous nerves that control erection and extend along the anterolateral side

of the prostate. Cavernous nerves regulate the erect state of the penis by controlling the relaxation and contraction of cavernous SMCs (52). According to research, up to 80% of prostate cancer patients suffer from ED after radical prostatectomy (50). Chen *et al.* (53) found that for benign prostatic hyperplasia (BPH) patients without sexual dysfunction, prolonged transurethral resection of prostate (TURP) before TURP may lead to an increased incidence of ED, and patients with smaller seminal vesicle volumes after TURP have a higher incidence of PE.

Nonsurgical treatments for prostate cancer, such as external beam radiation therapy, brachytherapy, or androgen deprivation therapy, may also impair EF (54) possibly through radiation-induced intraarterial microvascular arteritis, preexisting atherosclerosis, or accelerated body fibrosis (55).

### **Progress in the treatment of PE combined with ED**

The International Society for Sexual Medicine (ISSM) (56) and the European Association of Urology believe that every man with PE should be adequately screened for ED and treated first whenever it presents. Because ED and PE can coexist in the same patient within the entity of LCEE, both symptoms should be investigated and treated appropriately (57). We suggest evaluating the couple as a whole and using dedicated and validated psychometric tools (57) such as the Female Sexual Distress Scale-Revised-Premature Ejaculation Questionnaire (58), the male versions of the Orgasmometer scale (59) and the female versions of the Orgasmometer scale (60). The Guidelines recommend that for men who suffer from both ED and PE, treatment should begin with improving EF (56). A survey also suggests that men are less likely to seek treatment for PE than for ED (61). Chin *et al.* (31) believed that in the case of acquired PE and ED, the probability of ED leading to PE is approximately three times greater than that of PE leading to ED, so treating ED may improve the severity of PE. This relationship may be explained by the improved quality of erections after treatment of ED, which prolongs sexual intercourse and helps reduce the symptoms of PE (62).

### **Behavioral psychotherapy**

Lifestyle and risk factor changes must precede drug therapy or psychotherapy. Squeezing technology can delay ejaculation to a certain extent, and pelvic floor muscle

training can also increase muscle strength to improve sexual function (63). Physical exercise is the most effective way to increase nitric oxide and strengthen endothelial function (64). Moderate to vigorous intensity aerobic exercise has been reported to improve ED in patients (65). In short, behavioral therapy is considered promising and psychotherapy also has a certain effect, but this treatment takes time and has different effects (66).

### **Medical treatment**

Drug therapy is still the first-line treatment (19). SSRIs can be used to delay ejaculation, and PDE5 inhibitors can be used to improve EF. In the past, SSRIs were mostly used to treat PE. According to research, SSRIs are expected to increase IELT by 2.6 to 3 times (67). Waldinger *et al.* (68) conducted a placebo-controlled study of SSRI treatment for PE and found that the IELT of patients in the paroxetine treatment group increased from 30 seconds to 10 minutes. SSRIs were shown to ameliorate the disruption of central serotonin neurotransmission in PE patients (69). Daily SSRI treatment has a greater delayed ejaculation effect than does on-demand SSRI treatment but may increase serotonin adverse effects and drug dependence (70). Considering the high frequency of side effects and off-label use of SSRI drugs, researchers have specifically developed short-acting, on-demand dapoxetine in recent years. Dapoxetine 30 or 60 mg taken “as needed” significantly increases the vaginal ejaculation latency. Compared with placebo patients, most patients reported significantly improved outcomes after treatment with dapoxetine, indicating better control of ejaculation, greater satisfaction with ejaculation, and less ejaculation-related pain (71).

PDE5 inhibitors are first-line treatment options for ED, can help improve EF and may also help delay ejaculation (72). Currently, PDE5 inhibitors are mainly used to treat cavernous nerve injury (CNI)-ED, but clinical studies have shown that sildenafil is only effective in 35% of CNI-ED patients (73). A possible reason for this finding is that a series of complex pathological changes, such as cavernous fibrosis and cavernous smooth muscle atrophy, occur after the penis loses nerve control.

The use of proerectile drugs after RP is helpful in improving EF after surgery. Trials have shown that patients who receive PDE5 inhibitor or intracavernous injection have a higher recovery rate of EF after RP (74). Patients who do not respond to oral medications may receive intracavernous injections (75). Intracavernosal injection of alprostadil alone

is also a better treatment option. It is more effective when combined with other vasoactive drugs such as papaverine and phentolamine, and its efficacy can reach be as high as 90% (76). However, there are disadvantages such as urethral pain and increased risk of urinary tract infection (77).

### **Physiotherapy**

Low-intensity extracorporeal shock wave therapy (LI-ESWT) is an effective and noninvasive technique for revascularizing and restoring vascular function (78). The main advantage of Li-ESWT treatment is the restoration of natural erections and it is the only ED drug with curative potential (79). PRP and low-intensity shock waves used together have been shown to improve patients' ED (80). In addition, the vacuum erection device (VED) creates negative pressure in the penis and increases blood flow to produce an erection. In comparison, VED is more likely to be provided to elderly patients. It has high sexual satisfaction and an efficacy of up to 90% (81). However, there are also adverse reactions such as ejaculation obstruction and annular pain (55) and the underlying mechanisms of these treatments remain to be further studied. The ischiocavernosus and bulbocavernosus muscles play key roles in the discharge stage of ejaculation. Physical exercise therapy and neuromuscular electrical stimulation can enhance the contraction strength of the perineal muscles to control the ejaculation reflex, which can effectively improve patients with PE (82). In addition, transcutaneous posterior tibial electrical stimulation therapy can also inhibit ejaculation.

### **Surgical treatment**

For severe PE and ED, surgical treatment options, including selective dorsal penile nerve resection, penile subcutaneous implantation of biological flaps, glans penis injection of hyaluronic acid, pelvic floor muscle neuromuscular electrical stimulation, transcutaneous posterior tibial nerve stimulation and penile prosthesis implantation, are attracting increasing attention. One study reported that surgical reduction of the prostate can improve ED (83). A randomized controlled study comparing the effects of holmium laser prostatectomy and transurethral resection of the prostate on sexual function showed that the EF domain of IIEF after transurethral resection of the prostate was lower in the transurethral resection group. slightly improved (84). For patients who have failed medical therapy or who want a permanent solution, surgical implantation of

a penile prosthesis may be considered, but there are risks of infection, necrosis, postoperative shortening, and poor glandular swelling (48). Circumcision and selective dorsal neurotomy can effectively prolong the ejaculation time, but their efficacy has not been scientifically and systematically evaluated. Glans penis enlargement surgery provides a less invasive treatment method that can reduce the sensitivity of the glans penis and avoid serious side effects, but prompt retreatment is needed (85).

### **Comprehensive treatment**

A combination of multiple treatments may still be the most effective way to treat such complex sexual symptoms, with drug intervention or combination therapy being more effective than nondrug intervention (86). According to research, combined therapy can significantly improve patients' ejaculation control and EF. For example, statins combined with lifestyle changes may reduce ED symptoms compared with drug treatment alone (87). Combined treatment with psychological intervention and PDE5 inhibitors is better than PDE5 inhibitors alone or psychological intervention alone (88). Acupuncture combined with psychological intervention is also better than psychotherapy alone (89). There is evidence that behavioral techniques such as "stop-start" and "pinch" can be used in conjunction with topical anesthetics such as lidocaine-prilocaine cream to extend and optimize the treatment effects (90).

### **Emerging treatments**

In recent years, many treatment methods and technologies have emerged for PE and ED. Shechter *et al.* (91) proposed a novel approach to extend the on-demand duration to address lifelong PE by electrically stimulating the ejaculatory muscles using the In2 patch. This approach holds promise as a potential on-demand, noninvasive and drug-free treatment for PE. Injection of hyaluronic acid for glans penis enlargement treatment PE can significantly prolong the ejaculation time with fewer adverse reactions, but its effectiveness still needs further verification and requires high-level technical skills from doctors (92). Ma *et al.* (93) proposed a novel behavioral therapy for the treatment of primary premature ejaculation (PPE) through regular penile root masturbation (PRM). After 3 months of PRM training in nine patients, the median vaginal ejaculation latency increased from 60 to 180 seconds,

indicating that PRM may be effective in treating PPE. This approach has a short-term therapeutic effect, but further randomized controlled trials are still needed to verify its efficacy.

Jang *et al.* (42) reported that the herbal formula KH-204, which has antioxidant and hypolipidemic effects could minimize oxidative stress and improve high cholesterol levels by restoring endothelial dysfunction in a rat model of HC-induced ED. In patients with ED caused by blood pressure, KH-204 may be a potential treatment drug for ED. In patients with ED caused by cavernous nerve damage, brain-derived nerve growth factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) can promote the regeneration of cavernous nerves. Emerging treatments include small molecule drugs, stem cell therapy (SCT), microenergy therapy, and platelet-rich plasma (PRP) therapy (94). However, there are inevitable shortcomings, such as drug toxicity and side effects that require further monitoring; the long-term risks and optimal dosage of SCT are unclear, and the difficulty in obtaining autologous stem cells, low expansion capacity, and high cost also limit its use. Ruffo *et al.* (80) combined low-energy shock wave LISW and PRP injection for the treatment of ED and found that patient's IIEF-5 scores significantly improved, indicating improvement in the patient's EF. However, PRP has no standard protocol for its preparation and application, and there is no unified method for evaluating the results. Further research is still needed to illustrate the effectiveness of this method.

In addition, multiple microRNAs (miRNAs) have protective effects on EF and improve the effects of ED. However, the expression of some of these miRNAs is usually down-regulated in ED. Study has found that the expression level of miR-21 is downregulated in ED animal models, which may be related to increased fibrosis and SMC apoptosis (95). Targeting the recruitment of these underrepresented miRNAs may be an effective therapeutic option. Currently, the most studied methods of miRNA supplementation in ED mainly include the delivery of corresponding miRNAs through stem cells or exosomes (96). Chen *et al.* (97) first analyzed the impact of exosomes on improving ED in 2017. Peng *et al.* (98) found that exosomes released from Schwann cells promoted the neuroregeneration of MPG and MPG cavernous nerves, which may provide potential therapeutic options for ED treatment but still require further *in vivo* verification.

Patients have a high probability of suffering from ED after radical prostatectomy. A new generation of



neuroprotective drugs or cell therapies given before and after surgery may be able to limit damage at an early time point and protect patients' sexual function. In an animal trial by Arthur Burnett's team, the administration of glial growth factor 2 (GGF2) under the skin of rats before and after CNI increased intracavernous pressure by more than half upon nerve stimulation, which is a sign of EF. Carol Podlasek, a researcher at the University of Wisconsin-Madison, showed that rats receiving Sonic Hedgehog (SHH) were protected from damage to the cavernous nerve and its effects on sexual function by using a nanotech hydrogel system applied to the cavernous nerve and penis during surgery. Podlasek's team also reported that this drug can both provide neuroprotection against cavernous neurodegeneration and promote neuronal regeneration after injury (99).

Ji *et al.* (100) studied the role of mechanically regulated YAP/TAZ in ED and revealed that mechanically regulated YAP/TAZ signaling in SMCs upregulates adrenomedullin transcription, thereby relaxing SMCs to maintain erections. These findings also lay the foundation for exploring the mechanistic-YAP/TAZ-adrenomedullin axis as a potential target for the treatment of ED.

## Conclusions

PE combined with ED results in physical and psychological distress to patients, and has a great negative impact on their sexual life and quality of life. Research into the causes of PE and ED will help us better understand the development of this condition. In our previous article, we discussed the correlation between PE and ED and described a mutual influence between PE and ED, but the specific determining factors and potential factors have not been clearly identified. At present, a comprehensive treatment approach may be the most effective approach for this condition, but the treatment effect and prognosis still require further research and evaluation to provide better treatment options and improve patients' prognosis. In addition, maintaining a healthy lifestyle and quitting smoking can also help maintain sexual function. Progressive research on emerging treatments also offers hope for patients with PE and ED, but further validation and research are still needed.

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