

# Benign prostatic hyperplasia: risk factors and management

GPs in the UK will, on average, each have 50 patients between the ages of 60 and 80 years with moderate–severe lower urinary tract symptoms from benign prostatic hyperplasia (BPH). This article is the second part of a two-part review on the management of BPH in general practice. Part one discussed prevalence and diagnosis, and part two will look at management options

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Benign prostatic hyperplasia (BPH) is a common disease among older men, accounting for more than 80% of clinical presentations of prostate disease. Its prevalence increases with age.<sup>1</sup> Part one of this article reviewed the prevalence and diagnosis of BPH. This second part will focus on risk factors and management options.

## Risk factors for BPH

Age and the presence of circulating androgens are known risk factors. The condition does not develop in castrated men under 40 years.<sup>2</sup>

BPH appears to run in families, and men who have a first-degree relative with the condition who was aged under 60 years at the time of diagnosis have a 30% increased risk of developing it themselves.<sup>3</sup>

The incidence of histological BPH (diagnosed via biopsy or at autopsy) is similar across all racial groups studied, but the incidence of clinical BPH (diagnosed via symptoms, examinations and clinical investigations) is higher

among African-Americans than in Caucasians, which in turn exceeds that in Asian men.<sup>4</sup>

Diet is a potential modifiable risk factor. Asian populations are associated with soya-rich diets, and this may explain the low incidence of BPH in Asian men. Soya products are high in phyto-oestrogens (eg, genistein), which have an inhibitory effect on BPH (and prostate cancer) cells in vitro.<sup>5</sup>

## Pathogenesis

Testosterone and its active metabolite 5-dihydrotestosterone (5-DHT) are necessary for normal development and physiological control of the prostate.

The prostate consists of epithelial cells, formed into glands and ducts, and connective tissue stroma. The stromal element in turn consists of cells (predominantly smooth muscle cells with some myofibroblasts, fibroblasts, lymphocytes, macrophages and mast cells) and extracellular protein (eg, collagen).

Cells of both the epithelium

and of the stroma are stimulated by 5-DHT to produce hormones or growth factors. These hormones are either autocrine factors, which act locally on the same cells that produced them, or paracrine factors, acting on other nearby cells.

Epithelial cell growth and development, and stromal cell proliferation and stromal extracellular protein matrix production, are influenced by these autocrine and paracrine pathways. The theory is that if a growth factor imbalance occurs, this in turn leads to an imbalance between cell growth and programmed cell death, leading to both epithelial cell hyperplasia and stromal hyperplasia.<sup>6</sup>

The first sign of BPH histologically is the formation of nodules in the stroma surrounding the urethra. Nodule formation is then followed by hyperplasia of the epithelial cells of the glands and ducts of the prostate. Together, this causes compression of the urethra with progressively worsening obstruction.

The adult prostate weighs 20 g and has a volume of 20 ml. It grows with age. The largest body of

evidence for the progression of BPH comes from the Olmsted County epidemiological study in Minnesota. Average growth rates of 1.9% per year in men over 40 years were found—associated with this was a progressive worsening of symptoms and flow rates, and an increasing incidence of acute urinary retention (AUR) and surgery.<sup>7</sup>

The effect of  $\alpha$ -adrenergic tone is important, as up to 60% of the hyperplastic tissue in BPH consists of smooth muscle cells and connective tissues that are under adrenergic control via stimulation of their  $\alpha$ -1a receptors.

Surprisingly, there is no close correlation between overall prostate size and the degree of bladder outlet obstruction. This may be due to:

- Variation in relative amounts of stromal versus epithelial tissue in BPH
- Variation in adrenergic tone to stimulate smooth muscle cell contraction
- Variation in how the bladder responds to the effects of ageing and obstruction
- Variation in the degree of middle-lobe enlargement leading to ball-valve type bladder outlet obstruction without an overall increase in size of the prostate.

Nevertheless, the larger the prostate volume, the greater is the risk of BPH progression.

## Management

If malignancy has been excluded and the symptoms are mild (and they are not “bothersome” to the patient), conservative treatment or “watchful waiting” may be appropriate. Many men will be content to just be reassured that

they do not have cancer or that their condition is not going to deteriorate.

## Active treatment

The aims of treatment are twofold. The first aim is the short-term relief of symptoms and improvement in flow of urine. The second aim is the long-term need, because of the progressive nature of BPH, to prevent deterioration of symptoms, to prevent AUR and to prevent the need for prostate surgery.

Two classes of drugs are licensed for treatment of BPH:  $\alpha$ -blockers and 5- $\alpha$ -reductase inhibitors (5- $\alpha$ RI).

The  $\alpha$ -blockers cause relaxation of the smooth muscle of bladder neck and the smooth muscle component of the prostate.

The 2003 guideline of the American Urological Association (AUA)<sup>8</sup> states that the four most commonly used  $\alpha$ -blockers (alfuzosin, tamsulosin, terazosin, and doxazosin) have equal clinical effectiveness in improving symptoms and flow. Of men with symptomatic BPH, 60% will respond to  $\alpha$ -blockers with an average improvement of 30–40% in the International Prostate Symptom Score (IPSS). Urinary flow rates improve by 1.5–3.5 mls per second.<sup>8</sup> The response usually occurs within 14 days. But if there is not an initial response, the drug should be continued for three months before being stopped owing to lack of effectiveness.

The commonest side-effects of  $\alpha$ -blockers are dizziness, headache and postural hypotension. With tamsulosin and alfuzosin, 4–10% of patients discontinue the drug because of side effects. This is comparable to placebo. But

with terazosin and doxazosin, an additional 4–10% of patients discontinue because of side-effects.<sup>9</sup>

In general, the incidence of sexual side-effects (retrograde or delayed ejaculation) is roughly similar for alfuzosin, terazosin and doxazosin (ie, about 1% and thus comparable to placebo). But for tamsulosin, the rates are higher at 5–11%.<sup>10</sup> However, this drug is well tolerated by men. In placebo-controlled trials, abnormal ejaculation with tamsulosin resulted in discontinuation of treatment in <1% of cases.<sup>10</sup>

Both age and BPH are independent risk factors for erectile dysfunction. The main treatments for erectile dysfunction are phosphodiesterase type-5 inhibitors (PDE5-Is), and GPs have extensive experience of prescribing sildenafil, vardenafil and tadalafil. But as both  $\alpha$ -blockers and PDE5-Is cause vasodilatation, the question arises whether using both drugs simultaneously is safe. Data on co-medication is currently limited, but using a PGE5-I while taking an  $\alpha$ -blocker can lead to symptomatic hypotension. However for both sildenafil and vardenafil, co-medication with an  $\alpha$ -blocker is safe<sup>11,12</sup> providing the patient is stable on the  $\alpha$ -blocker and the initial dose of the PDE5-1 is low. Vardenafil may be taken at any time with tamsulosin, but with a dosing interval for other  $\alpha$ -blockers.

The 5- $\alpha$ RI are finasteride and dutasteride. These inhibit conversion of testosterone to its active metabolite 5-DHT, which is the main stimulator of prostate growth in BPH. This reduction in 5-DHT production leads to shrinkage of the prostate. This in turn leads to improvements in symptoms and urinary flow. But,

**Table 1:** Effectiveness of 5 $\alpha$ RIS<sup>13, 17-20</sup>

5-ARI	Mean reduction in DHT	Reduction in prostate volume at four years	Increase in flow rate in mls per second	Reduction in risk of AUR	Reduction in risk of prostate surgery
Finasteride	70%	20%	1.6 mls	57%	55%
Dutasteride	95%	27.3%	1.9 mls	48%	55%

unlike the  $\alpha$ -blockers, 5- $\alpha$ RIs can also reverse the pathological progress of BPH thereby, reducing the future risk of AUR and need for surgery (transurethral resection of the prostate; TURP).

Both drugs are effective in BPH (Table 1) and the larger the prostate, the greater the response. They are indicated in men with larger prostates (>30 mls). As specified in part one of this article, prostate-specific antigen (PSA) is essentially equivalent to prostate volume. This indication therefore equates to having a PSA level >1.5 ng/ml.

The side-effects of 5- $\alpha$ RIs relate to their action on levels of 5-DHT and testosterone. Both 5- $\alpha$ RIs are comparable in the incidence of associated reduced libido and erectile dysfunction at 3–5%, and ejaculatory dysfunction and gynaecomastia at 1–2%.

In patients taking 5- $\alpha$ RIs, PSA levels are reduced in patients taking 5- $\alpha$ RIs by 50% at six months. It is

important to double the subsequent PSA value to reach a true PSA value in prostate cancer assessment.<sup>13,14</sup>

### Combination therapy

The combination of finasteride and doxazosin was studied in the MTOPS (Medical Treatment of Prostatic Symptoms Treatment) trial.<sup>15</sup> Clinical progression was defined as one of the following:  $\geq 4$  point increase in IPSS score, AUR, recurrent urinary tract infection (UTI), incontinence or renal impairment. According to the results, the combination of finasteride and doxazosin reduced the risk of clinical progression by 66%. This reduction was significantly greater than for either monotherapy alone: doxazosin (39%) or finasteride (34%).

The combination of tamsulosin and dutasteride, compared with either agent alone, was studied in a group of men more likely to progress with BPH (worse IPSS

scores, higher PSA and prostate volume than in the MTOPS trial).<sup>16</sup> The COMBAT trial, at two years, showed significantly greater improvements in symptom score and bother factor for the combination group compared with either therapy alone. At two years, a significantly higher proportion of patients was satisfied in the combination group than either monotherapy group. At four years, the combination treatment reduced the relative risk of AUR or BPH-related surgery by 66% compared with tamsulosin alone (Table 2).

Clearly combination therapy is much more effective than a single  $\alpha$ -blocker or 5- $\alpha$ RI alone. Following the results of the COMBAT study, a new fixed-dose combination therapy that combines tamsulosin and dutasteride (Combodart) is now available.

### Phytotherapy

Saw Palmetto (*Serenoa repens*) or Dwarf American Palm Plant is used extensively by men in Europe for treatment of their BPH symptoms. Unfortunately there is a lack of long-term, double-blind, placebo-controlled trials to assess it properly. The most recent meta-analysis concluded: "Serenoa repens was not more effective than placebo for treatment of urinary symptoms consistent with BPH."<sup>21</sup>

**Table 2:** COMBAT study results<sup>14</sup>

5-ARI	Incidence of AUR	Incidence of Surgery
Tamsulosin	6.8%	7.8%
Dutasteride	2.7%	3.5%
Tamsulosin & Dutasteride	2.2%	2.4%

## QOF

The Department of Health gives significant importance to chronic obstructive pulmonary disease (COPD), a progressive disease that is associated with significant morbidity and adverse effects on quality of life, in the Quality & Outcomes Framework (QOF) component of the GP contract. The only active intervention that slows the decline in lung function is stopping smoking. Yet quality of life (QoL) studies comparing COPD with BPH show that in all respects other than physical functioning (seven out of eight scales), patients with lower urinary tract symptoms (LUTS) scored worse than COPD patients.<sup>22,23</sup>

The QOF does not recognise BPH, but it is a common condition that is becoming more common, and it can be assessed and treated in general practice. Treatment not only significantly improves symptoms, but it also reverses the underlying pathophysiology to prevent long-term complications. The cost of one month's treatment of BPH with an  $\alpha$ -blocker alone (for small prostates) ranges from £4.69 to £12.76. For combined treatment (for larger prostates), the cost per month varies from £11.18 to £24.49. Compare this with the treatment of COPD with inhaled steroid/long-acting  $\beta$ -agonist combination costing £40.92 to £76.00 per month. Additional anticholinergics for COPD vary in monthly cost from £5.05 to £36.27. Therefore, because of its effect on quality of life, its prevalence, and cost of its treatment, BPH deserves a place alongside the less prevalent and more expensive-to-treat COPD in the QOF.

## Treatment plan

BPH is diagnosed using the IPSS together with a history, directed examination and simple investigations. These essentially exclude other causes of LUTS and identify patients in primary care who need referral to secondary care.

Once these other causes have been excluded, treatment of BPH is directed by the severity of the symptoms, the degree of bother, and the PSA level (linked to the size of the prostate)

For patients with minor symptoms (IPSS  $\leq 7$ ) and a low bother factor, lifestyle advice is appropriate. This includes: reduction or avoidance of caffeine; double micturition (returning to fully empty the bladder a few minutes after initial voiding); not drinking after early evening; and avoiding constipation by eating more fibre.

For men with high bother factor and moderate or severe symptoms (IPSS 8–35), an  $\alpha$ -blocker should be prescribed alone for men with a small prostate (ie, PSA <1.5) or with an  $\alpha$ -blocker and 5- $\alpha$ RI for men with larger prostates (ie, PSA >1.5).

The treatment of men with moderate symptoms but low bother is more contentious. If his PSA is >1.5, he is at an increased risk of BPH worsening and would benefit from a 5- $\alpha$ RI. For him the pros and cons of treatment need to be considered more carefully. General practice is the ideal place to assess and treat men with uncomplicated BPH.

## Conclusion

This article reviews management of BPH in general practice.

This most prevalent and bothersome condition will assume

increasing importance with our ageing population. However, a series of effective and well-tolerated treatments for the condition are now available.

**Conflict of interest: I have worked as a consultant to GlaxoSmithKline.**

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