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Review Article

Benign Prostatic Hyperplasia (BPH): Perennial Plague of the Prostate

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Received: December 28, 2020; **Published:** Janaury 30, 2021

DOI: 10.31080/eccmc.2021.04.00356

Abstract

Benign prostatic hyperplasia (BPH) is a common condition with lower urinary tract symptoms (LUTS) in middle-aged and older men. BPH is the most prevalent non-malignant urological disorder. Nearly three hundred years ago, an enlarged prostate was recognized to cause urinary retention. LUTS include inconsistent urine flow, partial or complete urine retention, increased urinary frequency, difficulty emptying the bladder, nocturia, and dysuria. BPH is not a life-threatening condition; however, increased severity can cause urinary tract infections, bleeding, bladder stones, and kidney damage. BPH diagnosis is made by symptom score, quality-of-life (QoL) score, physical examination, and diagnostic imaging, such as ultrasonography, cystoscopy, and uroflowmetry. Age, genetics, and other factors, including lifestyle, affect BPH development and progression. Conservative treatment for BPH includes watchful waiting, pharmacological intervention, and specific lifestyle changes. There are a variety of surgical interventions available, the choice of which is based upon several factors. However, surgical intervention is a last resort for BPH treatment and is used primarily refractory from medications or in severe symptoms and complications. Invasive techniques include minimally invasive therapy and novel treatment modalities, as described in this paper.

Keywords: *Ablation; Prostate Enlargement; Saw Palmetto; Urinary Tract Infection; Watchful Waiting*

Abbreviations

BoNT: Botulinum Neurotoxin; BoNT-A: Botulinum Neurotoxin Type A; BPH: Benign Prostatic Hyperplasia; DHT: Dihydrotestosterone; HoLEP: Holmium Laser Enucleation of the Prostate; IGF-1: Insulin-Like Growth Factor 1; IPP: Intravesical Prostatic Protrusion; KTP: Potassium-Titanyl-Phosphate; LUTS: Lower Urinary Tract Symptoms; MIT: Minimally Invasive Therapy; PAE: Prostatic Artery Embolization; PSA: Prostate-Specific Antigen; QoL: Quality-of-Life: ThuVEP: Thulium Laser VapoEnucleation of the Prostate; TUIP: Transurethral Incision of the Prostate; TUR: Transurethral Resection; TURP; Transurethral Resection of the Prostate; TUNA: Transurethral Needle Ablation; UTI: Urinary Tract Infection

Introduction

In the 17th century, Herr first proposed that an enlarged prostate could cause urinary retention. Benign prostatic hyperplasia (BPH) is the most frequently occurring non-malignant urological disease, characterized by an enlarged prostate and bladder outlet restriction.

BPH is a common condition characterized by lower urinary tract symptoms (LUTS) in middle-aged and older men. Typically, the age at BPH onset is about 40 years, and nearly 70% of men develop BPH by 70 years of age. LUTS include inconsistent urine flow, partial or complete urine retention, increased urinary frequency, nocturia, and dysuria [1]. Although BPH is not a life-threatening condition, increased severity can cause urinary tract infections (UTIs), bleeding, bladder stones, and kidney damage [2]. The diagnosis of BPH depends on symptom score, quality-of-life (QoL) score, physical examination, and diagnostic imaging, such as ultrasonography, cystoscopy, and uroflowmetry.

Etiology of BPH

Age, genetics, growth factors, circulating hormone levels, neurotransmitters, chronic inflammation, and lifestyle are specific elements responsible for BPH development. Moreover, the disease is associated with pathological conditions, such as chronic inflammation [3], diabetes, and obesity [4].

Several studies have confirmed that BPH prevalence increases with age. Age-related chromosomal aberration due to hormonal imbalance in the prostate [5], abnormal tissue remodeling [6], and inflammation [3] have been reported to promote BPH development. Genetic studies have revealed that BPH is an autosomal dominant inherited condition in a few men [2,4].

Growth factor-mediated stromal cell growth and tissue remodeling results in prostate enlargement [7]. The development of epithelium and mesenchyme in the prostate is controlled by androgen. In the prostate, testosterone is converted to dihydrotestosterone (DHT) [8]. In BPH, a high level of serum DHT and its metabolite are detected [4]. Estrogen and selective estrogen receptor modulators possibly play a role in regulating stromal-epithelial interactions involved in prostatic cellular growth [9]. In benign prostatic epithelial cells, estradiol induces epithelial-to-mesenchymal transition [10], resulting in prostatic hyperplasia. The loss of E-cadherin and an increase in pSmad3 markers have been observed in BPH tissue samples. These findings indicate that BPH is caused by the accumulation of mesenchymal-like cells derived from prostatic epithelium cells [11].

In a histological study of surgical BPH specimens, the level of prostate enlargement directly correlated with the severity of inflammation [12]. An increases in the level of C-reactive proteins was evident in patients with LUTS [4]. Inflammation triggers cytokines' release and increases the concentration of growth factors, resulting in the abnormal proliferation of prostate cells [13]. In addition to advancing age, obesity contributes to the inflammatory processes [14]. Increased adiposity, body weight, and body mass index are associated with expanded prostate volume [4].

Comorbidities adversely affecting BPH

Diabetes and elevated plasma glucose, serum insulin-like growth factor 1 (IGF-1), and IGF-binding protein-3 expand prostate size, causing clinical BPH [15]. Patients with BPH are more susceptible to infections and vice-versa [16]. Heavy smoking, lack of physical activity, and high protein intake are the other factors associated with BPH [17].

Pathophysiology of BPH

The precise molecular mechanisms of BPH are unclear. In BPH, the prostate is enlarged due to smooth muscle and epithelial cell proliferation in the prostatic transition zone [18]. BPH may also be influenced by the accumulation of mesenchymal cells derived from prostatic epithelial cells [11]. Prostate enlargement leads to a blockage of the bladder outlet. The definitive diagnosis of the condition is facilitated by diagnostic imaging and the identification of serum biomarkers.

The serum level of prostate-specific antigen (PSA) correlates with prostate size. Therefore, serum PSA serves as a biomarker for BHP progression in the absence of malignancy. Men with a PSA of ≥ 1.5 ng/mL are at a higher risk for developing significant progressive BPH, over time [19].

DNA microarray can be used to identify and potentially differentiate symptomatic from asymptomatic BPH. JM-27 is upregulated in the diseased prostatic tissue [20] and is reflected in the serum [15] of patients.

The site of the tumor determines the degree of bladder outlet obstruction [21]. Prostate enlargement distorts the bladder neck and protrudes into the bladder lumen, as can be noted in ultrasonography. This protrusion is termed intravesical prostatic protrusion (IPP). The grading of IPP deliniates BPH's stage and progression and serves as a better predictor of an obstruction than prostate volume and serum PSA [22].

Treatment for BPH

Severe BPH can be life-threatening, affect organ functions, and deteriorate the patient's quality-of-life (QoL). of patients. Hence, it is vital to obtain a detailed patient history, pathogenesis, and disease progression risk in considering appropriate treatment. Other factors influencing treatment decisions are age, existing comorbidities, prostate size, and PSA level. BPH treatment options are as follows.

Watchful waiting

Watchful waiting is recommended for patients with lower-grade BPH with mild or no symptoms. This approach comprises lifestyle modifications, such as regular exercise, dietary changes, smoking and alcohol intake reduction or elimination, and regular follow-up visits to a healthcare provider[22].

Pharmacological intervention

Medications constitute the first-line treatment for BPH. Several hormonal drugs are prescribed to treat BPH.

Alpha-1 antagonists

Alpha-1 blockers relax the prostate's smooth muscle by inhibiting the effect of alpha-1 receptors in the urethra and bladder neck [23]. Terazosin, doxazosin, tamsulosin, and alfuzosin are long-acting alpha-blockers used in BPH treatment. These drugs provide quick symptomatic relief but do not prevent disease progression. A more selective alpha-blocker, silodosin, seems to have a comparable effect to other blockers [24]. Adverse effects of these drugs include fatigue, dizziness, and hypotension in elderly patients.

5-alpha reductase inhibitors

The 5-alpha reductase inhibitors block testosterone's conversion to DHT, reducing prostate volume and obstruction through epithelial atrophy [25]. The efficacy of the drug is more pronounced in patients with higher prostatic volumes than lower. Finasteride, the first approved 5-alpha reductase inhibitor, functions by inhibiting type II 5-alpha reductase [26]. Dutasteride inhibits both type I and II 5-alpha reductase [27]. Finasteride and dutasteride have been reported to prevent disease progression and reduce urine retention and the need for surgery in patients with BPH.

Although dutasteride displays more significant DHT inhibition than finasteride (> 90% vs. > 70%), both drugs have similar effects on clinical symptoms. Adverse effects of these drugs concern decreased androgenic stimulation, resulting in reduced sexual urges and erectile dysfunctions. Although 5-alpha reductase inhibitors reduce prostate cancer's overall incidence, they seem to increase the relative risk of high-grade malignancy [22].

Monotherapy with alpha-1 antagonists or 5-alpha reductase inhibitors is effective; nevertheless, outcomes seem to improve with combination therapy. A study by McConnell., *et al*. (2003) reported that treatment with doxazosin or finasteride alone resulted in a 34% and 39% risk reduction, respectively, whereas combination therapy resulted in a 66% clinical risk reduction [28]. Adverse effects of combination therapy are higher than monotherapy; only patients with a high prostate volume (> 30g) and non-responders to alpha-1 antagonist monotherapy are considered for combination therapy.

Antimuscarinic agents

Over-reactive bladder symptoms are an atypical adverse effect of BPH treatment. Antimuscarinic agents, such as tolterodine and fesoterodine, inhibit acetylcholine receptors in the bladder. This interference reduces bladder contraction and urine storage (characterized by increased urinary frequency and urgency). Antimuscarinic agents are preferred for short-term use and in combination with alpha-1 blockers [29].

Phosphodiesterase-5 inhibitor

Tadalafil, a phosphodiesterase-5 inhibitor, is also used for BPH treatment. The possible mechanisms of action include relaxation of smooth muscles in the lower urinary tract by increasing cyclic guanosine monophosphate, inhibiting local inflammation, and improving blood flow and oxygenation to the lower urinary tract [22].

Phototherapeutic agent

Saw palmetto, the extract of Serenoa repens berries, is a phototherapeutic agent that is commonly used in BPH treatment [30]. The extract inhibits 5α-reductase and blocks the binding of DHT to cytosolic androgen receptors in prostate cells. It is moderately effective in reducing nocturia and increasing urinary flow. However, it can aggravate chronic gastrointestinal conditions, such as peptic ulcers.

The oral administration of these agents appears superior to a placebo in improving BPH's subjective and objective symptoms in the patient. However, phytochemicals are limited by the lack of rigorous preclinical pharmacological testing and formal clinical trials. Moreover, the medication's active ingredients and dosage are not known, the quality of the drug is not publicly controlled, and the mechanism of action is not precisely understood.

Surgical intervention

Surgical intervention is a last resort for BPH treatment. Surgery seems to a benefit patients refractory from medications and with severe symptoms and complications, such as urinary retention, renal failure, and infection. It is also cost-effective in reducing long-term medical and allied spending. Available surgical approaches include traditional surgery and minimally invasive surgery.

Invasive technique

Transurethral resection of the prostate (TURP) remains the gold standard surgical treatment for BPH. However, the technique is associated with bleeding, infection, retrograde-ejaculation, low PSA level, and impotence. Monopolar TURP, which can result in transurethral resection (TUR) syndrome and other adverse effects leading to morbidity, has been replaced with bipolar TURP. A study by Karadeniz., *et al*. (2016) demonstrated that bipolar resection with 0.9% NaCl had minimal effects on serum sodium compared with monopolar resection [31]. However, some studies have indicated that both techniques are clinically equivalent and can lead to similar complications, such as retrograde ejaculation [32].

Other similar operative techniques include transurethral incision of the prostate (TUIP) and transurethral needle ablation (TUNA). Both of these techniques are useful for small-sized prostate and are less invasive than TURP [33].

Laser ablation therapy

Laser therapy is preferred to TURP as it is less invasive and associated with lower perioperative morbidity and hospitalization. First reported in 1996, Holmium laser enucleation of the prostate (HoLEP) is an endoscopic surgical intervention utilizing a pulsed laser for cutting the tissue [34]. It is similar to TURP in efficacy but is associated with lower perioperative morbidity and better urodynamic outcome [35]. The adverse effects of HoLEP include postoperative retrograde ejaculation and short-term postoperative complications [36]. HoLEP is an emerging surgical management approach for BPH.

Thulium laser vapoenucleation of the prostate (ThuVEP) is another type of surgical intervention, producing a clean and fast cut via vaporization. Thulium laser is considered superior to holmium laser and similar to TURP in efficacy and safety [16]. Although ThuVEP is more time-consuming than TRUP, it has many advantages, such as better serum sodium level control and lesser blood transfusion need [37].

Greenlight is a laser ablation therapy employing a high-powered potassium-titanyl-phosphate (KTP) photoselective vaporization system—absorbed in tissue with high oxyhemoglobin content. Additionally, Greenlight and HoLEP have been shown to have comparable efficacies and outcomes [38].

Each laser modality is on par or superior to the standard TURP. However, a significant concern with laser techniques is the steep learning curve of practitioner proficiency, varying in degree among the different modalities utilized.

Minimally invasive therapy

Minimally invasive therapy (MIT) is associated with the marginal use of anesthesia, reduced or no hospital stay, and a relatively rapid recovery period. An MIT employs physical retraction of the obstructing prostatic lobes without causing wounds.

Prostatic urethral lift (UroLift™) is a technique in which a delivery device is utilized to access the enlarged prostate (through the urethra), retract the obstructing prostatic lobes, and deliver transprostatic permanent implant through a needle. This method does not lead to sexual dysfunction. However, patients with significant prostate burden, history of urinary retention, previous operation, high PSA (>10 ng/ml), and UTIs are considered ineligible for the surgery [39].

Temporary or permanent intraprostatic stents are positioned endoscopically and placed in the prostatic urethra, opening the bladder outlet. Stents can be placed quickly, using local anesthesia. However, stent migration leads to failure, the removal of which requires general anesthesia. Permanent stents can lead to infection and dislodgement, causing a urinary obstruction or total incontinence [35]. The outcome of stents for BPH treatment remains understudied.

Other mechanical therapies are temporary implantable nitinol devices, such as the ZenFlow™ spring, implantable C-shaped ring (ClearRing™), and Butterfly™. These devices have shown promising results in terms of safety and efficacy. Studies assessing their effectiveness are ongoing [35].

Emerging treatments

Novel treatment modalities are emerging to improve the QoL of patients with BPH. However, long-term clinical data are needed to support the replacement of currently available treatments.

Fexapotide triflutate (NX-1207) is a new molecular entity that has shown potential in a clinical trial by significantly improving BPH symptoms in patients in the long-term, regarding to urine retention and incidence of surgery. The compound is locally injected, positioning it as a first-class treatment option [40]. Botulinum neurotoxin (BoNT) reduces contractibility and obstruction by the prostatic mass by downregulating alpha-1a receptors. Although promising, the application of botulinum neurotoxin type A (BoNT-A) is limited to select patients refractory to invasive procedures and long-term oral medications [35].

Prostatic artery embolization (PAE) is a radiologic procedure in which microspheres are injected through a catheter into prostatic arteries, resulting in prostatic growth impediment. The prostate size reduces due to decreased DHT, inflammation, and ischemia of intraprostatic vessels [41]. Water vapor therapy (REZUM™) involves the ablation of prostatic tissue, using sterile water in the form of steam [42]. Aquablation is the ultrasound-guided dissection of prostate tissue, using high-pressure saline, and is comparable to TURP's efficacy [43].

All of the therapies mentioned above preserve the patient's sexual ability with shorter operation time and less complications. The major disadvantage in considering these therapies is the lack of long-term clinical data.

Conclusion

The mechanism of benign prostatic hyperplasia remains unclear. A better understanding of the disease will aid in selecting appropriate therapy. Globally, BPH contrinues to grow in prevalence; however, there is a wide range of treatment options. Treatment choice is based primarily on the patient's condition and the physician's preference and expertise. As BPH continues to increase, further research for optimizing treatment is essential.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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Volume 4 Issue 2 February 2021