Management Approaches for Benign Prostate Hyperplasia Patients with Cardiovascular Co-Morbidities

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Introduction

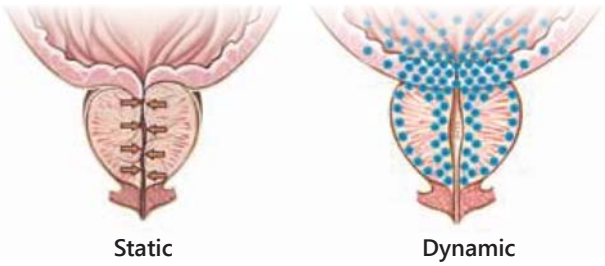
Benign prostatic hyperplasia (BPH) is the nonmalignant enlargement of the prostate gland occurring in >50% of men over 60 years of age, most of whom have lower urinary tract symptoms (LUTS).[1,] The two most well established causative factors of BPH include age and normal androgenic functions.[1] The prevalence of LUTS due to BPH increases with increasing age with moderate to severe symptoms occurring in 40 and 80% of men after the age 60 and by 80 years, respectively.[3] Clinically, BPH may be manifested as irritative LUTS such as urgency, frequency, nocturia and obstructive LUTS such as hesitancy, a weak and interrupted urinary stream, straining to initiate urination, and a sensation of incomplete bladder emptying. Prolonged obstructions may eventually lead to acute urinary retention (AUR), recurrent urinary tract infection (UTI), hematuria, bladder calculi, and renal insufficiency.[3]

BPH is characterized by stromal and glandular epithelial hyperplasia that occurs in the periurethral transition zone of the prostate.[3] Symptoms of BPH arise through two mechanisms i.e. static, in which the hyperplastic prostatic tissue leads to urethral compression and dynamic, wherein increased adrenergic nervous system and prostatic smooth muscle tone promotes obstruction of urinary flow (Figure 1). Additionally, both mechanisms increase resistance to urinary flow at the level of the bladder outlet.[4]

Benign prostatic hyperplasia and cardiovascular diseases: The comorbid association

BPH and LUTS patients have a considerably higher prevalence of cardiovascular disease (CVD) than the general population in old age.[5] Moreover, cardiovascular disease morbidity is twice as prevalent in patients starting drug treatment for BPH as compared to age-matched population controls.[6] A number of hypotheses have been created to explain traditional clinical risk factors of CVD such as age, male gender, cigarette smoking, inheritance, high blood pressure (BP), obesity, elevated fasting plasma glucose, diabetes mellitus, dyslipidemia, decreased physical activity and metabolic syndrome. However, recent studies speculate BPH as an insidious risk factor for CVD due to its role in causing nocturia-induced sleep disturbances, blood pressure (BP) variability, increased sympathetic activity, and non-dipping BP variations.[5] Additionally, BPH may be related to coronary ischemic heart disease or other cardiovascular pathologic conditions. A study was done in 52 men with bladder outlet obstruction to determine the correlation between cardiovascular disease and prostate

Figure 1: Static and dynamic components of benign prostate hyperplasia



Source: Unnikrishnan R, Almassi N, Fareed K. Benign prostatic hyperplasia: Evaluation and medical management in primary care. *Cleve Clin J Med.* 2017 Jan;84(1):53-64.

size in elderly men seeking medical attention for LUTS.[7] Study results showed that men with LUTS caused by a very large prostate had more risk factors for cardiovascular disease than those with a smaller gland. Specifically, men with a marked enlargement of prostate gland had higher arterial pressures and blood glucose concentrations. Additionally, they tended to have higher serum insulin and cortisol levels. The study also indicated that men with a large prostate are prone to develop metabolic syndrome including obesity, non-insulin-dependent diabetes mellitus, and low concentrations of HDL cholesterol.[7]

The metabolic syndrome comprises of a number of disorders including insulin resistance, hypertension and obesity all of which act as risk factors for cardiovascular diseases.[8] Numerous studies have reported a strong independent association between components of the metabolic syndrome and BPH/LUTS.[9,10] Studies on urological aspects of the metabolic syndrome also seem to indicate that BPH could be regarded as a new aspect of metabolic syndrome, and that an increased insulin level is a common underlying aberration promoting BPH.[8] Furthermore, metabolic syndrome and its risk factors are associated, via inflammation, with the pathogenesis, clinical implications, and progression of BPH/ LUTS (Figure 2).[9]

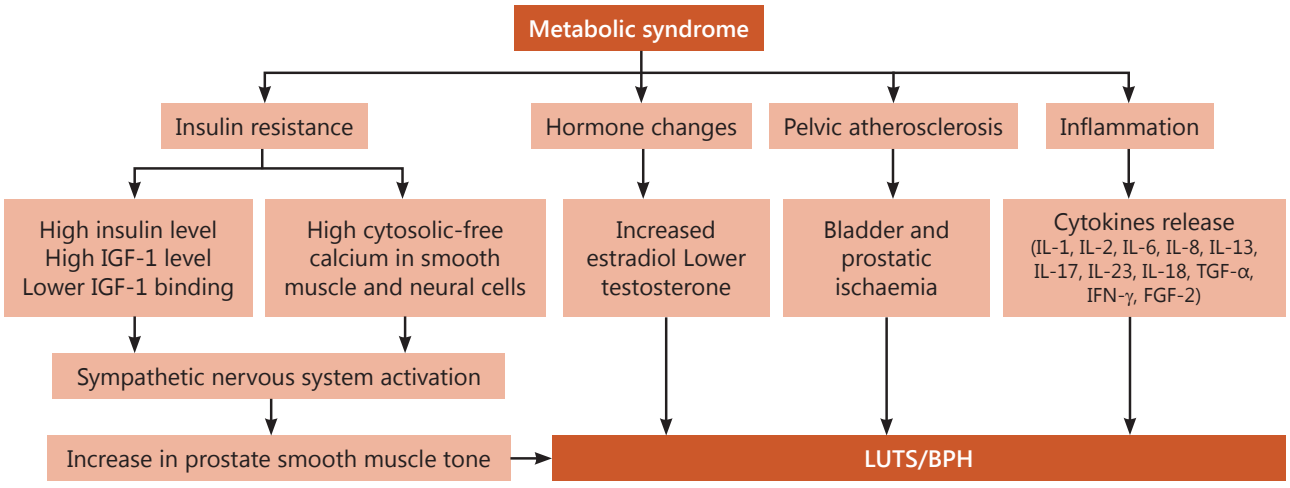
Medical management of BPH

BPH treatment objectives include reduction of symptoms, improving health related quality of life (HRQOL), and preventing disease progression to avoid potentially serious complications such as acute urinary retention (AUR) and the need for surgery.[11] Treatment choice depends on disease severity, co-morbidity, patient preferences, and the comparative efficacy and adverse effects of the available therapies.[11] An algorithm for diagnosing and managing benign prostatic hyperplasia is shown in Figure 3.[4]

Lifestyle management

A healthy lifestyle plays a critical role in cardiovascular health which is also true for benign BPH and LUTS. Studies have shown a clinically significant, independent, and strong inverse relationship between exercise and the development of BPH/LUTS. Numerous mechanisms for this relationship have been proposed, including decreased sympathetic tone, avoidance of metabolic syndrome, and reduced oxidative damage to the prostate.[12] Epidemiological data has shown a favorable relationship between increased physical activity and weight loss with decreased risks and progression of BPH and LUTS.[10] Moreover, a variety of lifestyle changes such as restricting fluid intake, avoiding foods or beverages that cause irritation (e.g., caffeine or alcohol), monitoring some

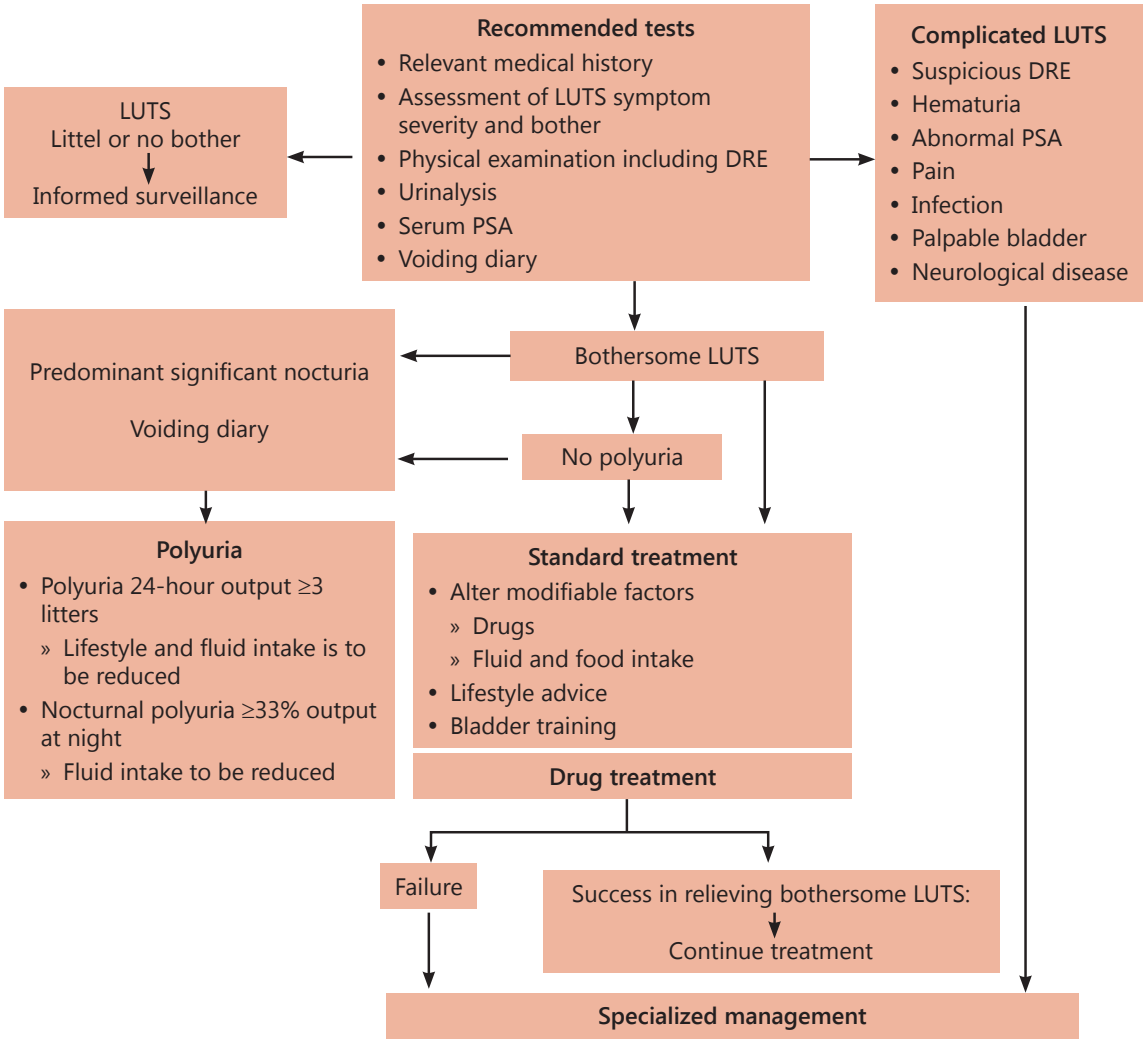
Figure 2: A proposed link between chronic inflammation, metabolic syndrome and benign prostatic hyperplasia/lower urinary tract symptoms



Abbreviations: BPH - Benign prostatic hyperplasia; FGF - Fibroblast growth factor; IFN - Interferon; IGF - Insulin-like growth factor; IL - Interleukin; LUTS - Lower urinary tract symptoms; TGF - Tumour growth factor.

Source: R Nickel JC. Role of Prostatic Inflammation in the Clinical Presentation of Benign Prostatic Hyperplasia. *European Urology Supplements*. 2015; 14: e1459–e1463.

Figure 3: An algorithm for diagnosing and managing benign prostatic hyperplasia



Abbreviations: LUTS - Lower urinary tract symptoms; DRE - Digital rectal exam; PSA - Prostate-specific antigen

Source: Unnikrishnan R, Almassi N, Fareed K. Benign prostatic hyperplasia: Evaluation and medical management in primary care. *Cleve Clin J Med.* 2017 Jan;84(1):53-64.

medications (e.g., diuretics, decongestants, antihistamines, and antidepressants), timed voiding (bladder retraining), pelvic floor exercises, and treatment for constipation are recommended for patients with BPH.[13]

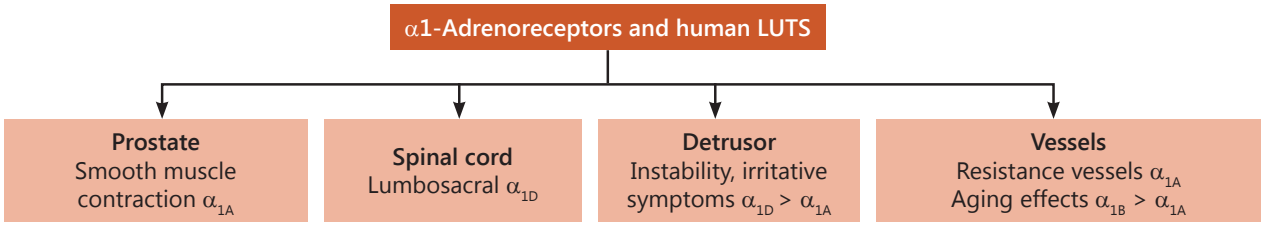
Drug therapy: A first-line option

Pharmacological management is the most common therapeutic approach for patients with BPH.[14] Drugs for BPH include alpha-adrenergic blockers, 5-alpha reductase inhibitors, anticholinergics, beta-3 agonists, and phosphodiesterase-5 inhibitors.[4] Additionally, statins and biguanides such as metformin may provide a dualistic benefit in prevention of coronary heart disease events and LUTS progression.[10] However, α-adrenoceptor antagonists are the most commonly prescribed initial treatment of LUTS suggestive of BPH.[14]

Alpha-adrenergic receptor blockers

Alpha-adrenergic receptor antagonists or alpha blockers are the mainstay in the treatment of symptomatic BPH. These drugs block the alpha-adrenergic receptors, which regulate the smooth muscle tone.[15] A series of α_1 receptor subtypes exists in humans designated as α_{1A}, α_{1B}, and α_{1D}.[16] Amongst these, α_{1A} subtype plays a primary role in mediating prostatic smooth muscle contraction while other subtypes most likely play secondary roles as shown in Figure 4.[16]

Figure 4: The role of α1-adrenoreceptors in lower urinary tract symptoms (LUTS)



Source: Kaplan SA. α-Blocker Therapy: Current Update. *Reviews in Urology.* 2005;7(Suppl 8):S34-S42.

By antagonizing the alpha-1a receptor, alpha blockers relax the smooth muscle in the prostate and bladder neck, thereby reducing bladder outlet resistance, and improving urinary flow.[4] Alpha1-blockers are effective regardless of prostate size, and provide a similar degree of symptom relief in patients with or without bladder outlet obstruction.[17] The US Food and Drug Administration (FDA) has approved 4 alphaadrenergic receptor antagonists for the treatment of LUTS, namely terazosin, doxazosin, tamsulosin, and alfuzosin. All these agents are long-acting alpha-1- blockers, well-tolerated, and demonstrate comparable dose-dependent effectiveness.[18]

Tamsulosin in BPH

The association of numerous adverse effects with non-selective and short acting alpha-1 blockers has led to the development of long acting alpha-1 adrenoceptor blockers such as tamsulosin. Tamsulosin is a uroselective alpha-blocker that has shown 20 to 38-fold greater α_{1A} subtype adrenergic receptor selectivity in comparison to α_{1B} receptors. This selectivity is associated with significantly reduced incidence of cardiovascular side effects and lack of interaction with antihypertensives. It has been in use for over more than a decade and was amongst the first drugs developed specifically to treat LUTS due to BPH. [19]

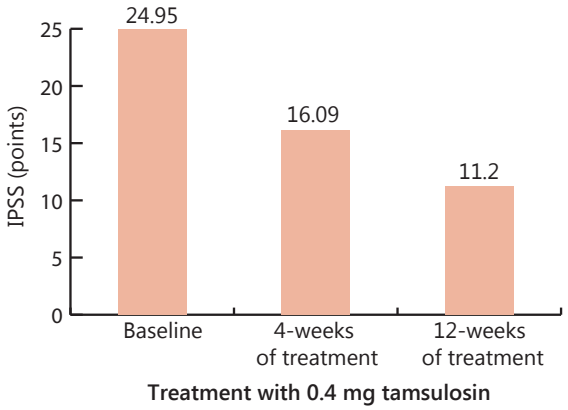
Tamsulosin, single doses of 0.4 mg has been reported to yield responder rates of 67% (placebo: 44%), 66% (placebo: 49%), 55% (placebo: 40%), and 70% (placebo: 51%) in terms of symptom improvement (≥ 25%) in shorter-term studies[20-23] and 81% (placebo: 59%) in a longer-term study.[24] A recent study was conducted by Milicevic et al with an objective to establish the efficacy and safety of a daily dose of tamsulosin 0.4 mg in patients with functional symptoms of BPH through an evaluation of reduction of subjective symptoms, quantified through the International Prostate Symptom Score (IPSS).[25] A total of 45 patients with LUTS/BPH were administered tamsulosin 0.4 mg over the course of 12 weeks. Checkups were scheduled at 4 and 12 weeks following the initiation of treatment, during which the values for IPSS and disease-specific quality of life (QLI) were obtained. The study results showed a reduction in symptoms after 4 weeks (35.51%) and 12 weeks (55.11%) of treatment, as quantified through IPSS (Figure 5). The QLI showed marked improvement of 44.54% after 4 weeks and 68.82% after 12 weeks of treatment.[25]

Tamsulosin – a safer option in BPH with CVD/ hypertension

In treatment of patients with BPH and hypertension, urologists could choose either to use alpha blockers to treat both hypertension and BPH, or to treat BPH using alpha blockers that do not interact with antihypertensive therapy.

Tamsulosin has been shown to be well tolerated with minimal effects on blood pressure. In a study conducted by Chapple, tamsulosin 0.4 mg had the lowest potential

Figure 5: Improvement in International Prostate Symptom Score (IPSS) with the use of 0.4 mg tamsulosin over 12 weeks



Source: Milicevic S, Bijelic R. Efficacy and safety of tamsulosin in the treatment of benign prostatic hyperplasia. *Med Arch*. 2012;66(3):173–6.

Table 1: Effects of tamsulosin therapy on blood pressure in patients with cardiovascular comorbidities

Patient Subgroup	Baseline Systolic (mm Hg)	Baseline Diastolic (mm Hg)	Post therapy Change Systolic/Diastolic (mm Hg)
Control	141 ± 0.2 (n = 4393)	84 ± 0.1	−3.6 ± 0.2/−1.7 ± 0.1 (n = 4218)
Diabetes	150 ± 0.5 (n = 1162)	89 ± 0.3	−4.7 ± 0.4/−2.9 ± 0.3 (n = 1109)
Hypertension	154 ± 0.4 (n = 1749)	91 ± 0.2	−5.2 ± 0.3/−3.5 ± 0.2 (n = 1673)
Other cardiovascular	150 ± 0.4 (n = 1638)	89 ± 0.2	−4.3 ± 0.3/−2.8 ± 0.2 (n = 1569)

Source: Michel MC, Mehlburger L, Bressel HU, Schumacher H, Schäfers RF, Goepel M. *J Urol.* 1998; 160(3 Pt 1):784-91.

to reduce blood pressure and caused less symptomatic orthostatic hypotension than terazosin.[17] Additionally, tamsulosin had a lower incidence of dizziness as compared to terazosin or doxazosin. Blood pressure monitoring was also conducted in 19,000 tamsulosin- treated patients in a study conducted by Michael et al (Table 1).[26] After 12 weeks of therapy, systolic and diastolic blood pressures were 3.6 and 1.7 mm Hg lower, respectively, than they were before treatment for controls and were comparable to the effects for placebo. Additionally, mean blood pressure reductions with concomitant antihypertensive therapy were not more than 2 mm Hg. The study confirmed lack of significant interaction between tamsulosin and other α-adrenergic-receptor antagonists given to treat hypertension.[26] Thus, selective α_1-blockers without antihypertensive effects, such as tamsulosin, can be combined safely and efficaciously with suitable first-line antihypertensives.[17]

Benefits of tamsulosin with ADS technology

Advanced delivery system (ADS) technology was developed to overcome the drawbacks of existing tamsulosin modified release (MR) formulation. The current MR formulation of tamsulosin is food dependent and should be dosed after breakfast or the first meal of the day. However, if it is taken in the fasting state, maximum plasma concentration (Cmax) and the area under the curve (AUC) increases by about 70% and 30%, respectively. Hence, non-compliance leads to increased tamsulosin exposure, which can lead to a higher risk for vasodilatation related adverse events like dizziness, headache, etc.[27] Therefore, tamsulosin with ADS technology is a new formulation/ delivery system of tamsulosin that shows improved pharmacokinetics compared with the standard MR capsules. This may translate to improved efficacy/safety ratio during the treatment of LUTS/BPH.

Technologies like multi-unit membrane-coated pellets, osmotic pump technology (OROS) and GeoMatrix have been developed and used for tamsulosin MR. However, these technologies are water-dependant and require water in gastro intestinal (GI) tract to release the active ingredient. Consequently drug release and absorption is impeded during the passage of the formulation through the colon where the amount of water is very limited.[27]

The ADS technology is a controlled release system of a gel matrix type that is composed of a gel-forming agent and a gel-enhancing agent as its major components. It provides pH-independent drug release and GI-agitation resistant gel formation. It ensures 24 hour consistent drug release throughout the entire GI tract. The drug gets sufficiently hydrated during its transit through the upper GI tract so that it is able to release sufficient amounts of the drug even in the colon where water is poorly available. Hence, tamsulosin with ADS may provide a safe, once daily treatment alternative for LUTS/BPH, enabling a constant release over a 24-hour period without the need for dose titration, an effect on blood pressure, food effect, and the risk for orthostatic hypotension.[27]

ADS technology has the following benefits:

- 24 hours consistent release in colon where water is poorly available
- Improved control of nocturia and IPSS
- Steady plasma levels after dosing with an improved Cmax/C24h ratio
- Better quality of sleep
- Independent of food intake
- Reduced Cmax related side effects
- Reduced incidence of postural hypotension

Combination therapy

The scientific rationale for combining 5α-reductase inhibitors and α_1-AR antagonists is based on their different and complementary modes of action helpful in managing both static and dynamic components in patients with BPH and symptoms of bladder outlet obstruction. Alpha blocker provides rapid relief of symptoms without targeting the underlying disease process while 5α-reductase inhibitors provide mid or more sustained relief of symptoms.[3] Combination therapy therefore results in symptom

improvement as well as risk reduction of disease progression and complications.

Results of a randomized, double-blind, multinational CombAT trial showed the benefits of using a combination of dutasteride (5α-reductase inhibitor) and tamsulosin (α_1-AR antagonists) over either therapy alone. A total of 4838 subjects were enrolled. The primary endpoint at the end of the initial 2-year study period was the change in IPSS from baseline. At 2 years, the mean decrease from IPSS baseline was 4.3 for the tamsulosin group, 4.9 for the dutasteride group, and 6.2 for the combination group. A statistically significant difference was achieved for combination therapy over dutasteride alone from month 3 and over tamsulosin alone from month 9. The increase in the peak urinary flow rate of the combination group was 2.4 mL/s, which was significantly greater than 1.9 mL/s and 0.9 mL/s in the dutasteride group and the tamsulosin group, respectively.[28] Overall, concomitant use of 5α-reductase inhibitors and α_1-AR antagonists in treatment of BPH is generally well-tolerated and is associated with better health-related quality of life.

Conclusion

Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate gland most commonly affecting the geriatric population. Moreover, cardiovascular disease morbidity is twice as prevalent in patients with BPH as compared to age-matched population controls. BPH treatment objectives include reduction of symptoms, improving health related quality of life (HRQOL), and preventing disease progression to avoid potentially serious complications such as AUR and the need for surgery. Tamsulosin has been found to be safe and effective in the treatment of BPH with significantly reduced incidence of cardiovascular effects and lack of interaction with antihypertensives. Delivery of tamsulosin with ADS technology has improved the efficacy and safety of the drug without an effect on blood pressure and without the risk for orthostatic hypotension.

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