Pathology and Medical Therapy of Benign Prostatic Hyperplasia

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Introduction

Benign Prostatic Hyperplasia (BPH) is a progressive condition characterised by prostate enlargement accompanied by lower urinary tract symptoms (LUTS). It contributes to, but is not the sole cause of LUTS. It is well known that BPH and the resultant LUTS is very common in elderly men and has a great impact on the patients’ quality of life. It was estimated that in the male population, a histological prevalence at autopsy of 50% in men aged 50-60 years and of 90% over 80 years was seen. 75% of men > 50 years old had symptoms arising from BPH, and 20-30% of men reaching 80 years old required surgery. Despite the fact that BPH is one of the commonest diseases that are managed by urologists and it has a big impact on public health, the aetiology and pathophysiology are still not yet clear.

Aetiology

Several mechanisms are now believed to be important in the development and progression of BPH:

Tissue Remodelling

McNeal demonstrated that BPH first develops in the periurethral transition zone of the prostate and all the BPH nodules develop either in the transition zone or in the periurethral region. Although early transition zone nodules appear to occur either within or immediately adjacent to the preprostatic sphincter, as the disease progresses and the number of prostatic nodules increases, they can be found in almost any portion of the transition or periurethral zone. The nodular enlargement is androgen-dependent and the tissue remodelling involves both the epithelium and fibromuscular stroma. These nodules are characterised by a reduced epithelium-to-stroma ratio, determined by an imbalance between growth and death programmes of stromal cells, leading to increased final stromal volume. The underlying mechanism may be attributable to the involvement of enhanced expression of anti-apoptotic cell death mechanisms in the human prostate, resulting in a growth imbalance in favour of cell proliferation that might ultimately support hyperplasia.

Hormonal Alterations

Although androgens do not cause BPH, the development of BPH requires the presence of testicular androgens during prostate development, puberty and ageing. Despite the fact that the serum level of testosterone decreases with age, it is known that the intra-prostatic levels of the active metabolite dihydrotestosterone (DHT) as well as the androgen receptor (AR) remain high. DHT is predominantly generated by prostatic 5-alpha reductase, which is present in fibroblasts of the stroma and in basal epithelial cells and recent androgen-responsive genes studies showed that androgen signalling is significantly elevated in hyperplastic tissue relative to the adjacent normal prostate.

Inflammation

BPH has been frequently observed to be associated with chronic prostatitis and now chronic inflammation is believed to support the process of fibromuscular growth in BPH. Many studies including major studies like the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial and the subgroup analysis of the Medical Therapy of Prostate Symptoms Study (MTOPS) found correlation between inflammation of the prostate and BPH. It was proposed that inflammation of the prostate caused tissue injury, and cytokines produced by the inflammatory cells might serve to drive local growth factor production and angiogenesis in the tissue as a wound healing process, resulting in tissue growth.

Metabolic Syndrome

BPH and the metabolic syndrome are believed to be associated according to recent studies. The metabolic syndrome is defined as abdominal obesity associated with hyperinsulinaemia, insulin resistance and two additional cardiovascular risk factors. Diabetes mellitus, hypertension, obesity and low high-density lipoprotein cholesterol (HDL-C) levels constitute risk factors for the development of BPH.

Pathophysiology

According to the classical model and belief, the size of the prostate increases with BPH, thus resulting in the obstruction of the urine flow that accounts for the LUTS. Therefore, the logic was previously surgery like prostatectomy or drugs that can reduce the resistance to urine flow can resolve LUTS. However, it is now known that the pathophysiology of BPH is much more complex: prostatic hyperplasia increases urethral resistance, resulting in compensatory changes in bladder function. The obstruction-induced changes in detrusor function, compounded by age-related changes in both bladder and nervous system function, lead to urinary frequency.
urgency and nocturia, the most bothersome LUTS. This concept can at least be partly proven from the study by Neal et al, which showed prostatectomy could resolve the emptying problem of LUTS but not the storage problem\textsuperscript{5}.

Half of the stromal hyperplasia is composed of smooth muscle elements\textsuperscript{5} and it was believed that the enlarged prostate caused obstruction via both dynamic and static mechanisms\textsuperscript{27}. The static component was due to the physical presence of the prostate obstructing the urine stream within the prostatic urethra and the dynamic obstruction was thought to be the result of smooth muscle hyperplasia and contraction\textsuperscript{28} and was mediated by alpha 1 adrenoceptor subtype\textsuperscript{29}.

As in most chronic diseases, BPH is progressive: it requires a long period to evolve from earlier tissue alterations to clinical onset with LUTS\textsuperscript{30} or if untreated, it is often complicated with bladder dysfunction and hypertrophy possibly leading to acute urinary retention (AUR).

**Medical Therapy**

Current strategies for treating men with LUTS are watchful waiting, pharmacologic therapies and surgery and this article will focus on medical therapy.

**Phytotherapy**

The most commonly used phytotherapies for BPH are extracts of Serenoa repens (sau palmetto), thought to have antiandrogenic, anti-proliferative and anti-inflammatory effects, and extracts of the African plum tree’s bark. Many patients found phytotherapies attractive as they have low side effects. A randomised, double-blind, placebo-controlled study did not show any benefit of Serenoa repens over the placebo arm in respect to symptom relief at 1 year\textsuperscript{31}.

**Alpha Blockers Monotherapy**

There are 3 subtypes of the alpha 1 adrenergic receptor: the alpha 1a, alpha 1b and alpha 1d receptors. The alpha 1a receptor subtype is the most dominant in the prostate and contraction of the human prostate is mediated predominantly by alpha 1a-adrenoceptors\textsuperscript{32}. Therefore selective blocking of this subtype can result in the reduction of the symptoms due to BPH by relaxing smooth muscle tone in the prostate and bladder neck. Alpha 1b receptor blockade is to be avoided as it is present in the capacity vessels and is responsible for hypotension and undesirable cardiovascular side effects\textsuperscript{33}. Other side effects of the alpha receptor blockers apart from orthostatic hypotension include dizziness, asthenia and nasal congestion. A unique side effect of this group of medications is the intraoperative floppy iris syndrome, which is characterised by miosis, iris billowing and prolapse in patients undergoing cataract surgery who have taken or are currently taking alpha receptor blockers. Therefore, it is critical for all patients taking alpha-1 receptor blockers to alert their ophthalmologist if they are contemplating cataract surgery.

Alpha blockers are one of the most effective forms of medical treatment to reduce symptoms in most men with LUTS suggestive of BPH. They are considered an appropriate option by the American Urological Association (AUA)\textsuperscript{34} and a large number of clinical studies have demonstrated its efficacy. Typically significant symptom relief could be obtained within 1-2 weeks of starting therapy and reduce symptom scores by 5-8 points on the AUA-SI scale, with no clear differences between the agents within the class\textsuperscript{34-35}.

Another important clinical use of alpha blockers is to treat acute urinary retention. A randomised, double blind, placebo-controlled study showed that starting an alpha blocker after catheterisation in acute urinary retention increased the chance of successful trial without catheter (TWOC)\textsuperscript{36}.

**Selective Short-acting Alpha 1 Blockers**

Prazosin was the first selective alpha 1 antagonist investigated for BPH. It was shown to be better tolerated than the non-selective alpha blocker phenoxybenzamine\textsuperscript{37} but still it requires multiple daily dosing, and side effects of postural hypotension is still problematic. Despite the fact that the side effects are quite prominent, Prazosin is still commonly prescribed in Hong Kong due to its low cost.

**Long Acting Selective Alpha 1 Blockers**

Terazosin was the first selective long-acting alpha 1 blocker investigated for the treatment of BPH. A multicentre, randomised, placebo-controlled trial showed statistically significant improvements over symptoms and peak flow rate\textsuperscript{38}. Doxazosin was the second alpha 1 blocker approved by the FDA for treating BPH. Two multicentre, randomised trials were performed comparing various doses of doxazosin with placebo\textsuperscript{39,40}. Although doxazosin has a longer half-life, the studies did not confirm any clinical advantage. Both terazosin and doxazosin exhibited lowering of blood pressure only in those men who were hypertensive at baseline\textsuperscript{41,42} which was desirable. The more common side effects of terazosin and doxazosin included dizziness (10-15%), fatigue (8%) and hypotension (1.5-4%).

Tamsulosin was the third alpha 1 blocker to be approved for the treatment of BPH. It was the first subtype selective alpha 1 antagonist and was tenfold more selective for the alpha 1a versus alpha 1b subtype\textsuperscript{43} but there was no demonstrable subtype selectivity of tamsulosin for the alpha 1a versus alpha 1d subtypes. Trials showed 0.4mg tamsulosin was able to achieve significant improvements in symptom scores and peak flow rate without the need for dose titration, in contrary to doxazosin and terazosin\textsuperscript{44,45}. However, the side effect profile of tamsulosin is quite similar to doxazosin and terazosin with dizziness, fatigue and hypotension, with the additional side effect of retrograde ejaculation or anejaculation\textsuperscript{46}.

Alfuzosin 10mg daily is the fourth alpha 1 blocker approved by FDA for the treatment of symptomatic BPH and it has no selectivity for the alpha 1 subtype. It has good tolerability and has significant clinical improvement in LUTS without dose titration\textsuperscript{47,48}. The AUA Guidelines Committee concluded that alfuzosin has comparable clinical efficacy with tamsulosin and the other approved alpha blockers but does not cause ejaculatory dysfunction\textsuperscript{49}.
Silodosin is a newer selective alpha 1a receptor blocker and effective for both storage and voiding symptoms in BPH patients versus placebo, especially in patients with severe symptoms (IPSS >= 20). Marks et al reported a pooled analysis of two phase 3 randomised trials which showed rapid significant improvement within 3-4 days of initiation of silodosin. The efficacy of the drug was also supported by urodynamic effect studies which showed improvement in peak flow rate, maximal bladder capacity and reduction of detrusor overactivity.

**5 Alpha Reductase Inhibitors**

The main circulating androgen, testosterone, is converted to di-hydroxytestosterone (DHT) by the enzyme 5-alpha reductase (5AR) and DHT is involved in the development of BPH. There are 2 isoenzymes of 5ARs: finasteride inhibits type 2 and dutasteride inhibits both type 1 and 2 isoenzymes of 5AR. They can reduce the intraprostatic DHT by 80-90% and lead to atrophy of the prostate and subsequently shrinkage in prostate volume by 25% in 2 years and reduce the serum prostate specific antigen (PSA) by approximately 50% over 6 months. In the patients whose PSA are monitored, doubling the PSA value of the patients on 5 AR inhibitors is necessary. IPSS can be reduced by IPSS 3-4 points and sustained improvement of peak flow rate by 2ml/s and reduce the risk of acute urinary retention as well as BPH-related surgery by greater than 50%. The symptom relief from 5ARIs is most pronounced in larger glands (>40 ml) and the AUA Guidelines do not recommend them for men who do not have evidence of prostate enlargement.

5ARIs generally provide less symptomatic improvement compared to alpha-adrenergic receptor blockers and their onset of action is slow and occurs at 3-6 months but they reduce the long-term risk of progression to acute urinary retention and surgery. The most notable side effects are sexual side effects: decreased libido, erectile dysfunction and ejaculatory disorder. Rarely, some men note breast tenderness.

**Combination of Alpha Blockers and 5ARs**

Alpha blockers and 5ARIs

Theoretically, alpha blockers provide early relief, whereas 5ARIs provide long-term disease management and this concept was confirmed with the Medical Therapy of Prostatic Symptoms MTOPS trial in 2003. MTOPS enrolled 3057 men with LUTS and clinical BPH and randomised them to treatment with placebo, doxazosin, finasteride, or a combination of doxazosin and finasteride over a period of 4 to 5 years. The combination treatment resulted in significantly better outcomes in terms of overall risk of clinical progression (defined as an increase above baseline of >=4 points in the AUA-SI, AUR, urinary incontinence, renal insufficiency or recurrent urinary tract infection) compared with either doxazosin or finasteride alone. But this observation was significant only in patients with a baseline prostate volume <25ml. The Combination of Avodart and Tamsulosin (CombAT) study investigated the effects of combination therapy with dutasteride and tamsulosin as opposed to each as monotherapy and that showed combination therapy had significant benefits for patients in terms of reduction in symptoms and prostate volume.

Although combination therapy has the benefits from both alpha blockers and 5AR inhibitors, the problem with this combination therapy is cost and the patients may suffer from sides effects from either or both of these drugs.

**Anticholinergics**

Current understanding about the pathophysiology of BPH shows the change in bladder function in association with BPH constitutes an important factor in the development and progression of bothersome LUTS in BPH. Anticholinergics block the parasympathetic pathway, thereby abolishing or reducing the severity of detrusor muscle contractions. It is believed that storage symptoms are more bothersome to the patients and in patients with prominent overactive bladder symptoms, anticholinergic drugs can be considered.

The Tolterodine and Tamsulosin in Men with LUTS and Overactive Bladder study recruited nearly 900 patients into placebo versus tamsulosin 0.4mg versus extended-release tolterodine 4mg versus a combination of tolterodine and tamsulosin. The conclusion was that the patients with voiding and storage problems did not respond to monotherapy with either alpha blockers or anti-muscarinic agents but had a statistically and clinically significant treatment benefit from combination therapy of an alpha blocker and an antimuscarinic agent. Side effects experienced by the patients were typical of the agents including dry eyes and mouth, constipation and retention of urine but the incidence of acute urinary retention was low. Similar improvement in symptoms was observed in patients who failed previous alpha blocker treatment and after treatment with alpha blocker and 5AR inhibitor combination therapy by the addition of anticholinergics.

**PDE-5 Inhibitors**

There is growing interest in using phosphodiesterase 5 (PDE-5) inhibitors in the management of BPH but the precise mechanism of action is not yet fully understood. Sildenafil and Tadalafil were found to provide improvement of IPSS by 6-7 points versus placebo but neither sildenafil and tadalafil improved the peak flow rate significantly. The combination of alpha blocker and PDE-5 inhibitor has also been studied and the patients in the combination group of receiving both alfuzosin 10mg daily and sildenafil 25mg daily had the greatest benefits in IPSS, peak flow rate and erection compared with either drug alone. However, PDE-5 inhibitors have officially been licensed only for the treatment of erectile dysfunction and pulmonary arterial hypertension. Treatment beyond these indications is experimental.

**Conclusions**

Medical therapy is indicated in patients with bothersome lower urinary tract symptoms and alpha blockers are usually the first option due to its rapid onset of action. In those patients with persistent bothersome storage symptoms, addition of an anti-muscarinic agent can be considered after assessment with post void residual volume measurement to rule out baseline urinary...
retention. The 5AR inhibitors are usually prescribed for long term treatment, especially those with bigger prostate volume. The patient’s individual condition and wish need to be evaluated together with consideration about the benefits, costs and side effects of the drug to facilitate decision making in determining the best medical treatment for the patient.

References


