

Review Article

# Prostatic Disease and Sexual Dysfunction

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Prostatitis and benign prostatic hyperplasia (BPH) are common prostatic diseases. Furthermore, the incidence of prostate cancer has recently shown a rapid increase, even in Korea. Pain caused by prostatitis may induce sexual dysfunction, including erectile dysfunction and ejaculatory disturbance. And BPH itself, or treatments for BPH, may affect sexual function. In addition, with increased detection of localized prostate cancer, surgical treatments and radiation therapy have also increased, and the treatments may cause sexual dysfunction. Aging is also an important factor in the deterioration of the quality of life of men. Deterioration of quality of life caused by prostate diseases may be affected not only by the prostate diseases themselves but also by the sexual dysfunction caused by the prostate diseases secondarily. Thus, consideration of these points at the time of treatment of prostate disease is required. Therapies suitable to each condition should be selected with an understanding of the close association of prostate diseases and associated sexual dysfunction with the quality of life of males.

**Key Words:** *Erectile dysfunction; Prostatic hyperplasia; Prostatic neoplasms; Prostatitis*

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## INTRODUCTION

Prostatitis and benign prostatic hyperplasia (BPH) are common prostatic diseases; the incidence of prostate cancer has recently shown a rapid increase, even in Korea [1]. Pain caused by prostatitis, which is most commonly localized to the perineum, suprapubic area, and penis, may induce sexual dysfunction, including erectile dysfunction (ED) and ejaculatory disturbance, and BPH itself, or treatments for BPH, may affect sexual function. In addition, with increased detection of localized prostate cancer, surgical treatments and radiation therapy have also increased, and the treatments may cause sexual dysfunction. With aging, such prostatic diseases occur simultaneously with sexual dysfunction [2-5], which is an important factor in the deterioration of the quality of life of men [6]. Accordingly, the association of prostatic diseases with sexual dysfunction was examined in the present article.

## EFFECTS OF PROSTATITIS ON SEXUAL FUNCTION

Prostatitis is the most common prostatic disease in men younger than 50 years of age and the third most common

urologic diagnosis in men older than 50 years of age [7]. The US National Institutes of Health (NIH) announced a new definition and classification for prostatitis, which has been widely accepted. Patients are divided into four categories by the NIH: acute bacterial prostatitis, chronic bacterial prostatitis, chronic prostatitis/chronic pelvic pain symptoms (CP/CPPS), and asymptomatic inflammatory prostatitis. CPPS is the most common presentation, particularly perineal, testicular, penile, and ejaculatory pain. Other genitourinary tract complaints include sexual dysfunction and voiding complaints [8,9].

In a multicenter study from China, 1,786 patients with chronic prostatitis participated in a survey using the NIH Chronic Prostatitis Index and five questions taken from the International Index of Erectile Function [10]. The overall prevalence of sexual dysfunction in these patients was 49%, and the prevalence of premature ejaculation and ED accounted for 26% and 15%. The conclusion of this study was that the rate of prevalence of sexual dysfunction in Chinese men with chronic prostatitis is high. In addition, age was associated with the prevalence of sexual dysfunction.

Considering the role of the prostate gland during ejacu-

lation, a clinical study from Italy researched the prevalence of chronic prostatitis in men with premature ejaculation [11]. Due to a higher occurrence of sexual dysfunction and infertility in male chronic prostatitis patients with premature ejaculation than in the control group, the study supposed a role for prostate inflammation in the pathogenesis of premature ejaculation. Brown et al reported on the case of a 31-year-old male with prostatitis and premature ejaculation who showed improvement by ciprofloxacin treatment [12]. A study of 145 men with premature ejaculation demonstrated the effectiveness of the treatment in patients primarily presenting with sexual dysfunction and without symptoms of prostatitis [13]. Ninety-five (64.8%) of these patients had chronic bacterial prostatitis and 74 were given antibiotics for 1 month according to the results of their culture and sensitivity test. After 1 month of antibiotic treatment, 74 patients with positive cultures had sterile final cultures. Sixty-two (83.9%) patients showed increases in their ejaculatory latency time and reported good control of their ejaculation.

Few studies have reported on the association of CP/CPPS with ED. Nonetheless, CP/CPPS is believed to exert adverse effects on the overall quality of life, and, consequently, to induce ED.

## EFFECTS OF BPH ON SEXUAL FUNCTION

Lower urinary tract symptoms (LUTS) are common in aging individuals with BPH, the primary cause of LUTS in men over 50. The presence of histological BPH at autopsy is approximately 8% in men ranging in age from 31 to 40 years, 50% in those ranging in age from 51 to 60 years, 70% in those ranging in age from 61 to 70 years, and 90% in those ranging in age from 81 to 90 years [14]. LUTS range from nocturia, urinary frequency, and urgency to a decreased and intermittent stream with incomplete bladder emptying and commonly result in a decreased quality of life.

Findings from epidemiological, pathophysiological, and clinical studies indicate that many of these men also suffer from declining sexual function, especially those undergoing treatment for their BPH-related urinary symptoms. Although urinary symptoms and quality of life may improve with BPH therapy, the resulting effects on sexual function vary according to medical, surgical, and minimally invasive approaches and have not been consistently reported.

The incidence of both BPH and sexual dysfunction increases with aging, which suggests the possibility of an association of the two diseases. Similarly, in a study of 1216 patients in Korea, Yong et al reported that the score for sexual function decreased with severity of LUTS and aging of patients [2].

### 1. Epidemiological evidence

Data from these studies have demonstrated consistent and compelling evidence for an association between LUTS/BPH and sexual dysfunction in aging men that is in-

dependent of the effects of age, other co-morbidities, and various lifestyle factors.

Data from the National Health and Social Life Survey (NHSLs), a population-based representative sample of US adults ranging in age from 18 to 59 years, demonstrated a high prevalence of sexual dysfunction in men (31%) and women (43%) [15]. Increasing age in men was associated with significantly higher prevalence rates of ED. Results of the NHSLs also indicated that LUTS were a significant predictor of ED.

A study of 2,476 Spanish men ranging in age from 25 to 70 years indicated that the prevalence of ED was 12% to 19%, with the rate dependent on the self-administered questionnaire used for assessment of sexual function [16]. Age-adjusted risk factors for ED included LUTS, rheumatic disease, circulatory disease, lung disease, diabetes, and hypertension.

A population-based multinational (4 countries) study, the UrEpik study, investigated the relationship between LUTS and sexual dysfunction in 4,800 men ranging in age from 40 to 79 years [17]. After adjustment for age and country, men with diabetes, hypertension, or LUTS had a greater risk of ED.

Some subsequent large-scale studies examining the relationship between LUTS and sexual dysfunction controlled not only for the effect of age but also for various medical co-morbidities and lifestyle factors (Table 1).

In the most comprehensive study conducted to date on the association of age, LUTS, concomitant co-morbidities, and male sexual dysfunction, the MSAM-7 analyzed survey results from 12,815 men ranging in age from 50 to 80 years in the United States and 6 European countries [19]. Overall, the results of this study strongly confirmed the relationship between LUTS and sexual dysfunction in men, independent of the effects of age, other co-morbidities, and lifestyle factors. Sexual activity, which was reported as a mean of 5.9 times each month for the total sample of men,

**TABLE 1.** Prevalence of sexual dysfunction and significant comorbidities of BPH

Study	Country	Prevalence	Comorbidities
Braun et al [3]	Germany	19%	LUTS, hypertension, diabetes
Martin-Morales et al [16]	Spain	12-19%	LUTS, CVD, diabetes, heart disease, hypertension
Boyle et al [17]	4 countries	21%	LUTS, diabetes, hypertension
Blanker et al [18]	Netherlands	3% (50-54 yr); 26% (70-78 yr)	LUTS, obesity, CVD, COPD
Rosen et al [19]	7 countries	49%	LUTS

LUTS: lower urinary tract symptoms, CVD: cardiovascular disease, COPD: chronic obstructive pulmonary disease

showed a significant decrease with increasing age and the severity of LUTS. Sexual dysfunction also showed a significant association with the severity of LUTS ( $p < 0.001$ ). Logistic regression analysis, which controlled for age, medical co-morbidities, tobacco use, and alcohol consumption, demonstrated that age and severity of LUTS were independent risk factors for sexual dysfunction.

The association of LUTS with sexual dysfunction in males after middle age has been demonstrated. However, to provide evidence for such results, studies characterizing the mechanism of the mediating effects of LUTS on sexual function are required.

## 2. Pathophysiological mechanisms

Increased smooth muscle tone in the prostate capsule and bladder neck can contribute to LUTS associated with BPH. Increased smooth muscle tone in the prostate in BPH is related to stimulation of  $\alpha_1$ -adrenergic receptors [20]. Other receptors that have been identified in human prostate tissue and that may play a role in LUTS associated with BPH include dopaminergic, muscarinic, serotonergic (5-HT<sub>2A</sub>), and histaminergic (H<sub>1</sub>) receptors [21]. Nitric oxide (NO), which is present in the human prostate [22] and modulates prostatic smooth muscle tone [23], may also have a role in the pathophysiology of LUTS associated with BPH.

In the penis, noradrenaline and endothelins are putative promoters of penile detumescence (contraction), whereas NO promotes penile erection (relaxation). Penile erection involves acetylcholine-mediated relaxation of the corpus cavernosal smooth muscle, with neurogenic NO considered the main factor responsible for rapid relaxation, and endothelial NO is thought to play a role in maintenance of the relaxed state [24,25].

**1) Alpha 1-Adrenergic receptors:** An imbalance in autonomic control of smooth muscle contraction and relaxation may play an important role in both LUTS and sexual dysfunction.  $\alpha_1$ -Adrenergic receptors are known to play an important role in mediating the tone of smooth muscle cells in various tissues. Various  $\alpha_1$ -adrenergic receptor subtypes, including  $\alpha_{1A}$ - and  $\alpha_{1D}$ -receptors in prostatic stromal cells, urethra, and bladder, have been identified in the lower urinary tract [26,27].

Penile detumescence and erection are dependent on the balance between contraction and relaxation of the corpus cavernosum smooth muscle [28]. In ED, the balance favors contraction (detumescence) rather than relaxation (erection). Noradrenaline is involved in the contraction of penile tissues via activation of  $\alpha_1$ -adrenergic receptors in the penile vasculature and corpus cavernosum smooth muscle, with androgens possibly regulating the responsiveness of these receptors [29].

Adrenergic-mediated contraction of smooth muscle may also be regulated by Rho and Rho-associated kinase [30], which has been found in human prostatic smooth muscle cells [31] and the vas deferens of the mouse [32]. Results of other studies have suggested a possible role for the Rho/Rho kinase pathway in the mechanism of penile smooth

muscle contraction [33,34]. Thus, alterations in  $\alpha_1$ -adrenergic receptor-mediated smooth muscle tone and its regulators may be a common component involved in LUTS associated with BPH and sexual dysfunction.

**2) Endothelial dysfunction:** Endothelial dysfunction refers to impaired endothelium-dependent vasodilation resulting from decreased bioactivity of NO [35]. Endothelial dysfunction has been associated with aging, cardiovascular disease, diabetes, hypertension, and hypercholesterolemia. Possible mechanisms responsible for endothelial dysfunction include accelerated breakdown of NO by reactive oxygen species, alterations in antioxidant defense systems, and alterations in the activity or expression of the endothelial NO synthase (eNOS) enzyme [36]. In aging men, decreasing levels of testosterone and reductions in the conversion of testosterone to estradiol by the aromatase enzyme may contribute to deficits in eNOS-derived NO [37].

In prostatic tissue from men with BPH, decreased nitrergic innervation was demonstrated in comparison with that in normal prostate tissue [38], which suggests a possible role for NO in the pathophysiology of BPH. Studies in animals also suggest that NO plays a role in preventing the bladder contractions that result in bladder hyperactivity, as observed in LUTS [39-41].

**3) Sex hormones:** Dihydrotestosterone (DHT), which is more potent than testosterone and demonstrates a higher affinity for androgen receptors, is predominantly produced peripherally from testosterone via the enzyme 5 $\alpha$ -reductase. Androgen receptors, which are present in both the stroma and the epithelium of the prostate, as well as in most blood vessel endothelial cells, smooth muscle cells, and fibrocytes [42], may play a role in the interaction between the stroma and epithelium of the prostate. Age-related changes in circulating hormone levels and an imbalance in the testosterone/estrogen ratio may play a role in the pathophysiology of BPH and sexual dysfunction.

## EFFECTS OF PROSTATE CANCER ON SEXUAL FUNCTION

In Korea, due to the westernization of dietary habits, the incidence of prostate cancer has shown a gradual increase in the past decade. Not only the psychological stress caused by the prostate cancer itself but also problems such as ED act as factors in the deterioration of quality of life. One study examining the view of prostate cancer patients with regard to sexual function in comparison with that of males without prostate cancer has been reported [43]. The level of stress in regard to the four categories—sexual desire, erectile function, level of satisfaction during sexual activity, and ejaculatory volume—was examined. Psychological burdens in prostate cancer patients were observed to be higher in all categories, and 25% more prostate cancer patients reported having sexual dysfunction than patients without prostate cancer. Furthermore, most males considered preservation of sexual function to be of importance; nonetheless, a trend in selection of treatment for prostate

cancer first was demonstrated [44]. Sexual function of prostate cancer patients is affected by radical prostatectomy, radiation therapy, hormone therapy, and other treatment methods; thus, the effect of each therapy on sexual function is summarized in the next section.

### 1. Radical prostatectomy

Erectile dysfunction after radical prostatectomy is a common complication and is caused by surgical nerve injury resulting in collagenization of smooth muscles in the corpus cavernosum [45-47]. Twelve months after radical prostatectomy, sexual function shows partial recovery, and diverse recovery rates have been reported, depending on investigators. It is influenced by the age of the patient at the time of surgery, presurgical sexual function of the patients, and whether nerve-preserving surgery was performed.

The age of the patients, as well as sexual function before surgery, are important factors that are closely associated with ED. According to several reports, if the age of the patient is relatively low, the rate of recovery of erectile function after surgery is high; in particular, in localized prostate cancer patients ranging in age from 40 to 49 years, recovery of erectile function was observed in 92% of patients [48-51]. In addition, patients with normal sexual function before surgery have an indication for nerve-preserving surgery, and patients taking phosphodiesterase 5 inhibitors for ED before surgery show severe ED after surgery regardless of nerve-preserving surgery [52]. In radical prostatectomy, ideal conditions for nerve-preserving surgery include localized prostate cancer with low prostate-specific antigen values, a low Gleason score histologically, a relatively low age of the patient, and no sexual dysfunction before surgery [53]. Bilateral nerve-preserving surgery in such localized prostate cancer patients has been reported to aid in recovery of sexual function after surgery [54].

### 2. Radiotherapy

Radiation therapy, the second most common therapeutic method for treatment of localized prostate cancer, can reduce complications of surgery. It can be divided broadly into external beam radiotherapy and brachytherapy [55]. Sexual dysfunction induced by radiation therapy is considered to be the result of vascular injury caused by radiation therapy [56]. According to a study reported by Sanda et al, patients treated with both external beam radiotherapy and brachytherapy showed sexual dysfunction from 2 months after treatment, and the probability of developing sexual dysfunction was high in older patients and patients simultaneously treated with hormone therapy [57].

### 3. Androgen deprivation therapy

Androgen deprivation therapy (ADT) is a treatment method applied to metastatic prostate cancer patients or patients detected as having biochemical recurrence after radical prostatectomy for treatment of localized prostate cancer. Sexual dysfunction is the most frequent complica-

tion of ADT, and it has been found that most patients understood the development of sexual dysfunction to be due to the treatments. Nonetheless, some patients were not satisfied with the deterioration of libido, ED, and other problems [58]. In addition, due the reduction of testosterone in the body caused by ADT, not only the size of the testis but also the length and volume of the penis are decreased, which may be recovered after termination of ADT.

## CONCLUSIONS

Prostatitis, BPH, and prostate cancer are representative diseases that develop in the prostate; they are closely associated with the male, and they exert significant effects on quality of life. In addition, deterioration of quality of life caused by prostate diseases may be affected not only by the prostate diseases themselves but also by the sexual dysfunction caused by the prostate diseases secondarily. Furthermore, sexual dysfunction may develop as a side effect after treatment of prostate disease; thus, consideration of these points at the time of treatment of prostate disease is required. Therefore, therapies suitable to each condition should be selected with an understanding of the close association of prostate diseases and associated sexual dysfunction with the quality of life of males.

### Conflicts of Interest

The authors have nothing to disclose.

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