Review Article

Korean Society for Sexual Medicine and Andrology (KSSMA) Guideline on Erectile Dysfunction

Ji Kan Ryu[1], Kang Su Cho[2], Su Jin Kim[3], Kyung Jin Oh[4], Sung Chul Kam[5], Kyung Keun Seo[6], Hong Seok Shin[7], Soo Woong Kim[8]

[1]Department of Urology, Inha University School of Medicine, Incheon, [2]Department of Urology, Yonsei University College of Medicine, Seoul, [3]Department of Urology, The Catholic University of Korea, School of Medicine, Seoul, [4]Department of Urology, Chonnam National University Medical School, Gwangju, [5]Department of Urology, Gyeongsang National University School of Medicine, Jinju, [6]Dr. Seo Kyung Keun Urology Clinic, Cheonan, [7]Department of Urology, Catholic University of Daegu School of Medicine, Daegu, [8]Department of Urology, Seoul National University College of Medicine, Seoul, Korea

In February 2011, the Korean Society for Sexual Medicine and Andrology (KSSMA) realized the necessity of developing a guideline on erectile dysfunction (ED) appropriate for the local context, and established a committee for the development of a guideline on ED. As many international guidelines based on objective evidence are available, the committee decided to adapt these guidelines for local needs instead of developing a new guideline. Considering the extensive research activities on ED in Korea, data with a high level of evidence among those reported by Korean researchers have been collected and included in the guideline development process. The latest KSSMA guideline on ED has been developed for urologists. The KSSMA hopes that this guideline will help urologists in clinical practice.

Key Words: Erectile dysfunction; Guideline; Phosphodiesterase type 5 inhibitors

EPIDEMIOLOGY AND RISK FACTORS FOR ERECTILE DYSFUNCTION

1. Epidemiology of erectile dysfunction

Recent epidemiological data have shown a high prevalence and incidence of erectile dysfunction (ED) worldwide. The Massachusetts Male Aging Study (MMAS), the first large-scale community-based study, reported that the prevalence of ED was 52% in men aged 40~70 years living in Boston, USA.[1] In that study, the prevalence of mild, moderate, and complete ED was reported to be 17.2%, 25.2%, and 9.6%, respectively. The Cologne Male Survey, a representative European epidemiologic study, reported that the prevalence of ED was 19.2% in men aged 30~80 years living in Cologne, Germany in a mail survey.[2]

The Asian Men's Attitudes to Life Events and Sexuality (Asian MALES), an epidemiologic study that was conducted on over 10,000 men aged 20~75 years in five Asian countries including the Republic of Korea (hereafter, 'Korea'), demonstrated that the overall prevalence of self-reported ED was 6.4%.[3] The prevalence of

Correspondence to: Soo Woong Kim
Department of Urology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea.
Tel: +82-2-2072-2426, Fax: +82-2-762-4665, E-mail: swkim@snu.ac.kr

self-reported ED varied depending on the country, and it was reported to be 8% in Korean men.[3] The Global Study of Sexual Attitudes and Behaviors reported that 15% of sexually active Asian men aged 40~80 years had ED and that 18% of Korean men had ED.[4]

In 2004, a large-scale survey for ED was conducted by the KSSMA, which was a representative epidemiologic study conducted in Korea.[5] In that study, 13.4% of 1,570 men aged 40~79 years, who were randomly selected in a stratified three-stage cluster sample of administrative districts (*gu*) nationwide, replied that they suffered from ED. The overall prevalence of ED was shown to be 32.4% (mild 10.6%, moderate 10.0%, and severe 11.8%) when ED was defined by an International Index of Erectile Function (IIEF)-5 score ≤17 points.[5] In a Korean study, which was conducted on 3,501 men aged 20 years or above who visited primary care physicians, the prevalence of ED was reported to be 36.6% (mild 24.7%, moderate 10.2%, severe 1.6%) when ED was defined by an IIEF-5 score ≤17 points.[6]

2. Risk factors for erectile dysfunction

Risk factors for ED include age, diabetes, hypertension, obesity, lack of exercise, dyslipidemia, smoking, depression, lower urinary tract symptoms, and pelvic surgery.

1) Age
The prevalence of ED increases in proportion to age, which has been confirmed in international studies, such as the MMAS, Cologne Male Survey, and Asian MALES study, as well as Korean studies.[1-5] In the Cologne Male Survey, the prevalence of ED was shown to be 53.4% in men in their 70s and 2.3% in men in their 30s.[2] In a Korean sample survey, the prevalence of ED was reported to be 4.2%, 13%, 30.1%, and 41.1% in men in their 40s, 50s, 60s, and 70s, respectively, which rapidly increased with increasing age.[5]

2) Diabetes
The MMAS reported that the risk of complete ED was three-fold higher in diabetic patients.[1] In a Korean sample survey, the risk of ED was reported to be 2.87-fold higher in diabetic patients.[5] Another study, which was conducted

on patients who visited primary care physicians, reported that diabetes was an independent risk factor of ED.[6] The study demonstrated that the prevalence of complete ED was 6-fold higher in Korean patients with type-2 diabetes than in healthy subjects, and that the prevalence of ED was 48.8%, 67.7%, and 79.3% in diabetic patients in their 40s, 50s, and 60s, respectively. In addition, the duration of diabetes, fasting glucose level, and HbA1c level were associated with the severity of ED.[7]

3) Hypertension
The MMAS showed that 15% of hypertension patients had complete ED.[1] In the MALES study, which was conducted in seven western countries, the prevalence of ED was reported to be 26% in hypertension patients.[8] In a cohort study that was conducted in the U.S., the prevalence of hypertension was 41.2% in men with ED and 19.2% in men without ED. After controlling for subject age, census region, and 9 concurrent diseases, the odds ratio was 1.38.[9] In a Korean study, the odds ratio for ED was reported to be 2.97 and 4.78 in patients with hypertension and with heart diseases, respectively.[5]

4) Overweight and lack of exercise
The odds ratio for ED was reported to be more than 60% higher in overweight males than in normal weight males.[10] For Korean men, central obesity was shown to be significantly correlated with ED,[11] and body mass index (BMI) and body fat percentage were also shown to be associated with ED.[12] The MMAS showed that physical activity status was associated with ED and that the odds ratio for ED decreased by approximately 70% in men who initiated physical activity at their middle age, relative to that for men who remained sedentary when the subjects were followed-up for more than 8 years.[13]

5) Dyslipidemia
The MMAS showed that the prevalence of ED had a negative correlation with the high density lipoprotein (HDL) level.[1] In a study where 3,250 subjects (25~83 years) without ED at their initial visit were followed-up for a period of 6~48 months, the odds ratio for ED was 1.83 in the group with a total cholesterol ≥240 mg/dl than in the group with total cholesterol <180 mg/dl; whereas it was

shown to decrease by 70% in the group with HDL ≥60 mg/dl compared to the group with HDL <30 mg/dl.[14] In a Korean study, the odds ratio for ED was reported to be 2.39 in patients with hypertriglyceridemia.[5]

6) Smoking

Smoking is a risk factor of ED by causing injury to the vascular endothelial cells. In the MMAS, the risk of complete ED was shown to significantly increase in smoking patients with coronary artery disease or hypertension, and the odds ratio for ED in smokers versus non-smokers was 1.97 in a follow-up study. In addition, passive exposure to cigarette smoke may act as an additional risk for ED both in non-smokers and smokers.[1,15] In a Korean study, the odds ratio for ED in smokers with a smoking level of 30 packs/year versus non-smokers was reported to be 1.36.[6]

7) Depression

The MMAS showed that ED was associated with depressive symptoms after controlling for potential confounders (odds ratio=1.82).[16] In a follow-up study, which was conducted on 1,380 males in Finland, ED was also associated with untreated and treated depressive symptoms. The prevalence odds ratio adjusted for potential confounders was 2.6 for untreated and 3.3 for treated depressive symptoms at the beginning of the follow-up. In addition, the adjusted incidence density ratio of depressive mood was 1.9 in men with ED relative to those without ED.[17] In Korean studies, the odds ratio of ED in patients with depression versus in those without depression was 1.6 to 3.6.[5,18]

8) Benign prostatic hyperplasia and lower urinary tract symptoms

In a study that was conducted on more than 10,000 subjects in a group of western countries, the odds ratio for ED was shown to be 7.67-fold higher in patients with severe lower urinary tract symptoms.[19] In a Korean study, benign prostatic hyperplasia and lower urinary tract symptom-related factors (international prostate symptom score, post-void residual, maximum urine flow rate) were significantly correlated with ED.[11,20]

9) Pelvic surgery and radical prostatectomy

ED may occur after pelvic surgery for curative treatments, such as prostate cancer, bladder cancer, and colorectal cancer. In particular, ED was reported to occur in 25∼75% of patients who underwent radical prostatectomy.[21] The loss and fibrosis of the cavernous smooth muscle due to cavernous nerve injury, as well as the lack of blood flow and oxygen supply due to vascular injury, are known to cause ED. Age and preoperative erectile function (EF) are the main factors that can predict the recovery of postoperative EF. A nerve-sparing technique should be applied to preserve postoperative EF.[22]

10) Medications

Antihypertensive drugs and psychotropic agents, such as antidepressants, may cause ED due to adverse drug reactions, and the discontinuation of such drugs does not always result in the recovery of EF. Although hypertension and psychiatric disorders should be treated prior to ED management, this potential adverse reaction, which might be irreversible, should be discussed before prescribing such medications.[23] Among antihypertensive agents, diuretics, nonselective α-blockers, and β2-blockers may cause ED, but angiotensin converting enzyme inhibitors, calcium channel blockers, α1-blockers, and angiotensin receptor blockers are known to have a low risk of ED.[24]

DIAGNOSIS OF ERECTILE DYSFUNCTION

1. Basic evaluation

The diagnosis and clinical evaluation of ED should be helpful in the determination of personalized treatment options by identifying the underlying causes via the investigation of risk factors and by determining the severity of ED. A thorough history-taking is essential for all patients who suffer from ED. In addition, a physical examination and laboratory tests should also be conducted.

1) History

It is important to thoroughly review the previous disease history of patients and their partners. Ideally, information on sexual behaviors should also be obtained by interviewing sex partners, even though this may not be possible in reality. An interview with patients should be performed in an independent place with sufficient time and a comfortable environment to maintain the patient's privacy.

(1) Sexual history

The presence of any risk factors related to ED should be determined. It is useful to explain concurrent risk factors to patients in advance to help the patient's understanding. The status of sexual behaviors before and after ED should be investigated. ED should be investigated whether it is transient or persistent, whether it is acute or chronic, and if it is accompanied by other sexual dysfunctions (ejaculation disorder, decreased sexual desire, and orgasm disorder). In addition, treatment methods previously conducted and their efficacy should also be reviewed. The clinician should also inquire about erectile rigidity, erectile maintenance time, and the presence of nocturnal penile tumescence. The sex-related diseases or menopause of partners should also be noted.

(2) Other history

It is necessary to determine the presence of any risk factors of cardiovascular diseases, as well as concurrent diseases, such as hypertension, diabetes, and dyslipidemia. Any history of injury, surgery, or radiation therapy should be reviewed. The patient should also be checked for concurrent voiding dysfunction or sleep disorder, along with smoking history, drinking history, and previous and current medications. The type, frequency, duration, and intensity of current exercise are also checked.

(3) Questionnaire

Questionnaires that are commonly used in Korea include the IIEF and IIEF-5. The IIEF has been used since 1999 after its Korean version was validated for its reliability and sensitivity.[25] It is comprised of 15 questions in five domains: EF, orgasm, sexual desire, intercourse satisfaction, and overall sexual satisfaction. It is difficult to use it in actual clinical practice as it is too long. Thus, the IIEF-5, which is a short version of the IIEF, is commonly used.[26] The IIEF-5 evaluates the sexual function of the past 6 months, using questions with score range from 0 or 1 point to 5 points. The IIEF-5 is useful for screening for ED and for determining the severity of ED. The Korean version of the IIEF-5 has a cutoff of 17 points, which determines ED and classifies ED into normal (18~25 points), mild (14~17 points), moderate (10~13 points), and complete ED (9 points or less) according to the total score of the questionnaire.[27]

2) Physical examination

A focused physical examination must be performed on every patient, with particular emphasis on the genitourinary, endocrine, vascular, and neurologic systems.[28] The physical examination may reveal unsuspected diagnoses, such as Peyronie's disease, prostatic enlargement, or cancer, as well as signs and symptoms indicative of hypogonadism.[29] Digital rectal examination of the prostate should be conducted in patients aged 50 years or higher. Height, weight, BMI, blood pressure, heart rate, and waist circumference should be measured.[30]

3) Laboratory tests

It is recommended that laboratory tests be conducted selectively according to the symptoms and identified risk factors. The fasting glucose level, lipid profile, and testosterone levels should, however, be measured in all patients. The testosterone level should be measured between 7 and 11 a.m. If hypogonadism is suspected during the disease history taking and physical examination, hormone tests for prolactin, luteinizing hormone (LH), and follicular stimulating hormone (FSH), should also be conducted.[31] If an additional test is required for prostatic diseases, serum prostate specific antigen (PSA) should be measured.

2. Evaluation of the cardiovascular system

It has been well known that the prevalence of cardiovascular diseases is high in patients with ED, and that cardiovascular disease and ED have common risk factors.[32] The hypothesis that ED is a harbinger of cardiovascular disease (particularly, coronary artery disease), while it remains asymptomatic, but for which symptoms might occur later, has been recently accepted as a proven theory.[33] Patients with coronary artery disease and their partners may be concerned about their sexual behaviors as they suspect that sexual activities might negatively affect the heart. According to the recommendation of the Princeton Consensus Panel, patients with ED should be classified into three groups according to the risk of heart disease, and then a proper treatment plan for each patient should be set up to predict the risks that might occur during sexual activities.[34,35]

Table 1. Cardiac risk stratification

Low-risk group	Intermediate-risk group	High-risk group
Asymptomatic, <3 risk factors for CAD (excluding gender)	≥3 risk factors for CAD (excluding gender)	High risk arrhythmia
Mild, stable angina	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (2~6 weeks)	Recent MI (<2 weeks)
LVD/CHF (NYHA class I)	LVD/CHF (NYHA class II)	LVD/CHA (NYHA class III/IV)
Post-successful coronary artery revascularization	Non-cardiac sequelae of atherosclerotic disease (e.g. cerebrovascular disease)	Obstructive hypertrophy and other cardiomyopathy
Controlled hypertension		Uncontrolled hypertension
Mild valve disease		Moderate-to-severe valve disease

Risk factors for CAD: age, diabetes, hypertension, obesity, dyslipidemia, smoking, sedentary lifestyle, male, familial history of early onset of coronary artery disease.
CAD: coronary artery disease, MI: myocardial infarction, LVD: left ventricular dysfunction, CHF: congestive heart failure, NYHA: New York Heart Association.

1) Patients with cardiovascular risk factors

Patients with ED should be classified into low-risk, intermediate-risk, and high-risk groups, according to their cardiovascular status (Table 1).[34,35] The risk factors of cardiovascular diseases include age, being male, hypertension, diabetes, smoking, dyslipidemia, a sedentary lifestyle, and a familial history of early onset of coronary artery disease. Three cardiovascular risk categories can be used as the basis for a treatment algorithm for initiating or resuming sexual activity.

2) Low-risk group

The cardiovascular system of the low-risk group is rarely influenced by sexual activities. Thus, the low-risk group does not require any additional examinations of the cardiovascular system. This group can have sexual activities without any particular examination and undergo treatment for ED.

3) Intermediate-risk group

As the risk of cardiovascular diseases is uncertain in the intermediate-risk group, a preliminary test is required before engaging in sexual activities. This group may be reclassified into low and high-risk groups, depending on the result of the test. An exercise treadmill test is useful for this group.[35] If necessary, the safety of the management of ED and sexual activities can be evaluated by a cardiologist.

4) High-risk group

The high-risk group is in an unstable and serious cardiac status. Thus, sexual activities may increase the risk of heart disease. The high-risk group should be examined by a cardiologist, and a treatment for the heart should be conducted in advance. Sexual activities are not recommended unless the cardiac status becomes stabilized after treatment or the safety of sexual activities is confirmed by a cardiologist.

3. Specific tests

ED can be managed in most patients after they undergo basic tests. However, some patients need specific diagnostic tests. For young men with a history of pelvic or perineal trauma, a specific test is required to check whether they could benefit from potentially curative vascular surgery. Specific tests are also needed for patients with primary ED or with penile deformities that might require surgical correction, e.g. Peyronie's disease. Other indications for specialized tests include patients with complex endocrine or psychiatric disorders or the request of the patient or his partner. Specific tests may also be conducted for medicolegal reasons, such as a divorce suit or sexual abuse.

1) Vascular studies
(1) Intracavernous injection test

In general, 10~20 μg of prostaglandin E1 (PGE1) is injected into the corpus cavernosum, followed by audio-vis-

ual sexual stimulation and genital self-stimulation. If neurogenic or psychogenic ED is suspected, the injection dose should be reduced due to the risk of priapism. A positive test is defined as a rigid erection (unable to bend the penis) that appears within 10 minutes after the intracavernous injection and lasts for 30 minutes.[36] Such a response may indicate a functional, but not necessarily normal, erection because it may coexist with arterial insufficiency or veno-occlusive dysfunction.[37] Therefore, its use as a diagnostic test for ED is limited. Its main clinical implication is that patients will respond to the intracavernous injection program.

(2) Penile duplex ultrasonography

Vasodilators are injected into the corpus cavernosum, and then the status of penile blood flow is measured using a Doppler spectrum analysis. The measurement of the peak systolic velocity (PSV) of the cavernosal artery and the end diastolic velocity (EDV), which indirectly reflects penile blood leak, is important. The PSV is the most important evaluation factor. A PSV >30 cm/s and an EDV <5 cm/s are generally considered to be normal.[36] The value obtained by dividing the PSV-EDV by PSV is called a resistive index, and the status is assessed to be normal if the resistive index is >0.8.[36] There is no need to continue vascular investigation when the duplex examination is normal.

(3) Penile arteriography and dynamic infusion cavernosometry/cavernosography

Internal pudendal arteriography should be selectively conducted for patients who have abnormal findings in penile duplex ultrasonography and who may be candidates for vascular reconstruction.[38] Like penile arteriography, dynamic infusion cavernosometry/cavernosography (DICC), in which a needle is injected into the penile corpus cavernosum, should also be selectively performed for patients who are being considered for vascular reconstructive surgery.[38] Patients are assessed to be normal if the flow amount, which is required to maintain intracavernous pressure ≥ 100 mmHg, is $3\sim5$ ml/min or less in a state of completely relaxed cavernosal smooth muscle, and if the pressure reduction, which is measured for 30 seconds in a state of halted infusion, is 45 mmHg or less when the intracavernous pressure reaches 150 mmHg.[39]

2) Pyschophysiological tests
(1) Nocturnal penile tumescence and rigidity test

An nocturnal penile tumescence and rigidity (NPTR) test should be performed for at least two consecutive nights, and it is mainly measured using Rigiscan® (Timm Medical Technologies, Inc., Minneapolis, MN, USA; a division of Plethora Solutions Holdings, Ltd., UK). A functional erectile mechanism is indicated by an erectile event of at least 60% rigidity recorded on the tip of the penis that lasts for 10 minutes or more.[40] A positive NPTR test strongly indicates psychogenic ED.

(2) Audiovisual sexual stimulation test

An audiovisual sexual stimulation test can be conducted as a screening test with relative ease, but its clinical usefulness is low as many factors can cause false negativity.

3) Neurologic test

A neurologic test is mainly conducted for medicolegal purposes in order to investigate whether ED is associated with an accident or surgery. An objective evaluation of autonomic cavernosal neurointegrity remains to be developed. A bulbocavernosus reflex latency test and somatosensory evoked potentials test, which assess the somatic nervous system, are typically performed, but the reference value that determines normal and abnormal status has not yet been clearly established.[41]

TREATMENT OF ERECTILE DYSFUNCTION

1. Goal and principle of the treatment of erectile dysfunction

The primary goal of ED treatment is to enable the satisfactory sexual activities of patients and their partners by recovering sufficient penile rigidity for sexual intercourse. Causes for ED, such as medication or lifestyle, are factors that can be addressed, and these factors should be corrected before or during the treatment of ED. Changes in lifestyle can not only improve ED, but also improve cardiovascular and metabolic diseases.

Psychogenic ED, arteriogenic ED caused by trauma in young patients, and ED caused by hormone abnormality can be cured via a specific treatment. However, as the treatments that are applied to most patients with ED are

not performed based on specific causes for ED, patients should be informed of a variety of treatment modalities, and an appropriate treatment should be selected considering treatment efficacy, safety, invasiveness, cost, and the preference of the patient and partner.

2. Lifestyle changes and the modification of risk factors

As lifestyle changes and the modification of risk factors are effective methods for treating ED, patients should be educated about such changes along with any specific treatment of ED, such as pharmacologic treatment. The potential advantages obtained by a change in lifestyle are particularly important in ED patients with specific cardiovascular or endocrine diseases, such as hypertension or diabetes.[42,43]

In the MMAS, the risk of ED was shown to decrease by 70% in the group that started and then continued exercise in middle age compared to the group that did not exercise, and regular exercise was shown to significantly decrease the incidence of ED in a follow-up study that was conducted for 8 years or longer.[13] In a prospective, randomized study that was conducted on obese men who had ED without concurrent disease for two years, systematic exercise and weight loss brought normal EF in approximately one third of the subjects.[44] In addition, a randomized study reported that regular aerobic exercise improved the efficacy of phosphodiesterase type 5 (PDE5) inhibitors.[45] However, a further long-term, prospective study is required on a larger scale in order to investigate the positive effects of lifestyle changes and risk factor control on ED.

3. Curable causes

1) Hormones

Endocrine disorders, such as hypogonadism, hyperthyroidism/hypothyroidism, and hyperprolactinemia, may become curable causes for ED.

(1) Hypogonadism

Patients should be diagnosed with hypogonadism if they have clinical symptoms and biochemical evidence related to testosterone deficiency, such as decreased sexual desire and a low serum testosterone level. If patients with ED have

hypogonadism, they are indicated for testosterone replacement treatment.[46] Various recommendations have been given for the diagnosis and treatment of late onset hypogonadism (LOH) in elderly men. A revision of the conventional recommendation has been presented by the Korean Society for Aging Male Research (KOSAR) in order to reflect the Korean context.[47]

As the serum testosterone level has diurnal variation, it should be measured from a blood sample collected between 7 and 11 a.m. If a patient has a serum total testosterone level ≥ 12 nmol/L (346 ng/dl), or free testosterone ≥ 250 pmol/L (72 pg/ml), testosterone replacement treatment is not required. If a patient has total testosterone ≤ 8 nmol/L (231 ng/dl) or free testosterone ≤ 180 pmol/L (52 pg/ml) with reference to the data obtained from young men, testosterone replacement treatment is required. If patients have a total testosterone level of $8 \sim 12$ nmol/L, they may receive testosterone replacement treatment unless other causes are observed.[47]

In a meta-analysis of 17 randomized studies that were conducted on ED patients to investigate the effect of testosterone replacement treatment, the result showed that EF was further improved by testosterone replacement when the testosterone level before treatment was lower.[48] However, the recovery of EF is not always observed in all patients via testosterone replacement alone, and multiple factors are involved in the pathogenesis of ED if the patient's age increases. Thus, it should be kept in mind that the effect of testosterone replacement treatment is relatively less in elderly patients than in young patients.[49]

(2) Hyperthyroidism/Hypothyroidism

Both hyperthyroidism and hypothyroidism may cause decreased sexual desire and ED. Ejaculation disorder is known to be more frequently observed in hyperthyroidism and hypothyroidism.[50] As the normalization of thyroid function may result in the recovery of sexual dysfunction, a priority should be given to the treatment of thyroid dysfunction.[50]

(3) Hyperprolactinemia

Hyperprolactinemia may cause ED, decreased sexual desire, and anorgasmia. An increase in the blood prolactin level commonly accompanies the deficiency in testoster-

one by inhibiting LH secretion. Prolactin measurement is recommended in men with decreased sexual desire. Hyperprolactinemia is mainly caused by stress, drugs such as potent sedatives, and chronic renal failure. However, the possibility of the prolactin-secreting pituitary gland tumor also exists, even though it is very rare. In the case of persistent hyperprolactinemia for unknown reasons, patients should be referred to the department of endocrinology.

2) Arteriogenic erectile dysfunction after trauma

If arteriogenic ED occurs in young patients after pelvic or perineal injury, arterial reconstruction surgery can be conducted when the focal narrowing is observed by penile duplex ultrasonography and selective penile arteriography, and when the veno-occlusive function is normal in DICC. These patients should have no other arterial or neurological risk factors. The long-term success rate was reported to be 60~70% in patients properly selected.[51] Venous surgery for veno-occlusive dysfunction is no longer recommended due to poor long-term results.[52]

3) Psychogenic erectile dysfunction

It is recommended that ED patients and their partners receive education and a consultation during the pharmacologic treatment of ED. The education should include the mechanism of penile erection using educational materials for better understanding, and should emphasize that ED can be cured. It is generally known that psychotherapy requires a long time and its effect varies.

4. First-line treatments

1) Phosphodiesterase type 5 inhibitors

When men are sexually stimulated, nitric oxide (NO) is released from the nerve terminal and vascular endothelial cells of the penile erectile tissues. NO diffuses into the adjacent penile cavernosal smooth muscle, increases the synthesis of cyclic guanosine monophosphate (cGMP), and decreases the cellular calcium concentration, thereby inducing the relaxation of penile cavernosal smooth muscle cells and penile erection. PDE5, which is abundant in penile erectile tissues, is an enzyme that degrades cGMP. PDE5 inhibitors competitively inhibit the activity of PDE5, thereby reinforcing penile erection by increasing the cGMP concentration in the erectile tissues. PDE5 inhibitors that are currently available in the Korean market include sildenafil, tadalafil, vardenafil, udenafil, mirodenafil, and avanafil. The pharmacokinetic data of these six drugs are presented in Table 2.

(1) Sildenafil

Sildenafil is an oral PDE5 inhibitor that was first released into the market in 1998. It is available in doses of 25 mg, 50 mg, and 100 mg. A 50 mg dose is generally recommended as an initial dose, and the dose should be increased or decreased according to the efficacy and adverse events of the drug. It has a half-life of approximately 3 hours in the blood. Its efficacy is observed approximately 30~60 minutes after oral administration, and then lasts for approximately 4 hours. A high-fat diet delays sildenafil absorption and reduces its blood concentration.[53] Alcohol does not affect the

Table 2. Pharmacokinetic data for the five PDE5 inhibitors used to treat erectile dysfunction in Korea

Parameter	PDE5 inhibitors					
	Sildenafil (100 mg)	Tadalafil (20 mg)	Vardenafil (20 mg)	Udenafil (200 mg)	Mirodenafil (100 mg)	Avanafil (200 mg)
T_{max} (h)	0.8~1	2	0.9	1.5	1	0.5
$T_{1/2}$ (h)	2.6~3.7	17.5	3.9	9.88	2.5	10.6
Action duration (h)	0.5~4	1~36	0.5~5	0.5~12	0.5~4	6
C_{max} (μg/L)	560	378	18.7	1,138	NA	5,161
AUC (μg/h/L)	1,685	8,066	56.8	7,898	NA	10,867
Protein binding (%)	96	94	94	NA	NA	99
Bioavailability (%)	41	NA	15	NA	24~43	NA

PDE5: phosphodiesterase type 5, T_{max}: time to maximum plasma concentration, $T_{1/2}$: terminal half-life, C_{max}: maximum plasma concentration, AUC: area under the curve, NA: not available.

pharmacokinetics of sildenafil. In a meta-analysis of the result of a placebo-controlled, double-blind study, which was conducted on more than 3,000 patients, the result of an assessment using the global assessment question (GAQ; Has the treatment you have been taking over the past study interval improved your erections?) showed that EF improved in 76% of the sildenafil group and in 22% of the placebo group during a study period of 12 weeks. In addition, EF improved in 65% of patients who had severe ED based on the IIEF questionnaire after sildenafil administration, whereas it was improved in 12% of the placebo group.[54] Sildenafil administration also showed a successful treatment outcome in diabetic patients. The score on questions 3 (frequency of penetration) and 4 (frequency of maintaining an erection after penetration) of the IIEF questionnaire was shown to be 3.61 and 3.25 points, respectively, in the sildenafil group, but only 2.71 and 2.19 points, respectively, in the placebo group, which showed that the scores were significantly higher in the sildenafil group than in the placebo group.[55]

In a Korean study that was conducted on 133 patients, who had ED based on various causes, the results of assessing the primary efficacy endpoints, that is, the scores for questions 3 (frequency of penetration) and 4 (frequency of maintaining an erection after penetration) of the IIEF questionnaire, showed that the scores on questions 3 and 4 of the IIEF questionnaire were shown to be 4.19 and 3.74 points, respectively, in the sildenafil group that received sildenafil for 8 weeks, but 2.67 and 2.07 points, respectively, in the placebo group, which showed that EF was significantly improved in the sildenafil group.[56]

(2) Tadalafil

Tadalafil is available in doses of 10 mg and 20 mg, and a dose of 5 mg, which was developed for daily administration, has been recently released onto the market. The most significant feature of tadalafil is that its efficacy lasts longer compared to the other PDE5 inhibitors. It has a blood half-life of approximately 17.5 hours and has efficacy that starts approximately 30 minutes after drug administration and lasts for 36 hours. Tadalafil absorption is rarely affected by food, and alcohol does not affect the pharmacokinetics of tadalafil.[57] In a 12-week dose-response study, the result of efficacy assessment, using the

GAQ questions, showed that EF was improved in 67% of the 10 mg tadalafil group and in 81% of the 20 mg tadalafil group, but in 35% of the placebo group.[58] Tadalafil administration was also effective in diabetic patients; the IIEF score after drug administration increased by 7.3 points in the tadalafil group and by 0.1 point in the placebo group, showing a significant increase in the tadalafil group.[59]

In a Korean study that was conducted on 121 patients who had ED based on various causes, the result of assessing the primary efficacy endpoints, such as the EF domain of the IIEF, Sexual Encounter Profile question 2 (SEP2; Were you able to insert your penis into your partner's vagina?), and Sexual Encounter Profile question 3 (SEP3; Did your erection last long enough for you to have successful intercourse?), showed that the IIEF EF domain score was 23.2 points and 15.4 points in the tadalafil and placebo groups, respectively, after drug administration, that the positive reply rate for the SEP question 2 was 85.4% and 67.7% in the tadalafil and placebo groups, respectively, and that the positive reply rate for the SEP question 3 was 71.2% and 31.4% in the tadalafil and placebo groups, respectively, which showed a significant improvement in EF in the tadalafil group.[60]

(3) Vardenafil

Vardenafil is available in doses of 10 mg and 20 mg. It has a blood half-life of approximately 3.9 hours, and its effect starts approximately 30 minutes after drug administration and lasts for 5 hours. A high-fat diet delays vardenafil absorption and reduces its blood concentration. Alcohol does not affect the pharmacokinetics of vardenafil.[61] From a meta-analysis of the results of a double-blind, placebo-controlled study, which was conducted on more than 4,000 patients, the result of efficacy assessment using the GAQ questions showed that EF was improved in 69% of the vardenafil group and in 26% of the placebo group.[62] Vardenafil was also effective in diabetic patients; the positive reply rate for the GAQ questions occurred in 72% of the vardenafil group and in 13% of the placebo group, and the IIEF EF domain score after treatment was 19 points and 12.6 points in the vardenafil and placebo groups, respectively; this was significantly higher in the vardenafil group than in the placebo group.[63]

In a study that was conducted on 306 patients with ED

from Asian countries including Korea, the IIEF EF domain score, which was a primary efficacy endpoint, was shown to be 24.2 points in the vardenafil group and 15.9 points in the placebo group after a 12-week treatment, which showed a significant improvement in the EF in the vardenafil group.[64]

(4) Udenafil

Udenafil is an oral PDE5 inhibitor that was developed by a Korean pharmaceutical company. It was released to the Korean market in 2005. It is available in doses of 100 mg and 200 mg, and a dose of 50 mg, which was developed for daily administration, has been recently released to the market. It has a blood half-life of approximately 9.9 hours, and its effect starts approximately 30 minutes after oral administration, and lasts for 12 hours. A high-fat diet and alcohol do not affect the pharmacokinetics of udenafil.[65] In a Korean study that was conducted on 167 patients who had ED based on various causes, the result of efficacy assessment using the IIEF EF domain score as a primary efficacy endpoint showed that the score increased by 7.52 points, 9.93 points, and 0.2 point in the 100 mg udenafil, 200 mg udenafil, and placebo groups, respectively, after a 12-week treatment, which showed a significant improvement of EF in the udenafil groups.[66] In addition, in a study that was conducted on 104 patients with ED, the result of efficacy assessment using the SEP question 3 (Did your erection last long enough for you to have successful intercourse?) as a primary efficacy endpoint showed a positive reply rate of 54.7% in the udenafil group, and 28.3% in the placebo group after a 12-hour drug administration.[67]

(5) Mirodenafil

Mirodenafil is an oral PDE5 inhibitor that was the second to be developed by a Korean pharmaceutical company. It is available in doses of 50 mg and 100 mg. It has blood half-life of approximately 2.5 hours, and its effect starts approximately 30 minutes after drug administration and lasts for 4 hours. A high-fat diet and alcohol do not affect the pharmacokinetics of mirodenafil.[68] In a Korean study that was conducted on 119 patients who had ED based on various causes, the result of efficacy assessment using the scores on questions 3 (frequency of pene-

tration) and 4 (frequency of maintaining an erection) of the IIEF questionnaire as primary efficacy endpoints showed that the scores for questions 3 and 4 were 4.4 points and 3.9 points, respectively, in the mirodenafil group, and in 3.1 and 2.5 points, respectively, in the placebo group after an 8-week administration, which showed a significant improvement of EF in the mirodenafil group.[16] Mirodenafil administration was also effective in diabetic patients; the IIEF EF domain score increased by 9.3 points in the mirodenafil group and 1.4 points in the placebo group, which showed a significant improvement of EF in the mirodenafil group.[69]

(6) Avanafil

Avanafil is the oral PDE5 inhibitor that has been most recently released to the Korean market. It is available in doses of 100 mg and 200 mg. It has a blood half-life of 10.6 hours, and its effect starts approximately 15~30 minutes after drug administration and lasts for 6 hours. A high-fat diet may delay avanafil absorption, but does not affect absorption quantity. In a 12-week dose-response study, which was conducted on more than 600 patients in the U.S., the result of efficacy assessment using the IIEF EF domain score, and SEP questions 2 and 3 as primary efficacy endpoints, showed that the IIEF EF domain score was 22.2 and 12.8 points in the 200 mg avanafil and placebo groups, respectively, and that the positive reply rate for the SEP questions 2 and 3 was 77% and 57%, respectively, in the avanafil group, and 48% and 12%, respectively, in the placebo group, which showed a significant improvement of EF in the avanafil group.[70] In a Korean study that was conducted on 208 patients with ED based on various causes, the IIEF EF domain score increased by 8.5 and 8.8 points in the 100 mg and 200 mg avanafil groups, respectively, and by 3.5 points in the placebo group after a 12-week administration. The increases were significantly higher in the avanafil groups than in the placebo group.[71]

(7) Selection of phosphodiesterase type 5 inhibitors and their preference

The efficacy and tolerability of the six PDE5 inhibitors currently available in the Korean market have been validated in several objective studies. Based on these previous results, many domestic and international studies compar-

ing the efficacy of PDE5 inhibitors and patient preference have been done. However, an objective comparison of the efficacy of and patient preference for each PDE5 inhibitor is limited due to the various inclusion criteria, differences in the peak efficacy time and efficacy duration for each PDE5 inhibitor, as well as the difficulty in conducting a randomized blind study. Thus, the choice of PED5 inhibitors should be based on the patient's experience under a physician's guidance regarding the characteristics of each PDE5 inhibitor, whether it is a short-acting or long-acting agent, and adverse events.

(8) Use of phosphodiesterase type 5 inhibitors: on-demand versus daily medication

In studies using animal models with ED, such as models of diabetes or cavernous nerve injury, daily administration of PDE5 inhibitors was found to preserve penile structure and function.[72,73] In addition, daily administration has the advantage of allowing for spontaneity of sexual activity. In a clinical study that was conducted on patients with ED, daily administration of tadalafil and sildenafil improved endothelial function. The improved endothelial function was maintained for a certain period of time after the discontinuation of daily medication, but EF returned to its pre-treatment status. These findings indicate that the improvement of endothelial cell function by daily administration is not necessarily connected to the improvement of EF.[74,75]

In a placebo-controlled study, in which 342 patients with ED received tadalafil (5 mg) daily for 12 weeks, the IIEF EF domain score after the treatment was shown to be 23.7 and 15.1 points in the tadalafil and placebo groups, respectively. Also, the positive reply rate for the SEP2 question was shown to be 86.8% and 60%, and the positive reply rate for the SEP3 question was shown to be 71% and 37.3% in the tadalafil and placebo groups, respectively, which showed a significant improvement in the EF in the tadalafil group. Furthermore, the patients and their partners had high sexual satisfaction in the tadalafil group.[76] In a Korean study, in which 239 patients with ED received udenafil at doses of 25 mg, 50 mg, and 75 mg daily for 12 weeks, EF was improved more in the udenafil 50 mg and 75 mg groups than in the placebo group.[77] In a long-term open-label trial, in which 234 and 238 patients

with ED received tadalafil (5 mg) daily for one and two years, respectively, the IIEF EF domain score increased by 10.4 and 10.8 points in the two groups, respectively. A total of 57.9% and 57.8% of the two groups had normal EF with an IIEF score of ≥26 points.[78] However, following a 4-week discontinuation of tadalafil after the 1-year open-label extension, the mean IIEF-EF domain score declined markedly to a near-baseline level.[78]

In a study that compared the efficacy of on-demand administration of tadalafil (20 mg) versus daily administration of tadalafil (10 mg) in 141 patients who had ED for various reasons, EF was improved more in the daily administration group than in the on-demand administration group.[79] However, in a study that compared the efficacy of the on-demand administration of tadalafil (20 mg) versus the daily administration of tadalafil (5 mg) in patients who had ED after radiation therapy for prostatic cancer, the improvement of EF was shown to be similar between the two groups.[80] In a study that compared the efficacy of on-demand administration of vardenafil (10 mg) versus daily administration of vardenafil (10 mg) in patients with mild or moderate ED, no difference in the improvement of EF was found between the two groups.[81] Thus, an additional large-scale study that investigates drug efficacy according to the causes of ED is required in order to objectively compare the efficacy of daily administration versus on-demand administration of PDE5 inhibitors. It would be desirable to determine the administration method according to the preference and characteristics of patients.

(9) Treatment of patients non-responsive to phosphodiesterase type 5 inhibitors

Approximately 30~35% of patients with ED were reported to have no response or a poor response to PDE5 inhibitors.[82] In general, if no response is observed after PDE5 inhibitors are administered at their maximum dose, taken four or more times with proper sexual stimulation, patients are considered to be non-responsive to PDE5 inhibitors.[83] The most common cause of non-responsiveness to PDE5 inhibitors is inadequate drug medication. It is known that approximately 30~50% of initially non-responders become responders via a proper prescription and education for correct use.[82-86] The necessity of sexual stimulation, drug-specific optimal administration time, and in-

fluences by foods must be included in the education with a prescription. The correction of risk factors, such as diabetes, hypertension, and dyslipidemia, is generally recommended, but no concrete evidence that the correction of such risk factors increases responsiveness to PDE5 inhibitors is currently available.

However, regular aerobic exercise was reported to improve the efficacy of PDE5 inhibitors in a randomized controlled study.[45] In addition, testosterone replacement therapy was reported to be effective in non-responders to PDE5 inhibitors who showed a low or lower normal testosterone level.[87,88] Some patients were reported to be responsive after changing to another type of PED5 inhibitor.[89] Another study reported that daily administration of PDE5 inhibitors was effective in patients who were non-responsive to the on-demand administration of PDE5 inhibitors.[86] However, no randomized placebo-controlled study has been conducted to support the aforementioned result. If patients are still non-responsive to PDE5 inhibitors, other treatment methods, such as a vacuum constriction device or intracavernous injection, should be applied.

(10) Safety and adverse effects of phosphodiesterase type 5 inhibitors

① **Cardiovascular safety of phosphodiesterase type 5 inhibitors:** The results of various randomized controlled studies, open-label studies, and postmarketing surveillance studies have shown that PDE5 inhibitors did not increase the incidence of myocardial infarction. It was also shown that PDE5 inhibitors did not negatively affect the results of an exercise stress test conducted on patients with stable angina.[90,91] The results of accumulated preclinical and clinical studies support the potential benefit of PDE5 inhibitors in the treatment of cardiovascular disease.[92]

② **Common adverse effects of phosphodiesterase type 5 inhibitors:** Common complications caused by PDE5 inhibitors include headache, facial flushing, indigestion, nasal congestion, dizziness, visual disturbances, and myalgia. In general, these complications occur within 2 weeks after the administration of PDE5 inhibitors, and then spontaneously disappear over time. Thus, the discontinuation of PDE5 inhibitors due to complications is rare.

③ **Contraindicated drugs during phosphodiesterase type 5 inhibitor administration:** If patients are taking organic nitrates (nitroglycerine, isosorbide mononitrate, or isosorbide dinitrate) or other nitrates, such as nicorandil, which are used as anti-angina agents, PDE5 inhibitors are contraindicated. If the aforementioned drugs are used with PDE5 inhibitors, life-threatening hypotension may occur due to excessive blood vessel relaxation caused by cGMP accumulation. If patients who have received PDE5 inhibitors complain of chest pain, nitrates should be halted for at least 24 hours if they have received sildenafil and vardenafil, which have a short half-life, and for at least 48 hours if they received tadalafil, which has a long half-life. Concomitant medication of antihypertensive agents with PDE5 inhibitors may decrease blood pressure. However, severe orthostatic hypotension rarely occurs. If an α-blocker for the treatment of benign prostatic hyperplasia is administered with PDE5 inhibitors, a precaution should be given, as the concomitant administration may cause orthostatic hypotension. Each product description of PDF5 inhibitors includes precautions on concomitant use with α-blockers. PDF5 inhibitors should initially be administered at a low dose to minimize adverse effects. In case patients do receive an α-blocker, it is recommended that they take sildenafil and vardenafil at least 4 hours and 6 hours, respectively, after the administration of the α-blocker. In a Korean study, the concomitant medication of an α-blocker with udenafil or mirodenafil at an interval of 6 hours was shown to be safe and without decreased blood pressure.[93,94]

2) Vacuum constriction devices

Vacuum constriction devices provide passive engorgement of the corpora cavernosa together with a constrictor ring placed at the base of the penis. A cylinder is placed over the penis, air is pumped out with an attached pump, and the resulting tumescence is maintained by a constriction ring. Although vacuum constriction devices are highly effective in inducing erections, regardless of the etiology of the ED (70~90%), reported satisfaction rates vary widely from 27% to 94%.[95] Satisfactory outcomes increase if both patients and their partners sufficiently understand the treatment method before using the device. In case patients are insufficiently responsive to oral drugs or

intracavernous injection therapy, vacuum constriction devices can be used concomitantly.

Penile erections with these devices are not normal since they do not use physiological erection pathways. All rigidity is distal to the constriction band and the crura are not involved in the erection, causing some degree of instability, leaving a potential for pivoting at the base and often requiring manual assistance to insert the penis into the vagina. The common adverse events include pain, inability to ejaculate, bruising, and numbness, which occur in less than 30% of patients.[96] To avoid serious adverse events, such as skin necrosis, the use of the devices should be limited to 30 minutes. Excessive negative pressure can cause bruising and hematoma, and to avoid injury to the penis, only devices containing a vacuum limiter should be used.

5. Second-line treatment: Intracavernous injection

Intracavernous injection of vasodilators is used secondarily in patients in whom first-line therapies, such as oral PDE5 inhibitors or vacuum devices, have failed. PGE1 (alprostadil) alone, or a combination of papaverine, phentolamine, and PGE1 (bimix=papaverine+phentolamine, trimix=bimix+PGE1) is recommended.[97] Verapamil, vasoactive intestinal peptide, and forskolin can be additionally mixed with the main drugs, but clinical data on these drugs are insufficient. Papaverine has a relatively high rate of complications, such as prolonged erection and cavernous fibrosis, and phentolamine induces a significant penile erection when combined with papaverine or PGE1.[97] PGE1 monotherapy has a high efficacy rate ($\geq$ 70%) and the lowest rate of prolonged erection (1%).[98,99] Disadvantages of this therapy include penile pain (approximately 50%), a relatively high cost, and low stability (decrease in efficacy after 3 months in a cold storage condition and one week at room temperature).[100] In the comparative studies, bimix was found to be effective and inexpensive, while prolonged erection and cavernous fibrosis were more common, and the success rate was lower than that of trimix. Trimix was shown to have a better efficacy rate (92%) and less pain, but a higher risk of prolonged erection and cavernous fibrosis compared to PGE1.[101-103] In a multicenter study on lyophilized trimix (Standro®; Shin Poong Pharm, Co. Ltd., Seoul, Korea) developed in Korea, the success rate per trial and per patient were 74.1% and 91.2%, respectively, whereas the complication rate was less than 1%.[104] The add-on of PDE5 inhibitors may achieve significant penile erection in patients who are non-responsive to trimix, but the risk of complications (33%), such as dizziness, might increase.[105]

The self-injection dose of vasodilators is determined based on the overall consideration of a patient's age, causes and severity of ED, and penile size. For example, lyophilized trimix (Standro®) is injected initially at a dose of 0.05~0.15 ml depending on the age in patients with psychogenic or neurogenic ED, and at 0.2~0.25 ml with increments of 0.02~0.05 ml for organic ED. The drug is administered using a syringe with a 30-gauge needle or automatic injector on at least two-day intervals, but not to exceed three times a week. Once the initial injection dose is determined at the hospital, instructions should include the following: injection techniques, injection frequency, and potential complications (prolonged erection, pain, bleeding of the injection site, swelling, infection, and cavernous fibrosis).[97] These patients should be followed at an interval of 3~6 months, to evaluate the efficacy and adverse events, and to adjust the dosage.[97]

In general, the risk of prolonged erection ($\geq$4~6 hours) is greater in the early phase of injection therapy, and more frequently occurs when papaverine rather than PGE1 is used.[97] If penile erection is persistent after puncture and aspiration of blood using a syringe with a 19-gauge needle, alpha-adrenergic agonists (phenylephrine, epinephrine) are administered. Phenylephrine (10 mg/ml) is diluted up to 100~500 μg/ml with normal saline, and then 1 ml of the diluted solution is injected each time.[106] Epinephrine (1 mg) is dissolved in 1,000 ml of normal saline, and then 10~20 ml of the diluted solution is injected intracavernosally at intervals of 5 minutes.[107] If rigid erection persists with these methods, shunt surgery should be considered.[108]

Although the success rates of intracavernous injection therapy were about 70~85%, low treatment compliance and high drop-out rates (41~68%) were observed. The majority of the drop-outs occurred within the initial 2~3 months.[109-111] Of the 216 Korean patients with ED, 49.5% discontinued treatment, most drop-outs occurred within the first 1 month, and the most common cause was fear of injection.[112]

6. Third-line treatment: penile prosthesis

The penile prosthesis shows high patient satisfaction. As it is an invasive and irreversible treatment method, however, it should be considered as a last treatment option in patients with ED who are non-responsive to other treatments or who cannot undergo other treatments due to adverse effects.

Penile prostheses are classified into inflatable (2 or 3 pieces) and non-inflatable types (semi-rigid). Most patients prefer the 3-piece inflatable penile prosthesis, which is most similar to a natural penile erection. A non-inflatable penile prosthesis has the disadvantages of constant penile rigidity, a hard texture, and a high risk of erosion, whereas it has the following advantages: ease of use by the patient, a relatively low cost, and a low malfunction rate. In the case that the inflatable penile prosthesis is economically burdensome or the patient has difficulty in using the hands due to stroke, a non-inflatable penile prosthesis can be considered as a first option. It was also reported to be suitable for elderly patients with a low frequency of sexual intercourse.[113] A non-inflatable penile prosthesis can be considered for inexperienced physicians in the case of difficulty in cavernous dilatation due to severe cavernous fibrosis or reservoir insertion from a previous pelvic surgery. In a Korean study, a high patient satisfaction rate and low rate of complications were observed in spinal injury patients after a non-inflatable penile prosthesis was applied.[114]

As a penile prosthesis insertion is an invasive and expensive surgery, proper consultation with patients and their partners is required before surgery. During the consultation, information on other treatment options, types, and features of the penile prosthesis, and advantages and disadvantages, expected price, and potential complications of each prosthetic device should be sufficiently discussed.

The major complications of a penile prosthesis are mechanical failure and infection. The frequency of mechanical failure has gradually decreased due to the ongoing improvements in the design of prosthetic devices. Thus, the frequency of mechanical failure of a 3-piece penile prosthesis (AMS 700CX/CXM[TM] [American Medical Systems, Inc., Minnetonka, MN, USA], Mentor Alpha I[TM] [Mentor Corp., Santa Barbara, CA, USA]), which has recently been in common use, was reported to be less than 5% in a five-year follow-up study.[115,116] In a Korean study that reported the results of a long-term follow-up on a 3-piece penile prosthesis (AMS 700CX/CXM[TM]), the success rates of the penile prosthesis 3 years, 5 years, and 10 years postoperatively were shown to be 95%, 91%, and 75.5%, respectively.[117] As infection is a serious complication that requires removal of the prosthesis, both physicians and patients should take precautions. If a proper technique and broad-spectrum antibiotics, including those for both Gram negative and positive bacteria, are used, the infection rate should be 2~3%. To further reduce the infection rate, studies using a prosthesis containing antibiotics or a hydrophilic-coated prosthesis have been conducted.[118,119] In the case of urinary tract infection or skin infection of the surgery site, the surgery should be delayed. To reduce the risk of infection, the surgery site should be shaved immediately before the surgery, and antibiotics should be administered one hour before the surgery, and then maintained 24~48 hours after the surgery. If infection occurs, all prostheses, in principle, should be removed and antibiotic treatment should be performed, followed by reoperation 6~12 months later. On the other hand, another study reported that the success rate was 82% in patients who underwent penile prosthesis implantation immediately after the removal of the infected prosthesis and sufficient cleaning using various types of antibiotics.[120] Other known complications include pain, hematoma, erosion, self-expansion, penile shortening and fibrosis, urethral rash, and the displacement of the penile prosthesis.

7. Erectile dysfunction after radical prostatectomy

ED is a common complication of radical prostatectomy for prostate cancer. Its occurrence rate varies, ranging from 25% up to 75%.[21] The major cause of ED after radical prostatectomy is the injury of the cavernous nerve that is located at the posterolateral aspect of the prostate. Nerve injury and subsequent ED seem to cause the structural and functional deformity of cavernous endothelial cells and smooth muscle cells.[121] In the early 1980s, Walsh and Donker,[122] and Walsh et al[123] presented the concept of nerve-sparing radical prostatectomy, and reduced the incidence of ED significantly by applying the technique.

Since then, the introduction of the new anatomical concept of the neurovascular bundle, which is responsible for penile erection,[124,125] and the development of surgical techniques using a laparoscope and robot,[126,127] have further reduced the incidence of ED. However, ED that occurs after radical prostatectomy is still a major complication. The occurrence rate of ED after radical prostatectomy significantly varies depending on the study. This difference is likely to be attributable to the difference in the characteristics of subjects and surgical techniques. In the case of bilateral nerve sparing surgery, the postoperative recovery of EF was shown to be better in patients who were young and had good EF before surgery.[128,129]

The treatment of ED that occurs after radical prostatectomy is similar to that used for the general ED population. Although, PDE5 inhibitors are the first-line treatment for radical prostatectomy-induced ED, the response rate to PDE5 inhibitors is lower in these patients than in the general ED population. Patients who have undergone bilateral nerve sparing show a better response to PDE5 inhibitors. In a placebo-controlled study that was conducted on 440 patients who had ED after bilateral nerve sparing radical prostatectomy, 10 mg and 20 mg of vardenafil were shown to improve EF (GAQ question) in 59.7% and 71.1% of the patients, respectively, which was significantly higher than 11.5% in the placebo group.[130] In a placebo-controlled study that was conducted on 303 patients, who had normal EF before surgery but had ED after bilateral nerve sparing radical prostatectomy, the post-operative IIEF EF domain score was shown to be 17.7 and 13.3 points in the tadalafil and placebo groups, respectively. The positive reply rate to the SEP2 question was shown to be 53.9% and 32.4% and 40.5% and 19.4% to the SEP3 question in the tadalafil and placebo groups, respectively. The results showed a significant improvement of EF in the tadalafil group.[131]

A small-scale study conducted by Montorsi et al[132] showed that the recovery of EF can be improved if alprostadil intracavernosal injection therapy is conducted immediately after nerve sparing radical prostatectomy, providing an important theoretical foundation to the concept of penile rehabilitation treatment. Although studies on the daily administration of PDE5 inhibitors have been frequently performed, few double-blind, placebo-controlled studies

have been conducted so far. Furthermore, even with long-term administration of over 36 months, the efficacy was shown to be insignificant. These findings demonstrate the limitation from a cost-efficiency perspective.[133]

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