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Review Article

Benign Prostatic Hyperplasia: from Bench to Clinic

Tag Keun Yoo, Hee Ju Cho

Department of Urology, Eulji University School of Medicine, Seoul, Korea

Benign prostatic hyperplasia (BPH) is a prevalent disease, especially in old men, and often results in lower urinary tract symptoms (LUTS). This chronic disease has important care implications and financial risks to the health care system. LUTS are caused not only by mechanical prostatic obstruction but also by the dynamic component of obstruction. The exact etiology of BPH and its consequences, benign prostatic enlargement and benign prostatic obstruction, are not identified. Various theories concerning the causes of benign prostate enlargement and LUTS, such as metabolic syndrome, inflammation, growth factors, androgen receptor, epithelial-stromal interaction, and lifestyle, are discussed. Incomplete overlap of prostatic enlargement with symptoms and obstruction encourages focus on symptoms rather than prostate enlargement and the shifting from surgery to medicine as the treatment of BPH. Several alpha antagonists, including alfuzosin, doxazosin, tamsulosin, and terazosin, have shown excellent efficacy without severe adverse effects. In addition, new alpha antagonists, silodosin and naftopidil, and phosphodiesterase 5 inhibitors are emerging as BPH treatments. In surgical treatment, laser surgery such as photoselective vaporization of the prostate and holmium laser prostatectomy have been introduced to reduce complications and are used as alternatives to transurethral resection of the prostate (TURP) and open prostatectomy. The status of TURP as the gold standard treatment of BPH is still evolving. We review several preclinical and clinical studies about the etiology of BPH and treatment options.

Key Words: *Etiology; Lower urinary tract symptoms; Prostatic hyperplasia; Therapy*

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Corresponding Author:
Tag Keun Yoo
Department of Urology, Eulji General Hospital, Eulji University School of Medicine, 68 Hangeulbiseong-ro, Nowon-gu, Seoul 139-872, Korea
TEL: +82-2-970-8305
FAX: +82-2-970-8517
E-mail: ytk5202@eulji.ac.kr

INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common diseases, and its incidence has accelerated recently. BPH usually occurs in men in their 50s, and 80% of men in their 70s suffer from BPH-related lower urinary tract symptoms (LUTS) [1]. Although BPH is not a fatal disease, the morbidity from BPH and its potential risk of complications diminishes quality of life (QoL) and causes huge social financial problems [2,3]. BPH-related LUTS are a consequence of dynamic and static obstruction. In the past, age, genetics, and testosterone were regarded as the primary causes of prostate enlargement, but recently, food, exercise, lifestyle, and metabolic syndrome have been recognized as other major causes of BPH and have been widely researched [4]. There have been many changes in the treatment pattern of BPH. Alpha-blockers and 5-alpha reductase inhibitors are becoming the first-line treatment option owing to their excellent efficacy and convenience of administering without severe adverse effects. Laser surgery as a substitute for previous BPH surgery such as transurethral resection of the prostate (TURP) and open prostatectomy has also been attempted. Several research studies on etiologies and treatment options have been published from various preclinical and clinical aspects. This article presents the scientific foundation of prostate enlargement and some reports about innovative trials of BPH therapy.

ETIOLOGY

Age and the presence of androgens are established factors associated with BPH, but the exact cause of BPH is unknown. Previous studies have focused on the links of BPH-related LUTS with inflammation, stromal-epithelial interaction, and the role of androgen receptors. Various etiological models of BPH have recently been evolving rapidly.

1. Metabolic syndrome

In the 1980s, several studies showed that insulin resistance caused various compensatory endocrine aberrations. Increased serum insulin levels, one of the major endocrine aberrations, are associated with type 2 diabetes, coronary disease, hypertension, and dyslipidemia. To date, this cluster of disorders is named the metabolic syndrome (MetS) [5,6]. Metabolic syndrome is increasing in countries with Western lifestyles, and the prevalence of MetS is around 34 to 39% in the United States [7]. An pattern of increasing prostate volume in patients with type 2 diabetes was reported [8], and the possibility of association between MetS and BPH has been investigated in the past decades in several studies [8,9]. Of those studies of MetS, 19 of 22 established aspects of MetS that are indicated as risk factors of BPH. Increased fasting plasma insulin level, increased body weight, type 2 diabetes, increased body mass index, treated hypertension, and lower high-density lipoprotein cholesterol were confirmed to be risk factors of prostate enlargement, and patients with MetS had a higher annual growth rate of the prostate [10-12]. Vikram et al. [13] reported overgrowth of prostate volume in hyperinsulinemic rats induced by a high-fat diet, and a reduction of the fasting plasma insulin level caused shrinkage of prostate volume. The hypothetical link between hyperinsulinemia and BPH was suggested as follows: an increased insulin level, a compensatory phenomenon by insulin resistance, causes an increased density of growth hormone receptors in the liver and then results in an increased hepatic production of insulin-like growth factor 1, which promotes the proliferation of prostate cells [14,15].

Hyperinsulinemia is correlated with enhanced glucose metabolism in the ventromedial hypothalamic neuron, which causes increased sympathetic activity of smooth muscle contraction in the prostate and bladder neck, which increase LUTS [16]. In an animal model, increased sympathetic tone was positively correlated with the increased growth rate of the prostate [17], and elevated C-reactive protein (CRP) in MetS also decreased nitric oxide (NO) synthesis in endothelial cells. Diminished NO and NO synthesis activity may lead to increased smooth muscle proliferation and prostatic enlargement [18,19].

2. Lifestyle, food, and exercise

In past research, the effect of food on prostate enlargement has been controversial. According to a study that analyzed data from the placebo arm in the Prostate Cancer Prevention Trial (PCPT), which enrolled 18,880 men aged over 50 years, high consumption of red meat and a high-fat diet was suggested to raise the risk of BPH, and high consumption of vegetables was associated with a reduced risk of BPH. Lycopene and supplementation with vitamin D could lower the risk of prostate enlargement, but vitamin C, vitamin E, and selenium were reported as not being related [20]. Physical activities were also shown to reduce the possibility of prostate enlargement, LUTS, and LUTS-related surgery [21]. In a meta-analysis that enrolled 43,083 male patients, intensity of exercise was related to reduction of risk of prostate enlargement [22]. A negative correlation between the intake of alcohol and prostate enlargement has been shown in many research studies. In the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, the protective effects of alcohol were noted, particularly for beer and liquor consumption. Men who consumed alcohol moderately were 30% less likely to have clinical BPH, 40% less likely to undergo TURP, and 20% less likely to have nocturia [23]. However, in a meta-analysis of the last 19 studies, incorporating 120,091 patients, men who consumed 35 g or more of alcohol per day had a 35% decreased risk of BPH but an increased risk of LUTS compared with men who did not consume alcohol [24].

3. Inflammation

Among patients enrolled in the Reduction by Dutasteride of Prostate Cancer Event study, histologic inflammation was shown in more than 78% men and the severity of LUTS and the intensity of inflammation were related [25,26]. Another study that enrolled 3,942 patients with BPH showed that 43% of patients had histologic inflammation and 69% of them had chronic inflammation. Also, inflammation in the prostate increased significantly with the increase in prostate volume and age [27]. The data from the placebo arm of the PCPT demonstrated that elevated CRP and interleukin-6 (IL-6) concentrations may increase the risk of BPH [28]. A number of inflammatory cells and proinflammatory cytokines may be involved in the proliferation of the prostate. Kramer et al. [29] concluded that T-lymphocytes, B-lymphocytes, and macrophages are chronically activated in BPH and produce IL 2, interferon gamma (IFN γ), and transforming growth factor β (TGF β), which result in fibromuscular growth of the prostate. Proinflammatory cytokines released from adjacent inflammatory cells were shown to induce the expression of cyclooxygenase-2 (COX-2) in epithelial cells, which then elevated the proliferation rate of cells in the prostate. In 79% of patients with BPH, IL-17 produced by activated T-cells was increased and this overexpression of IL-17 could play a role in increasing COX 2 expression [30,31]. In a report by Penna et al. [32], human prostate stromal cells were shown to act as antigen presenting cells, activating alloantigen-specific $CD4^+$ T cells to produce IFN-γ and IL-17.

Local hypoxia can play a role as one of the inflammatory mediators by inducing lower levels of reactive oxygen species, which can promote neovascularization and fibro-

blasts to myofibroblast transdifferentiation. In particular, increased secretion of vascular endothelial growth factors fibroblast growth factors, fibroblast growth factor FGF-7, TGF-β, FGF-2, and IL-8 was observed under the hypoxic condition in vitro [30].

Direct causality between inflammation and prostate enlargement is not evident. But, the T cell activity and associated autoimmune reaction seem to induce epithelial and stromal cell proliferation.

4. Epithelial-stromal cell interaction and growth factor

In the normal state of the prostate, epithelial cells and stromal cells are very closely associated. Through this interaction between these cells, homeostasis of growth and regression of the prostate can be maintained. A variety of growth factors, such as epidermal growth factor (EFG), TGF-α, TGF-β, and basic FGF (bFGF), are involved as facilitators in the epithelial-stromal interaction [33].

EGF and TGF-α are the most powerful mitosis-promoting factors for epithelial cells. Prostate tissue and prostate fluid include a lot of EGF. The promoting effect of the androgen is thought to be mediated by the EGF, but it is not clear which cells produce EGF or TGF-α.

TGF β has various biological characteristics and is increased in BPH. TGF-β inhibits the function of epithelial cells and is involved in growth arrest and apoptosis. The effect of TGF-β for matrix cells is unclear but it seems to engage the differentiation of matrix cells to the smooth cell phenotype or a variation of extramatrix cells [34]. TGF-β is distributed in smooth muscle actin-positive cells under immunohistochemistry stain. Thus, the origin of TGF-β is thought to be smooth muscle cells.

Basic FGF is a strong promoting factor of cellular mitosis and is over-expressed in BPH. In animal experiments, the over-production of bFGF results in glandular proliferation resembling significant clinical prostatic hyperplasia. Under normal conditions, bFGF is produced by both epithelial and stromal cells, but even though the bFGF is emitted out of cells, bFGF is locked up within the extracellular matrix. The function of bFGF in target cells may be one of the most important factors in understanding the etiology of BPH. The imbalance of these growth factors is accepted as the reason for the abnormal prostate growth.

5. Androgen receptor

The growth of the prostate is dependent on circulating androgen and the intracellular steroid signaling pathway via androgen receptor. The transactivation of the androgen receptor is found in the transactivation domain encoded by exon 1 of the *AR* gene (Xq11-12), which contains polymorphic CAG and GGN (also GGC) repeats encoding polyglutamine and polyglycine tracts, respectively [35]. It is still unclear whether polymorphism of the androgen receptor affects proliferation of the prostate [36]. Some studies have reported that reduced CAG or GGN repeats in the *AR* gene are positively correlated with larger prostate size, whereas recent studies reached the opposite conclusion [36-38]. Given the significant variation in reported findings, CAG or GGN polymorphism of the *AR* gene may not play a major role in the progression of BPH [39].

CLINICAL APPROACH

BPH-related LUTS can be treated by surgical and medical therapy, and the choice of treatment is based on the severity of disease, risk of progression, and patient morbidity. Various surgical and medical treatment options are available to improve LUTS in BPH patients (Table 1). Recently, the dynamic component of BPH has been emphasized, with a focus on symptoms rather than prostate enlargement, which has led to a shift from surgery to medical treatment. However, the efficacy of pharmacotherapy remains somewhat limited. Many minimally invasive surgical treatments, such as laparoscopic surgery and laser surgery, have been developed, but controversy remains over whether these minimally invasive surgical treatments are

TABLE 1. Treatment options for benign prostatic hyperplasia

Watchful waiting		
Nonsurgical treatment	Medical treatment	Alpha-adrenergic blockers
		5-Alpha reductase inhibitor
		Phosphodiesterase 5 inhibitors
		Aromatase inhibitors
		Plant extracts (phytotherapy)
		Combination of these agents
Surgical treatment	Minimally invasive & endoscopic surgery	Transurethral resection of the prostate
		Transurethral needle ablation of the prostate
		Transurethral microwave therapy of the prostate
		Transurethral incision of the prostate
		Intraprostatic stents
	Laser surgery	Vaporization of the prostate
		Enucleation of the prostate
	Invasive surgery	Open simple prostatectomy
		Laparoscopic simple prostatectomy

alternatives for TURP as the gold standard treatment.

1. Alpha-adrenergic blockers

Quick and excellent efficacy without significant adverse effects has made the alpha-adrenergic antagonists, including alzusosin, doxazosin, tamsulosin, and terazosin, the first-line therapy of BPH-related LUTS. Although minor differences in adverse effects between these drugs have been presented, their efficacy in reducing LUTS is comparable. Alpha-adrenergic receptors (ARs) are distributed in the smooth muscle of the whole body. To date, four unique α1-AR subtypes (α1A, α1B, α1D, and α1L) have been identified, but the role of the α1L subtype has yet to be established [40,41]. α1A-AR subtypes are predominant in human prostate and urethra. Distributions ratios of the α1A-AR and α1D-AR subtypes are 69.3% and 27.3% in the urethra and 85% and 15% in prostatic tissue, respectively [42,43]. The α1D-AR subtype is mainly expressed in the detrusor muscle of the bladder and the sacral region of the spinal cord, and blockade of the α1D-AR subtype can relieve irritative symptoms [40,44].

Silodosin is a selective α1A-AR antagonist and its affinity to the α1A-AR subtype is 583-fold that to the α1B-AR and 56-fold that to the α1D-AR. The affinity of tamsulosin to the α1-AR subtype is higher than that of silodosin but the affinity of tamsulosin to the α1A-AR subtype is 15 fold that to the α1B-AR and 3-fold that to the α1D-AR; thus, the selectivity of silodosin to α1A-AR is greater than that of tamsulosin [45]. The selectivity of alpha-adrenergic blockers to the subtypes of ARs is summarized in Table 2.

In a randomized, double-blind, active- and placebo-controlled phase III study, 457 patients were divided into 3 groups (silodosin, n=176; tamsulosin, n=192; placebo, n=89). Silodosin 4 mg PO BID, tamsulosin 0.2 mg PO once daily, or placebo were administered for 12 weeks. The total International Prostate Symptom Score (IPSS) and maximal uroflow rate (Qmax) in the silodosin and tamsulosin groups were improved significantly. The mean intergroup differences in total IPSS and Qmax between the silodosin and tamsulosin groups were not significant, and reduction of the voiding symptom score in the silodosin group was superior to that in the tamsulosin group. Adverse effects occurred more frequently in the silodosin group than in the tamsulosin group. The most common adverse effect in the silodosin group was ejaculatory disorders (22.3%) such as retrograde ejaculation, compared with 1.6% in the tamsulosin group [46]. These ejaculatory disorders were caused by smooth muscle relaxation in the bladder neck and vas deferens [47,48]. The high selectivity of silodosin to the α1A-AR is a distinguishing feature of this agent compared with other AR antagonists, but to prove the significant clinical differences caused by the pharmacologic features of silodosin, further large-scale study is needed.

Naftopidil is an α1D-AR subtype-selective antagonist. Whereas the affinity of tamsulosin and silodosin to the α1A-AR subtype is 3-fold and 56-fold that to the α1D-AR, the affinity of naftopidil to the α1D-AR subtype is 3-fold that to the α1A-AR subtype [49]. In comparative crossover studies between tamsulosin 0.2 mg and naftopidil 50 mg, both AR antagonists reduced the total IPSS and no intergroup differences were identified. In the naftopidil group, however, storage symptoms such as daytime frequency, urgency, and especially nocturia were improved more than in the tamsulosin group [50,51], and the mean first desire to void and mean maximum desire to void were significantly higher than in the tamsulosin group (188.4 ml vs. 339.4 ml) [51]. In other studies, no data about irritative symptom improvement were reported. Additional study is needed to make solid conclusions.

2. 5-Alpha-reductase inhibitor

5α-Reductase converts testosterone to dihydrotestosterone (DHT), which is more potent than testosterone in the prostate. 5α-Reductase inhibitor (5-ARI) acts as an androgen suppressor causing regression of epithelial elements in the prostate. Consequently, prostatic enlargement, the static component of bladder outlet obstruction, is diminished. Finasteride (a type 2 5-ARI) and dutasteride (a dual inhibitor of both type 1 and type 2 5α-reductase) decrease the DHT level in the prostate by 80% and 94%, respectively, and the serum half-life of finasteride is 6 to 8 hours and that of dutasteride is 5 weeks [52,53]. This pharmacologic discrepancy between these drugs makes a minor difference in efficacy and adverse effects.

In the Medical Therapy of Prostatic Symptoms Trial that compared monotherapy and combination therapy with doxazosin and finasteride, combination therapy lowered the risk of BPH progression compared with monotherapy with doxazosin or finasteride (67% for combination therapy, 39% for doxazosin, 34% for finasteride) and was superior in improving the American Urological Association Symptom Index score and Qmax compared with monotherapy and placebo [54]. According to the Combination of Dutasteride and Tamsulosin study, which enrolled 4,844 men ≥50 years of age with prostate volume ≥30 g and a clinical diagnosis of BPH, combination therapy reduced the relative risk of clinical progression, the risk of acute urinary retention, and BPH-related surgery significantly and

TABLE 2. Selectivity of α-adrenergic blockers to AR subtypes

	Alfuzosin	Doxazosin	Tamsulosin	Terazosin	Silodosin	Naftopidil
Selectivity to AR subtypes	Nonselective	Nonselective	α1A=α1D>α1B	Nonselective	α1A>α1D>α1B	α1D>α1A>α1B

AR, alpha-adrenergic receptor.

induced greater symptom benefit than either monotherapy at 4 years [55]. Guidelines for the management of BPH by the American Urological Association and the European Association of Urology recommend the use of 5-ARIs for male patients with LUTS caused by an enlarged prostate.

3. Phosphodiesterase 5 inhibitor

There has been increasing interest in the use of phosphodiesterase type-5 (PDE5) inhibitors to treat BPH-related LUTS. The current postulated mechanisms of action of PDE5 inhibitors in improving BPH-related LUTS include the following. First, inactivation of cGMP-mediated ρ-kinase; second, increase of nitric oxide synthase (NOS) and NO activity in the prostate; third, decrease of autonomic hyperactivity affecting the bladder, prostate, and penis; and fourth, reduction of pelvic ischemia [56,57]. Activated ρ-kinase inhibits smooth muscle myosin phosphatase. This action leads to the sensitization of myofilaments to Ca^{2+}, which results in smooth muscle contraction [58]. Increased NO and cGMP by PDE5 inhibitors relaxes the smooth muscles of the lower urinary tract and could be used for the treatment of LUTS [59]. Autonomic hyperactivity, an aspect of MetS, promotes contraction of the endothelium and ultimately could lead to the occurrence of LUTS [60]. Chronic ischemia and arterial insufficiency caused by bladder and penile atherosclerosis promote structural and functional changes of the bladder, prostate, and penis that also lead to LUTS [61].

In a study by McVary et al. [62], male patients with BPH and erectile dysfunction were administered 50 to 100 mg sildenafil and placebo daily for 12 weeks. Compared with that in the control group, IPSS and QoL in the sildenafil group were reduced (IPSS, 6.32 vs. 1.93 points; QoL, 0.97 vs. 0.29 for sildenafil and placebo; $p < 0.0001$). In another study, 2.5, 5, 10, or 20 mg tadalafil was administered to BPH patients daily for 12 weeks. Except for the 2.5 mg tadalafil group, all other tadalafil groups improved significantly in terms of IPSS and QoL compared with the placebo group. Also, 5 mg tadalafil showed the most superior risk-benefit profile. The mean IPSS reductions were 4.87 for tadalafil 5 mg and 2.27 for the placebo group ($p < 0.001$). The mean improvements in the International Index of Erectile Function-Erectile Function domain score in the tadalafil groups were superior to that in the placebo group (6.97 for tadalafil vs. 2.20 for placebo, $p < 0.001$) (Table 3) [63]. In a randomized, placebo-controlled study to assess the efficacy of twice-daily vardenafil 10 mg for 8 weeks, the mean IPSS reduction was significant in the vardenafil group compared with placebo (5.9 for vardenafil vs. 3.6 for placebo, p=0.0013). However, no significant difference in Qmax was found between the groups [64]. These preclinical and clinical studies have provided hopeful evidence that PDE5 inhibitors may be an effective and acceptable treatment option for BPH, but at the present time, the high cost of PDE5 inhibitors is a significant obstacle. Cost-efficacy analysis must be conducted.

4. Phytotherapy

Many kinds of complementary and alternative medicines have been used as treatment methods for BPH, and herbal therapy is considered to be the mainstay among those treatments [65]. Millions of people worldwide have used herbal agents to treat BPH-related LUTS, and recently, interest in these agents has increased through advertisements in the mass media and online shopping. Saw palmetto, one of the most popular herbal medicines, is an extract of the fruit of *Serenoa repens* composed of fatty acids and phytosterols. In a past meta-analysis, saw palmetto was shown to increase self-rated improvement, increase the peak flow rate, and in particular improve nocturia, but controversy over its effects remain [66].

The mechanism of the effect of saw palmetto is poorly defined. Investigators have proposed antiandrogenic activity via 5-alpha reductase inhibition and subsequent prevention of the conversion of testosterone to dihydrotestosterone [67], an anti-inflammatory effect [68], competitive inhibition of androgen binding, a decrease in the bioavailability of the sex hormone-binding globulin [69], and inhibition of growth factor-induced prostatic cell proliferation [68,70].

In 2011, a double-blind, multicenter, placebo-controlled randomized study to investigate the efficacy of saw palmet-

TABLE 3. Changes from baseline to 12 weeks in IPSS and IIEF in tadalafil treatment groups

Improvement of symptoms	Placebo	Tadalafil (mg)			
		2.5	5	10	20
Total IPSS	2.27±0.49	3.88±0.5	4.87±0.49[a]	5.17±0.49[a]	5.21±0.5[a]
Irritative symptoms	0.99±0.23	1.58±0.23	1.89±0.23[a]	1.96±0.23[a]	2.07±0.23[a]
Obstructive symptoms	1.26±0.33	2.23±0.33	2.94±0.33[a]	3.13±0.32[a]	3.12±0.33[a]
QoL	0.49±0.11	0.74±0.11	0.86±0.11[a]	0.92±0.10[a]	0.88±0.11[a]
IIEF-EF	2.20±1.03	5.59±1.01[a]	6.97±1.01[a]	7.98±1.0[a]	8.34±1.01[a]

Roehrborn et al., 2008 (J Urol 2008;180:1228-34).

Values are presented mean±SD.

IPSS, International Prostate Symptom Score; QoL, quality of life; IEEF-EF, International Index of Erectile Function-Erectile Function domain.

[a]: p-value < 0.05 compared with placebo.

to was reported [71]. Three hundred sixty-nine men ≥45 years of age with Qmax≥4 ml/s and IPSS of 8 to 24 were enrolled and administered saw palmetto for 72 weeks. The dose of saw palmetto was 320 mg per day, which was escalated to 960 mg per day if needed. Administration of saw palmetto had no significant effect in terms of IPSS, Qmax, or adverse effects compared with placebo.

5. Surgical therapy

Although the proportion of medical therapy and the use of several effective minimally invasive treatments have been increasing as a primary treatment for BPH, TURP remains the predominant treatment method [72]. TURP has been considered the gold standard treatment of BPH. Detection of prostate cancer in BPH patients with previously negative transrectal ultrasonography prostate biopsy is one of the advantages of TURP. Kim et al. [73] investigated 1,341 BPH patients with a previous negative biopsy result who underwent TURP. They concluded that TURP could immediately improve bladder outlet obstruction and provide an early diagnosis of clinically significant transition zone prostate cancer. Another study showed the excellent survival rate of patients with prostate cancer (stage pT1a) that was detected through TURP [74]. Deciding on a therapy in patients with mild LUTS, elevated prostate-specific antigen (PSA) levels, and multiple negative previous biopsy results is a challenge for urologists. In these patients, bladder outlet obstruction may account for an elevated serum PSA level. TURP could improve LUTS without severe surgery-related morbidity. Decreasing the level of serum PSA after TURP helps urologists to monitor prostate cancer development by PSA [75].

Complications of TURP have been a challenging problem, but the rate of complications, including transurethral resection syndrome (TUR syndrome), postoperative bleeding, and reoperation, has decreased. A cooperative study of 13 participating institutions evaluating 3,885 patients by Mebust et al. [76] that was published in 1989 reported a transfusion rate of 6.4%, an intraoperative complication rate of 6.0%, and a mortality rate of 0.1%. After a decade, Borboroglu et al. [77] reviewed 520 consecutive patients who underwent transurethral prostatectomy between 1991 and 1998. They reported decreased immediate and postoperative complication rates (0.4% for transfusion, 2.5% for intraoperative complications, and 0% for mortality). In the 2000s, Reich et al. [78] prospectively evaluated 10,654 patients undergoing TURP in the state of Bavaria, Germany, from January 2002 until December 2003. This study reported intra- and perioperative morbidities as follows: transfusion rate 2.9%, TUR syndrome 1.4%, reoperation 5.6%, and mortality 0.1% (Table 4). These advances in intra- and perioperative outcome have continued and the transfusion and reoperation rate are decreasing in patents who undergo TURP by an experienced surgeon.

One of the most outstanding technical advancements is the use of bipolar TURP. Bipolar devices allow TURP with saline irrigation, which lessens water intoxication and negates unwanted stimulation of the obturator nerves and cardiac devices. Bipolar TURP is an effective and safe surgical treatment method with additional advantages over monopolar TURP, even in patients with large prostates. Vigorous complications including massive bleeding requiring transfusion and TUR syndrome associated with bipolar TURP are rare [79,80].

Open simple prostatectomy can remove large prostate adenomas completely without complications like TUR syndrome, and reoperation caused by recurred prostate hyperplasia is extremely rare. However, massive hemorrhage and a long hospital stay were problematic. With the aim of addressing these complications and the disadvantages of both surgeries, in 2002, the first research on the efficacy and safety of laparoscopic simple prostatectomy was reported [81]. In 2006, Baumert et al. [82] compared perioperative outcomes of the first 30 consecutive laparoscopic simple prostatectomies performed by 1 surgeon and 30 consecutive open simple prostatectomies for patients with large-sized BPH of more than 100 g. The average operation time of laparoscopic surgery was longer than that for standard surgery but intraoperative blood loss (367±363 vs. 643±647 ml), hospital stay (5.1±1.8 vs. 8±4.8 days), irrigation time (0.33±0.7 vs. 4±3.5 days), and duration of catheter indwelling (4±1.7 vs. 6.8±4.7 days) were shorter in laparoscopic prostatectomy. Several other studies also reported significant improvement of IPSS and Qmax in patients with huge BPH by laparoscopic retropubic prostatectomy. No severe complications such as postoperative incontinence were reported [83,84].

To reduce the disadvantages including postoperative bleeding, the long period of catheterization, and TUR syndrome, many kinds of laser surgery have been used, of

TABLE 4. Intraoperative and early postoperative complications of TURP

	Mebust et al. (1989) [76] (n=3,885)	Borboroglu et al. (1999) [77] (n=520)	Reich et al. (2008) [78] (n=10,654)
Transfusion (%)	6.4	0.4	2.9
TUR syndrome (%)	2.0	0.8	1.4
Urinary tract infection (%)	2.3	2.1	3.6
Voiding failure (%)	6.5	-	5.8
Mortality (%)	0.1	0	0.1

TURP, transurethral resection of the prostate.

which potassium-titanyl-phosphate laser vaporization of the prostate and Holmium laser enucleation of the prostate (HoLEP) are the most representative. Kang et al. [85] investigated the efficacy and complications of Greenlight HPS laser photo-selective vaporization of the prostate (PVP) in treating 104 BPH patients. Without delayed hematuria, obstructive retention, or TUR syndrome, improvement of IPSS and Qmax were maintained for at least 12 months postoperatively. The only major postoperative complication in this study was mild dysuria (n=14, 13.4 %). Kim et al. [86] analyzed the clinical data of 74 patients who underwent PVP laser vaporization of the prostate with 2 years of follow-up. IPSS and uroflowmetry with postvoid residual urine volume (PVR) were assessed at 1, 3, 6, 12, and 24 months postoperatively. Significant improvements at 1 month after surgery compared with baseline were maintained up to 24 months postoperatively. Although the safety and efficacy of PVP are brilliant, the need for additional laser fibers in dealing with large prostates and the loss of prostate tissues for pathologic testing are considerable limits of PVP.

HoLEP can be used in treating patients with huge BPH without these problems. The holmium laser, with a wavelength of 2,140 nm, conducts through saline and has excellent hemostatic properties. There is potentially no limit to the size of a prostate that can be treated with HoLEP. Krambeck et al. [87] reported significant improvement of IPSS (from 19 to 6.5 at 6 months postoperatively) and Qmax (from 8.2 ml/s to 18.5 ml/s at 6 months postoperatively) in treating patients with BPH (average size of prostate, 217 g) without any severe complications. In another study that analyzed long-term operative outcomes of 164 consecutive HoLEP cases, the median PVR declined by 87.5%, whereas the mean Qmax rate was increased by 94% and the mean IPSS and median QoL scores were decreased by 63.2%, and 56.6%, respectively, at 6 months postoperatively. Postoperative complications included transient incontinence (8.5%) and urinary retention (4.3%), and 3% of patients required readmission due to delayed hematuria [88]. The relatively high occurrence rate of transient incontinence (1.4 to 44%) is one of the most problematic complications in HoLEP [89-91]. The slow learning curve is also a challenge, and the operative time is still longer compared with standard TURP [90,92]. If technical advancements to reduce transient incontinence and operation times are developed, HoLEP can become the mainstay in treating patients with large BPH.

CONCLUSIONS

Benign prostatic hyperplasia is one of the most common problems that urologists deal with in the clinic. The prevalence of BPH increases from approximately 50% at 60 years of age to 90% in men older than 85 years. The etiologies of BPH are still not well defined. To date, multi-factorial and chronic conditions including metabolic syndrome, genetics, inflammation, and lifestyle have been studied to prevent BPH progression. Patients' demands for effective, safe, and easy treatment options have led to several trials of medicine and minimally invasive surgeries such as laser or laparoscopic surgery. To date, admirable advancements in understanding the causes of BPH progression and in developing new gold standards of treatment have been achieved. However, unsolved problems remain in the preclinical and clinical aspects of BPH.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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