Benign prostatic hyperplasia

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Abstract | Benign prostatic hyperplasia (BPH), which causes lower urinary tract symptoms (LUTS), is a common diagnosis among the ageing male population with increasing prevalence. Many risks factors, both modifiable and non-modifiable, can increase the risk of development and progression of BPH and LUTS. The symptoms can be obstructive (resulting in urinary hesitancy, weak stream, straining or prolonged voiding) or irritative (resulting in increased urinary frequency and urgency, nocturia, urge incontinence and reduced voiding volumes), or can affect the patient after micturition (for example, postvoid dribble or incomplete emptying). BPH occurs when both stromal and epithelial cells of the prostate in the transitional zone proliferate by processes that are thought to be influenced by inflammation and sex hormones, causing prostate enlargement. Patients with LUTS undergo several key diagnostic investigations before being diagnosed with BPH. Treatment options for men with BPH start at watchful waiting and progress through medical to surgical interventions. For the majority of patients, the starting point on the treatment pathway will be dictated by their symptoms and degree of bother.

Lower urinary tract symptoms (LUTS) affect both men and women and can be caused by various conditions. Benign prostatic hyperplasia (BPH) is a frequent cause of LUTS in men and is a common histological finding — particularly in ageing men. Although 'normal' prostates in adult men are typically 15–30 ml in volume, and glands >30 ml are commonly deemed 'enlarged', no strict cutoff value has been defined and, for many physicians, enlarged prostate volume is a subjective finding on examination. Furthermore, the extent of prostatic enlargement varies considerably because the extent of hyperplasia is variable[1].

BPH is characterized by a proliferation of both stromal and epithelial cells of the prostate in the transitional zone surrounding the urethra[2] (FIG. 1). However, to date there is no evidence to suggest that men with LUTS due to BPH are at an increased risk of prostate cancer[3]. Furthermore, although common, BPH rarely causes death. Instead, the disease results in compression of the urethra, causing resistance to urine flow known as bladder outlet obstruction (BOO). This resistance can also result in obstruction-induced changes of bladder function, such as overactivity of the detrusor muscle or, conversely, reduced contractility of the detrusor muscle[2]. BOO can present as LUTS, infections or retention, as well as other conditions. BPH and BOO impose considerable burden on the health of older men and on health care costs.

As the world population ages, the incidence and prevalence of BPH and LUTS have rapidly increased[1]. Historical studies have examined non-modifiable risk factors — including age, genetics and geography — that have important roles in the aetiology of BPH and BOO[4]. However, several modifiable risk factors present new opportunities for treatment and prevention. In this Primer, we discuss the roles of these modifiable risk factors in BPH pathogenesis, including sex steroid hormones, the metabolic syndrome and cardiovascular disease, obesity, diabetes, diet, physical activity and inflammation. We also describe the current treatment paradigms and the future research trajectory of the condition.

Epidemiology

Approximately 50% of men >50 years of age will have pathological evidence of BPH, with this number increasing to >80% as men reach their eighth decade of life and older[5]. Furthermore, as men age, the likelihood of developing associated LUTS increases in a linear manner[6] (FIG. 2). However, many clinical epidemiological studies use different scales when measuring the severity of BPH depending on the defining terms, which can lead to differing data outcomes of the same disorder. The predictors of BPH progression and complications are outlined in BOX 1. For example, a community-based study from the Netherlands reported a 19% prevalence for BPH and LUTS in men 55–74 years of age when accounting only for a prostate volume of >30 ml and an International Prostate Symptom Score (IPSS) of >7 (REF. 7). The IPSS is a validated questionnaire to assess

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LUTS that consists of eight questions, seven of which relate to voiding symptoms (including slow urinary stream, splitting or spraying of the urinary stream, intermittent urinary stream, hesitancy, straining to void and terminal dribbling) or bladder storage symptoms (including increased frequency, urgency and incontinence), and the last question relates to quality of life (QOL)[8]. However, the prevalence rate dropped to 4% when the maximal urinary flow rate (Qmax) and post-void residual (PVR) volume (that is, the volume of urine left in the bladder after micturition) were taken into account[7]. Furthermore, of the 2,372 men who participated in the National Health and Nutrition Examination Survey (NHANES) III study[9], 10.7% reported having three or four LUTS symptoms.

Several studies have examined the geographical variations in BPH and LUTS prevalence. Men from Southeast Asia have significantly smaller prostate volumes than men from western countries[10]. Although differences in geographical prevalence for prostate disease (including BPH) have been documented, the reasons for such differences are poorly understood. However, these differences could be due to genetic factors and/or environmental differences[10]. Furthermore, dynamic changes in environmental factors might also contribute to the development of BPH.

Mechanisms/pathophysiology

The pathophysiology underlying the development of BPH is complicated and poorly understood. Many risks factors, both modifiable and non-modifiable, can increase the risk of development and progression of BPH and LUTS. Although many of these risks have not been fully studied, they might be beneficial in providing information to assist in counselling of patients and help to form strategies for the prevention and treatment of BPH.

Risk factors

The risk factors for BPH include metabolic syndrome, diabetes, obesity, hypertension, diet and sex hormone levels. Typically, these factors do not occur in combination, but in certain men they can overlap.

Age. BPH increases with age, which has been confirmed by numerous studies. For example, in a study of 278 men (mean age at the start of the study: 58 years) enrolled in the Baltimore Longitudinal Study of Aging who had undergone at least two MRI scans to determine prostate volume, the median prostate volume was 28.1 ml (range: 4.4–135.0 ml) on the first MRI and 31.1 ml (range: 8.7–237.3 ml) at the end of the study period with a median follow-up of 4.3 years[11]. It was reported that prostate volume increased at a median rate of 0.6 ml per year (range: −9.9 to 62.1 ml), which represented a median annual change of 2.5%[11]. Although symptom severity cannot be correlated directly with prostate volume, having a large prostate volume is a risk factor for the development of LUTS. That is, larger prostates are associated with increased risks of urinary retention, increased future need for surgery and clinical progression of BPH[12].

The incidence of LUTS also increases with age. For example, a prospective study examined the incidence and progression of LUTS in men enrolled in the

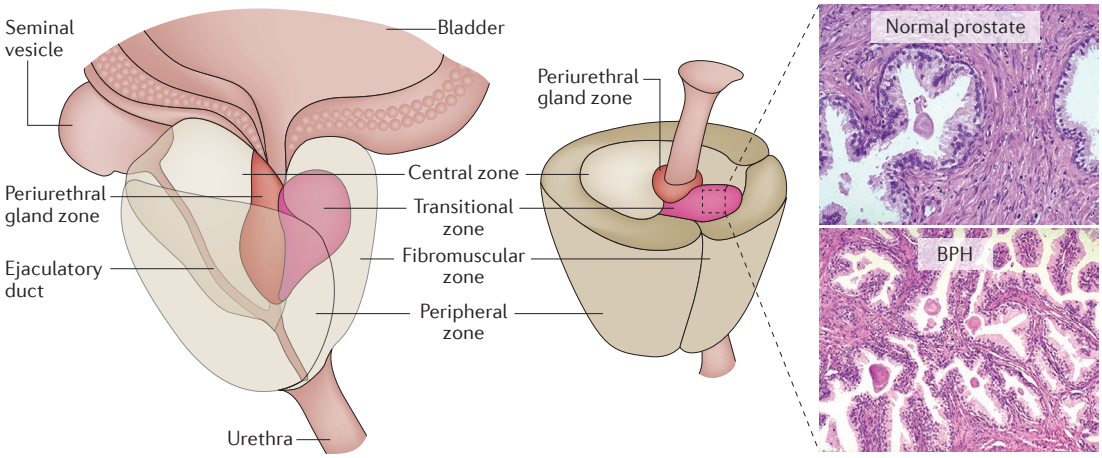

Figure 1 | **BPH.** The commonly used concept of zonal anatomy of the prostate was first proposed in 1968 by McNeal[144]. He proposed that the prostate has four distinct regions: the non-glandular anterior fibromuscular zone (or stroma) and the glandular peripheral, central and transitional zones. Later work by McNeal[145] introduced the anatomical concept of the transitional zone as the principal site of benign prostatic hyperplasia (BPH). The size of the prostate remains stable until approximately 40 years of age, after which hyperplasia of the prostate gland typically develops[146]. Histological slides of both a normal prostate and BPH tissue are included. BPH typically exhibits considerable pleomorphism in terms of stromal/epithelial ratio; here, the BPH section shows proliferation of the glandular epithelial cells.

Health Professionals Follow-up Study[6]. The incidence cohort included 25,879 men who were followed up for 16 years, who had not previously had surgery to treat LUTS and had an IPSS of 0–7 on the initial questionnaire. The progression of LUTS was monitored in 9,628 men who entered the analytic group when they first achieved an IPSS of 8–14 and were deemed to have progressed if they required subsequent surgery, subsequent medication use or experienced a rise in IPSS to ≥15. Incidence and progression rates for LUTS significantly increased with age, and progression rates were higher than incidence rates[6] (FIG. 2).

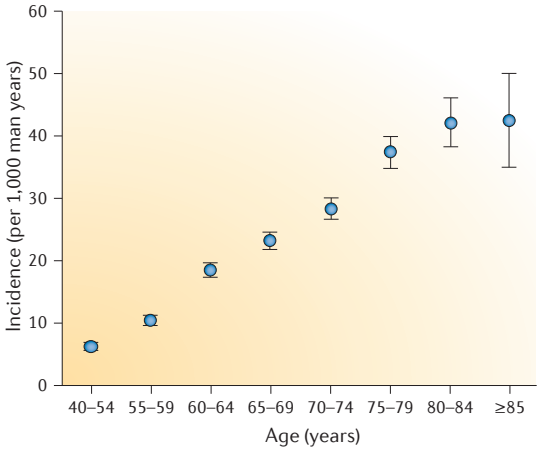

Figure 2 | **Incidence of lower urinary tract symptoms.** The term lower urinary tract symptoms (LUTS) is increasingly used to cover the symptoms caused by benign prostatic hyperplasia (BPH). Here, the incidence of LUTS in a large prospective cohort of men in the Health Professionals Follow-Up Study[6] from the United States shows progression with age. Error bars indicate standard error. Reproduced with permission from REF. 6, Elsevier.

Metabolic syndrome. Metabolic syndrome includes hypertension, dyslipidaemia, glucose intolerance, central obesity and insulin resistance with compensatory hyperinsulinaemia[13]. New findings on the development of BPH and BOO support the notion that metabolic syndrome can influence the natural course of these conditions. For example, in a study of 158 patients with LUTS secondary to BPH, significantly larger prostate glands were observed in men with individual components of metabolic syndrome[14]; these men also had faster annual prostatic growth than those without components of metabolic syndrome. Specifically, the annual prostatic growth rate was increased by 47% in men with type 2 diabetes mellitus, 17% in men with hypertension, 36% in obese men, 31% in men with low levels of HDL cholesterol and 28% in patients with high levels of fasting insulin[14]. A recent meta-analysis on the relationship between metabolic syndrome and BPH reported that patients with metabolic syndrome had significantly higher total prostate volumes than those without[15]. Further meta-regression analysis showed that the differences in prostate volume were significantly higher in obese patients, older patients and in those with low serum concentrations of HDL cholesterol. However, no difference was noted between patients with and those without metabolic syndrome for IPSS[15].

Men with LUTS also have significantly higher levels of glycosylated haemoglobin (indicating poorer control of blood glucose) than men without LUTS[9]. Having three or more components of metabolic syndrome is associated with an increased risk of having LUTS[9]. However, the effect of diabetes on LUTS and, in particular, bladder dysfunction is thought to be multifactorial[16]. Urothelial dysfunction, detrusor physiology and neuronal impairment are involved in bladder dysfunction and have been reported to occur subsequently in LUTS[17], complicating the diagnosis of LUTS that is purely related to BPH. Bladder dysfunction related to diabetes can manifest as either detrusor overactivity or poor detrusor function[16]. A similar effect on bladder function can be seen with atherosclerosis and hypoperfusion[18]. Various experimental animal studies have shown that a chronic reduction of bladder perfusion can initially cause detrusor overactivity, but if severe or chronic, bladder underactivity can also occur[18]. These recent studies outline that LUTS related to the different components of metabolic syndrome are multifactorial and cannot be purely attributed to BPH.

The evidence to date suggests that sex hormones might also contribute to the association between BPH and metabolic syndrome, but the relationship is complex and requires further investigation[19]. Indeed, men with BPH and LUTS tend to have low levels of androgens and increased levels of oestrogens; these same patterns are observed in men with metabolic syndrome[13]. One study examined whether metabolic syndrome and the associated prostatic changes are prevented by the administration of testosterone[20]. Male rabbits fed a high-fat diet for 12 weeks all developed hypogonadism and clinical features of metabolic syndrome; fibrosis, hypoxia and inflammation in the prostates were also evident. A subset of these rabbits was supplemented with testosterone, which normalized the prostatic changes. The data also showed that testosterone played some part in protecting rabbit prostates from metabolic syndrome-induced hypoxia, fibrosis and inflammation[20]. A study by the same authors[21] looking at BPH specimens from 244 men showed that fat (namely, reduced levels of HDL cholesterol and increased levels of triglycerides) and increased levels of insulin could increase inflammation in BPH and that testosterone counteracts lipid-induced and insulin-induced prostatic alterations.

Obesity. Increased levels of adipose tissue have been shown to be associated with greater prostate volume[22,23]. The effect of obesity on the risk of symptomatic BPH was assessed in 5,667 men enrolled in the placebo arm of the Prostate Cancer Prevention Trial[24]. Over a period of 7 years, participants were assessed annually with their weight and body circumferences measured and also had their LUTS evaluated using the IPSS questionnaire. In the study, 'total BPH' was defined as receipt of treatment or report of two IPSS values of >14 and 'severe BPH' was defined as receipt of treatment or

Box 1 | **Predictors of BPH progression**

Baseline characteristics

- Age >60 years
- Prostate volume of >30 ml
- Prostate-specific antigen level of >1.4 ng per ml
- IPSS of >7
- Qmax of <12 ml per second
- PVR volume of >50 ml

Dynamic characteristics

- Increasing IPSS
- Increasing bother
- Previous acute urinary retention
- Increasing PVR volume
- Failure to respond to medical therapy

Complications of BPH*

- Symptom progression (17–40%)
- Acute urinary retention (1–2% per year)
- Urinary tract infection (0.1–12%)
- Bladder calculi (0.3–3.4%)
- Renal insufficiency (<2.5%)
- Haematuria

BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptom Score; PVR, postvoid residual; Qmax, maximal urinary flow rate. *The numbers in brackets refer to the proportion of patients that experience these complications.

report of two IPSS values of ≥20. Each 0.05 increase in the waist-to-hip ratio (a measure of abdominal obesity) was associated with a 10% increased risk of total BPH ($P < 0.003$) and severe BPH ($P < 0.02$)[24]. In addition, another study of 422 men enrolled in the Baltimore Longitudinal Study of Aging examined metabolic factors associated with BPH[25]. Compared with men of normal weight (body mass index: <25 kg per m^2), the age-adjusted odds ratio for prostate enlargement for overweight men (body mass index: 25–29.9 kg per m^2) was 1.41 (95% CI: 0.84–2.37), for obese men (body mass index: 30–34 kg per m^2) was 1.27 (95% CI: 0.68–2.39) and for severely obese men (body mass index: ≥35 kg per m^2) was 3.52 (95% CI: 1.45–8.56) ($P = 0.01$). Furthermore, both higher fasting plasma glucose concentration and diabetes were positively associated with prostate enlargement[25].

Although the underlying physiology of the relationship between obesity and BPH has yet to be determined, a potential explanation is systemic inflammation. Obesity is one component of the metabolic syndrome, and both are associated with systemic inflammation and oxidative stress[26]. Indeed, several lines of evidence connect BPH to inflammation. For example, the NHANES III study[27] showed that higher levels of serum C-reactive protein are associated with an increased risk of LUTS. Furthermore, the presence of inflammation has been implicated as the stimulus that leads to the development of prostate cancer and it is, therefore, assumed that BPH might represent a non-malignant pathway that is promoted by oxidative stress and inflammatory mediators[13].

Diet. Like many other risk factors, a clear correlation between diet and the development of BPH and LUTS has not been shown. However, some evidence suggests that various macronutrients and micronutrients might influence the risk of developing BPH and LUTS. Initially, milk and dairy products were thought to increase the risk of BPH and LUTS[28]; however, a later study has shown no association[29]. That case–control study[29] was conducted in Italy and evaluated a wide range of foods on the risk of developing BPH in 1,369 men <75 years of age who were previously surgically treated for BPH and 1,451 age-matched controls who had been admitted for various acute, non-neoplastic conditions. A significantly increased risk for BPH was shown with more-frequent consumption of cereals (odds ratio: 1.55), bread (odds ratio: 1.69), eggs (odds ratio: 1.43) and poultry (odds ratio: 1.39). By contrast, inverse associations were observed for the consumption of soup (including minestrone) (odds ratio: 0.74), legumes (odds ratio: 0.74), cooked vegetables (odds ratio: 0.66) and citrus fruits (odds ratio: 0.82)[29]. In addition, fruit might have a protective role in preventing BPH[28]. Furthermore, one review suggested that the low occurrence of BPH in Asian men, as well as in vegetarian men, can be attributed to low-fat and high-fibre diets[30].

Genetics. To date the vast majority of genetic studies in prostatic diseases have focused on prostate cancer rather than BPH. However, a recent study from China reported that variants in 2q31 and 5p15 are associated with aggressive (defined by multiple criteria) BPH[31]. Another study reported that rs103294, a single-nucleotide polymorphism of *LILRA3* (encoding leukocyte immunoglobulin-like receptor A3), which has been shown to be associated with prostate cancer risk in a Chinese population, was associated with risk of developing BPH[32]. It was also noted that individuals with risk allele 'C' of rs103294 had increased risk for BPH[32].

The genetic susceptibility of BPH has previously been demonstrated in a cohort of 909 men undergoing prostatectomy for BPH. It was reported that the first-degree relatives of men from this cohort had a fourfold increased risk of developing BPH that required surgery compared with the relatives of control men[33]. The mode of inheritance for BPH has been suggested to be autosomal dominant for certain men[34]. Furthermore, twin studies have suggested that heritability is an important determinant of disease severity in BPH, including the development of LUTS. In a study of monozygotic and dizygotic twins, heritability accounted for 82.6% of the variability in IPSS in men >50 years of age[35]. In a similar study, the concordance rates for LUTS in 1,723 twin pairs were higher in monozygotic than in dizygotic twins[36]. That study[36] suggested that 72% of the risk of high-to-moderate and severe LUTS was attributable to genetic factors.

Pathogenesis

Sex hormones. Testicular androgens are required in the prostate for the development of BPH (FIG. 3). The enzyme steroid 5α-reductase 2 (also known as 3-oxo-5α-steroid

4-dehydrogenase 2), which is bound to the nuclear membrane, converts testosterone into dihydrotestosterone (DHT), the principal androgen in the prostate accounting for 90% of total prostatic androgen. The levels of intraprostatic DHT continue to remain high with ageing[2]. The stroma and epithelium of the prostate interact via cellular signalling mechanisms mediated by DHT and DHT-dependent growth factors[37].

Despite the pathophysiological mechanism of BPH not being fully understood, animal and human studies suggest that the development of BPH involves the disruption of the DHT-supported homeostasis between cell proliferation and cell death allowing proliferative processes to predominate[38,39]. It has previously been hypothesized that DHT acts on prostate cells via endocrine, paracrine or autocrine mechanisms[38] and plays a

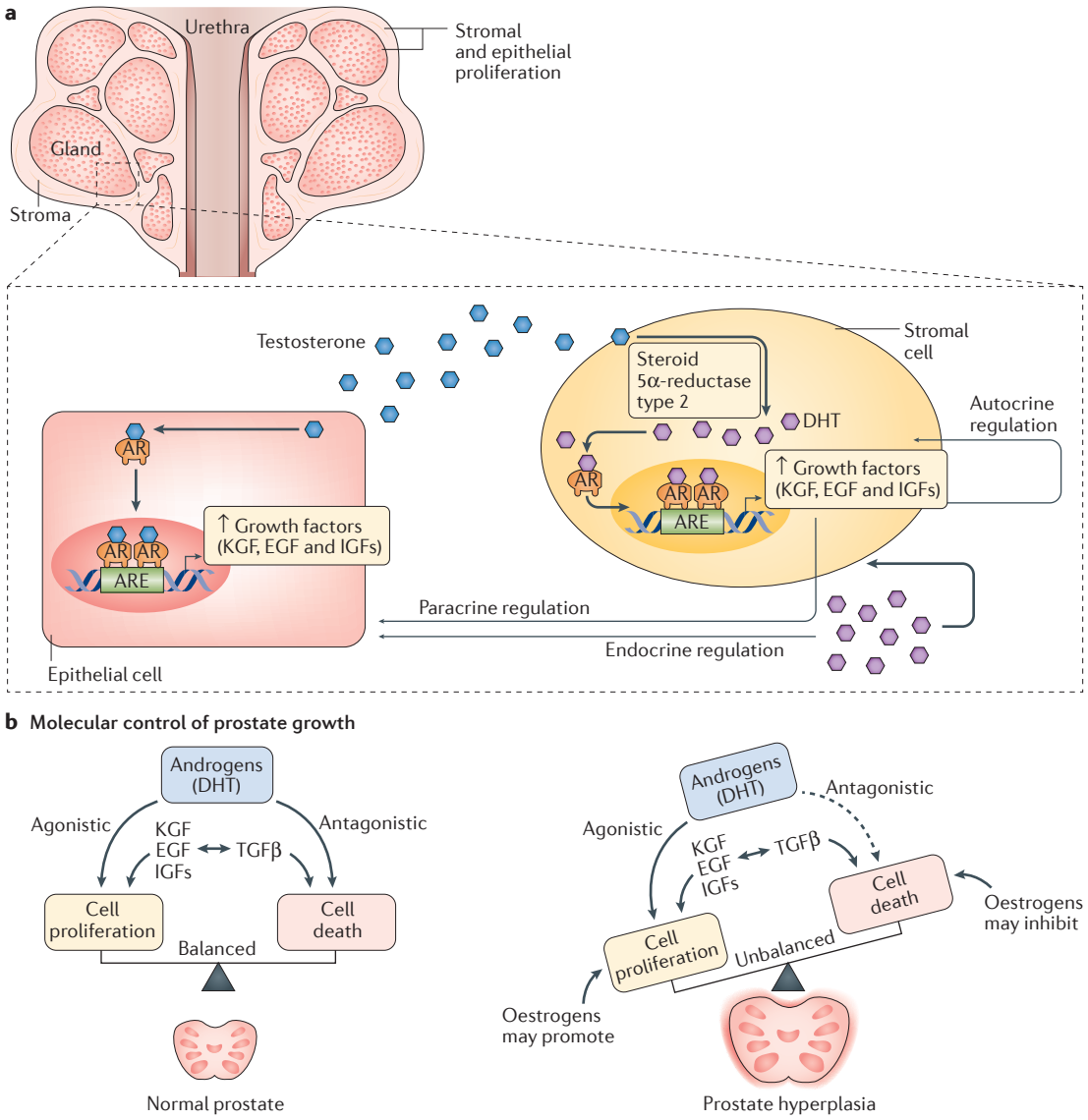

Figure 3 | **Role of testosterone in BPH. a** | Testosterone (produced in the testes) diffuses into stromal and epithelial cells of the prostate. Testosterone and its derivatives interact with the androgen receptor (AR), which upon binding translocates to the nucleus and binds to the androgen response element (ARE), promoting the expression of genes encoding various growth factors (including keratinocyte growth factor (KGF), epidermal growth factor (EGF) and insulin-like growth factors (IGFs). In stromal cells, most of the testosterone is converted to dihydrotestosterone (DHT), which then acts in an autocrine manner to promote stromal proliferation. DHT can also diffuse into the adjacent epithelial cell to act in a paracrine manner. DHT produced peripherally in the liver and the skin can also diffuse from the circulation into the prostate to act in an endocrine manner. Another site of DHT production is the basal cell (not shown). **b** | Benign prostatic hyperplasia (BPH) probably develops as a result of an imbalance between mechanisms that regulate cell death and cell proliferation. Growth factors such as KGF, EGF and IGFs, which are AR target genes, are probably involved, as is transforming growth factor-β (TGFβ), which is negatively regulated by androgens. In part **b**, the dashed arrow indicates a less antagonistic effect (than in the left panel) and the double-headed arrows indicate the bidirectional relationship of the growth factors. Part **b** from REF. 2, Nature Publishing Group.

key part in regulating the homeostasis between apoptosis and cell proliferation[40]. Growth factors stimulated by DHT, including epidermal growth factor (EGF), keratinocyte growth factor (KGF) and insulin-like growth factors (IGFs), modulate cellular proliferation in the prostate in humans[39]. The expression of transforming growth factor-β (TGFβ), which modulates apoptosis, is also influenced by DHT[41,42]. Overall, rather than increased levels or activities of these growth factors that contribute to BPH, the interactions between growth factors and steroid hormones might alter the balance of cell proliferation versus cell death to result in BPH (FIG. 3b). Indeed, in men with BPH and those without BPH, intraprostatic DHT concentrations are maintained with ageing, supporting this notion[39].

Inflammation. As described above, inflammation in men with BPH can be related to underlying metabolic syndrome and/or obesity. By contrast, an infective aetiology that triggers the development of BPH and prostatic remodelling has also been suggested, with several studies reporting the presence of heterogeneous bacterial and viral strains in BPH biopsy specimens[43]. In the inflammatory state, stromal cells in men with BPH induce the production of pro-inflammatory cytokines and chemokines[43]. The link between inflammation and BPH was first described in the 1990s, with extensive infiltration of activated T cells shown in human BPH tissues[44]. T cells are known to secrete various growth factors that promote stromal and glandular hyperplasia of the prostate.

More recently, the pathways of specific inflammatory mediators have been studied to assess their potential role in the pathogenesis of BPH. In particular, increased levels of IL-2, IL-4, IL-7, IL-17, IFNγ and their relevant receptors have been identified in BPH tissue[45–47]. IL-2, IL-7 and IFNγ have been shown to stimulate the proliferation of prostatic stromal cells *in vitro*[48]. Chronic inflammation in BPH has also been associated with focal upregulation of cyclooxygenase 2 in the glandular epithelium, generating pro-inflammatory prostaglandins, which cause prostate cell proliferation[43,49]. One study profiled tissue microarrays from 282 patients who underwent surgery for BPH[48]; the majority of the cohort were reported to have had inflammatory cells infiltrating BPH tissues. T lymphocyte markers were positive in 81% of specimens, B lymphocyte markers in 52% and macrophage markers in 82%[48]. Patients with high-grade inflammation were noted to have significantly higher IPSS values than those with low-grade inflammation (21 versus 12) and larger prostate volumes (77 ml versus 62 ml)[48].

Smooth muscle. A substantial proportion of the prostate gland is made up of smooth muscle and it is thought that its contractile properties are similar to those of other smooth muscle organs[50]. Both active and passive forces in the prostate tissue have a role in the pathophysiology of BPH. However, the factors that determine passive tone in the prostate are unclear, although the adrenergic nervous system has been reported to regulate active smooth muscle tone[51]. The most common adrenoceptor subtype present in prostate tissue is α1A, which in turn mediates active tension in human prostatic smooth muscle[52]. Stimulation of these receptors results in a dynamic increase in prostatic urethral resistance causing symptoms of outflow obstruction. Previous studies have demonstrated that the density of stromal α1A-adrenoceptors is increased in BPH tissue[53–55].

Bladder structure and function

The bladder is sensitive to conditions such as those imposed by ageing[56] or neurological diseases[57]. For example, BOO caused by BPH has been shown to affect bladder structure and function. The response of the bladder to obstruction is primarily an adaptive one; certain LUTS in men with BPH can be related to changes in bladder function as opposed to obstructive symptoms[58]. In the 1970s, it was shown that, despite surgical intervention for obstruction due to BPH, approximately one-third of men continued to have symptoms of voiding dysfunction on inflow cystometry and pressure–flow analysis of micturition[58]. Such changes include both detrusor overactivity and deceased compliance, resulting in patients experiencing symptoms of frequency and urgency as well deterioration in the strength of the urinary stream and incomplete emptying. Trabeculation (thickening) of the bladder wall is the predominant endoscopic finding in these patients and has been attributed to an increase in collagen content in the detrusor[59–61].

The mechanism for this process has been examined in experimental animal models. It has been demonstrated that, initially, BOO can lead to the development of smooth muscle hypertrophy in the bladder[62,63], which is associated with intracellular and extracellular changes in smooth muscle cells. The changes include altered expression of contractile proteins, abnormalities of calcium signalling, impaired cell–cell communication and mitochondrial dysfunction[62,63]. Ultimately, smooth muscle aberrations result in detrusor overactivity as well as impaired contractility. It has also been shown that hypertrophy in smooth muscle leads to a change in the expression of the myosin heavy chain isoform[64] and to an alteration in the expression of various thin filament-associated proteins[65,66]. This finding is in contrast to how skeletal muscle adapts to stress, in which genes encoding contractile proteins are upregulated — leading to an increase in normally organized contractile units that assemble in the muscle cell[64,67]. The experimental animal evidence to date suggests that smooth muscle cells revert to a secretory phenotype in response to prolonged obstruction, leading to an increased production of detrusor extracellular matrix (collagen)[63].

Diagnosis, screening and prevention

As BPH is a common condition affecting a considerable proportion of men, screening and prevention of the disease are not pertinent. However, the relevant investigations to diagnose the condition are discussed below.

Establishing a diagnosis

Several key diagnostic tools and investigations are used to diagnose BPH in men who present with LUTS. The European Association of Urology and the American Urological Association have published guidelines for the investigation of LUTS related to BPH[68,69].

The first and most important tool in the assessment and diagnosis of BPH is the medical history of the patient[69,70]. By taking a detailed history, one can establish potential causes and relevant comorbidities of LUTS, some of which might contribute to LUTS. A detailed medication history is also necessary, including lifestyle habits (such as fluid intake). A physical examination, including a digital rectal examination (DRE) and urinalysis, is the next step in diagnosis. Further investigations, such as uroflowmetry and measuring PVR volume, should help to confirm the presence of obstructive symptoms attributable to BPH.

Physical examination. A physical examination should be performed, particularly focusing on the urinary tract. The suprapubic region should be examined for signs of bladder distension. The penis should be examined for evidence of phimosis, meatal stenosis or abnormal penile lesions, which could account for causes of LUTS[70]. A neurological examination should also be performed on the lower limbs to rule out a possible underlying neurological condition that might result in urinary symptoms. A DRE should be performed on all patients with LUTS. A DRE facilitates the estimation of prostate volume, although less accurately than transrectal ultrasonography (TRUS; FIG. 4), and can also assess the shape and consistency of the prostate and identify the presence of firm or hard areas or nodules, which can raise suspicions of prostate cancer[71].

Symptom questionnaires. Patients are typically asked to complete a validated questionnaire — several of which are available — to objectively assess their symptoms[70]. Both the American Urological Association[69] and the European Urological Association[70] recommend the IPSS. Patients with a score of 1–7 are referred to as 'mildly symptomatic', those with scores of 8–19 as 'symptomatic' and those with scores of 20–35 as 'severely symptomatic'.

Frequency charts and bladder diaries. Other tools recommended for the diagnosis of LUTS caused by BPH include a frequency volume chart (FVC) and bladder diary[72]. For a FVC, the patient measures the volume and time of each void. A bladder diary includes additional information, such as the type of fluid consumed, the use of incontinence pads or activities performed at the time of documentation. Urine production in a 24-hour period can vary, therefore, to ensure the accurate completion of the FVC, a period of 3 days is recommended[73] as recording for >3 days increases the likelihood of non-compliance[74]. The FVC can also be useful to document if nocturia is the predominant complaint, which indicates that the patient has a different pathology causing their symptoms[75,76].

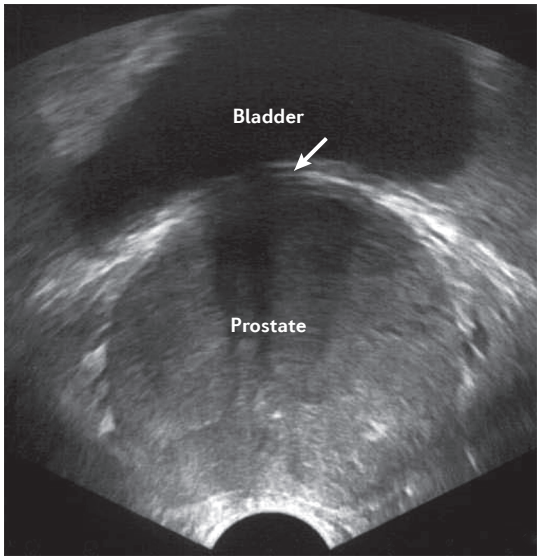

Figure 4 | **Transrectal ultrasonography.** A sonographic image of an enlarged prostate using a transrectal probe. The prostate is evident below and adjacent to the bladder. The prostate is enlarged with the upper or proximal margins 'bulging' or 'indenting' into the bladder (arrow). This enlargement will lead to bladder outflow obstruction and subsequent lower urinary tract symptoms.

Urinalysis. A urine specimen should be collected for analysis to detect material in the urine associated with metabolic disorders, renal dysfunction or urinary tract infections. The European Urological Association guidelines[68] state that, although the evidence for urinalysis is limited, general expert opinion is that the benefits of using it outweigh the costs. Hence, routine urinalysis (either dipstick analysis or microscopic evaluation) must be included in the primary evaluation of a patient presenting with LUTS[70]. The American Urological Association[77] recommends that urinalysis is performed using a dipstick test. Further examination with urinary sediment and culture is necessary if abnormal dipstick findings are noted. If haematuria is noted, appropriate investigations such as cystoscopy and imaging of the renal tract should be carried out according to published guidelines[78]. Apart from noting the presence of leukocytes and nitrite, which are probably indicators of infection, urinalysis also determines the presence of proteinuria, glycosuria and ketonuria. These findings may indicate the presence of a nephrological or an endocrinological condition and should be appropriately investigated by the relevant specialist.

Measurement of PVR volume and uroflowmetry. Measuring PVR volume in patients with symptoms of BPH can be easily performed by non-invasive transabdominal ultrasonography. The American Urological Association[77] states that determination of the PVR volume is optional in the initial diagnostic assessment and during subsequent monitoring as a safety parameter, whereas the European Urological Association guidelines[70] state that measurement of PVR volume in men with LUTS should be a routine part of the assessment.

High PVR volumes (>200–300 ml)[79] might not necessarily be attributable to obstruction caused by BPH but rather poor detrusor function[80,81]. A prospective study in 160 men 40–89 years of age compared different parameters, including PVR volume with pressure–flow studies, to detect BOO. The results showed that a PVR threshold volume of 50 ml had a positive predictive value of 63% and a negative predictive value of 52% to predict BOO[82]. Furthermore, serial measurement of PVR volume might be used to follow up patients with LUTS due to BPH and to identify patients at risk of developing urinary retention[83].

Uroflowmetry is another commonly used non-invasive assessment tool for patients with LUTS. The key parameters noted include the Qmax, flow pattern and volume voided. As Qmax is prone to within-subject variation[84,85], it is recommended that at least two flow rates should be obtained, both with a >150 ml of urine voided[77]. Reynard *et al.*[86] studied 1,271 men 45–88 years of age in 12 centres worldwide over a 2-year period, analysing symptom questionnaires, voiding diaries, uroflowmetry and pressure–flow data. They reported that a Qmax of <10 ml per second had a positive predictive value of 70% for BOO[86]. As for PVR volume, uroflowmetry is often used for monitoring treatment outcomes[70].

Prostate-specific antigen test. The level of prostate-specific antigen (PSA) has been shown to reflect prostate volume[87]. One community-based study from the Netherlands showed a 72% chance of having a prostate volume of >30 ml when the serum PSA level was in the range of 2.1–2.5 ng per ml[87]. The higher the PSA level, the greater the likelihood of an enlarged prostate — with a 69% chance of having a prostate volume of >40 ml with a PSA level of 4.1–7.0 ng per ml[87]. An analysis of the pooled placebo-controlled BPH trials also reported that the PSA level has a good predictive value for assessing prostate volume[88]. However, PSA testing should not be routine; the benefits and risks of testing should be discussed with the patient[89]. In particular, the test is used in prostate cancer diagnostics, therefore, the possibility of a need for a prostate biopsy and associated risks should be discussed. The European Association of Urology[70] recommends that PSA testing should only be performed if it can assist in decision making in patients at risk of BPH progression.

Other important clinical considerations

As a result of the obstructive symptoms caused by BPH, damage to the upper tracts (ureters) can occur — leading to hydronephrosis (in which the kidneys become swollen with urine) and possible deterioration in renal function.

Renal function. Renal function can be assessed by measuring the levels of serum creatinine or estimated glomerular filtration rate (GFR), which must be performed if renal impairment is suspected[70]. Renal impairment can be suspected on the basis of history or clinical examination. Urinary retention, hydronephrosis and renal insufficiency are more common in patients with obstructive symptoms due to BPH[90]. Approximately 11% of men with LUTS have renal insufficiency; however, diabetes mellitus or hypertension are the most likely causes of the increased creatinine concentration in this group[90]. In addition to these factors, advancing age also has a role in the loss of kidney function, with progressive decreases in GFR and renal blood flow with ageing[91]. Specifically, peak GFR (approximately 140 ml/min/1.73 m^2) is typically reached after the fourth decade of life, after which it declines by approximately 8 ml/min/1.73 m^2 each decade[92,93].

A study of renal ultrasonography in 556 consecutive patients with BPH concluded that only patients with increased levels of creatinine require ultrasonography of the kidney[94]. Men with BPH who are due to undergo surgery for the management of symptoms will have their renal function assessed because patients with renal insufficiency are at an increased risk of developing postoperative complications[95].

Urinary tract imaging. The routine use of upper tract imaging is not recommended for patients with BPH[70,77]; however, it might be necessary in patients who have a urinary tract infection, urolithiasis, renal insufficiency and/or haematuria. Patients with LUTS and haematuria should be investigated according to published guidelines[78]. The prostate can be imaged by several modalities including TRUS, CT and MRI[70]. TRUS or transabdominal ultrasonography are the most easily performed, although TRUS is more accurate for assessing prostate volume[96,97]. TRUS is also useful in determining the degree of intravesical prostatic protrusion, which is the distance between the bladder neck and the tip of the prostate median lobe. The degree of intravesical prostatic protrusion has been shown to correlate with the severity of BOO on urodynamics, with a positive predictive value of 94%[98]. Routine use of urethrocystoscopy is not required for patients with uncomplicated LUTS (which include those without a history of urinary tract infections, haematuria, bladder stones, predominantly irritative symptoms or a secondary pathology such as bladder cancer) according to the American Urological Association[77]. However, patients with a history of microscopic or macroscopic haematuria should be investigated appropriately with urethrocystoscopy as per guidelines[78]. Patients who have suspected anatomical abnormalities, such as a urethral stricture, might require urethrocystoscopy as such findings might change the type of treatment recommended[70].

Pressure–flow studies. Although not necessary in the routine assessment of patients with BPH, urodynamic pressure–flow studies might be necessary to measure the relative contribution of the bladder and the prostate to lower urinary tract dysfunction. Pressure–flow studies are the only method to determine if LUTS are due to BOO or due to an underactive detrusor. A reported 11–40% of men with LUTS have evidence of detrusor underactivity on urodynamics[99,100]. The European Association of Urology[70] recommends that men <50 years of age or those >80 years of age who are being considered for surgery should undergo pressure–flow studies. Those patients with a Qmax of >10 ml per second should also be considered for pressure–flow studies when surgical intervention is being explored. If a patient had a previous unsuccessful surgical treatment for BPH, pressure–flow

studies should be performed to assess detrusor function. In addition, when considering surgery, pressure–flow studies can be used in patients who cannot void >150 ml on uroflowmetry or who have a PVR volume of >300 ml. Patients with a history of previous radical pelvic surgery should be assessed appropriately with pressure–flow studies before intervention[101].

Management

Treatment options for men with LUTS start at watchful waiting and progress through medical to surgical interventions. For the majority of patients, the starting point on the treatment pathway will be dictated by their symptoms and degree of bother. In a minority of patients, the presence of complicating factors, such as urine retention, bladder stones or renal impairment, will necessitate a more-aggressive approach that is independent of symptoms. Determination of prostate volume can be useful before selecting the type of treatment that is suitable for a patient; a surgeon will consider prostate volume before proceeding with transurethral resection (in which the prostate tissue is removed through the urethra), enucleation or, in some cases, an open prostatectomy for patients with considerably large prostates.

Watchful waiting

Patients with mild symptoms (IPSS of ≤7) and no complicating factors or those with moderate symptoms and minimal bother can be managed with watchful waiting. Watchful waiting includes advice about lifestyle changes that can help to ameliorate or circumvent symptoms. These changes include advice about volume, type and timing of liquids consumed, avoidance of caffeine (a diuretic), abstinence of alcohol consumption in the evening and regulation of bowel movements with avoidance of constipation[70]. Over-the-counter 'decongestants' commonly used for cold and flu symptoms should also be avoided as they can exacerbate symptoms owing to their α-adrenergic agonist effects at the bladder neck causing urinary retention[102]. Although watchful watching avoids the risks and costs associated with medication and surgical procedures, patients should be warned that symptoms can worsen overtime. A longitudinal study over a period of 4 years, which involved almost 400 men, demonstrated that the cumulative clinical progression rate was 6%, 13%, 15%, 24%, 28% and 31% at 6, 12, 18, 24, 36 and 48 months, respectively; 4.9% of men developed acute urinary retention within the 48-month follow-up period[103].

Medical therapy

The aim of medical therapy is to improve symptoms, lower the risk of progression and improve QOL. There are many pharmaceutical options, with guidelines and algorithms readily available to help guide selection[68] (FIG. 5). Different categories of medical therapies are used for LUTS due to BPH, including those used to reduce BOO and to treat bladder overactivity.

As described, the pathophysiology of BOO in men with BPH has been attributed to both static (prostatic tissue) and dynamic (smooth muscle) factors. As the α1A-adrenoceptor is the predominate receptor in prostate stromal smooth muscle[104], medical therapies target this and other adrenergic receptor subtypes (namely, the α1B-adrenoceptor and the α1D-adrenoceptor). Blockade of these α1A-adrenoceptors (which are also expressed to some extent in the bladder neck) results in smooth muscle relaxation and subsequent improvement in the passage of urine. Selective α1-adrenergic antagonists, including tamsulosin and silodosin, are often regarded as first-line medical therapy for men with LUTS. Tamsulosin exhibits a modest degree of selectivity for the α1A-adrenoceptor versus the α1B-adrenoceptor, whereas it shows no selectivity for the α1A-adrenoceptor versus the α1D-adrenoceptor[105]. Silodosin shows 162/1 selectivity for α1A-adrenoceptors versus α1B-adrenoceptors[106]. Both drugs can produce rapid and considerable improvement in symptoms within 3–4 days of treatment initiation and this benefit is durable for >12 months[68]. Symptom improvement has been shown to be associated with increased Qmax, increased bladder capacity and decreased detrusor overactivity[107,108]. The main adverse effect for both drugs is relative anejaculation[109].

The nitric oxide–cyclic GMP (cGMP) pathway is another pathway involved in smooth muscle contractility. Phosphodiesterase type 5 (PDE5) negatively regulates smooth muscle contraction by hydrolysing cGMP (which is crucial to muscle relaxation via its effects on intracellular calcium levels). Accordingly, inhibition of PDE5 leads to the relaxation of smooth muscle in the bladder neck, urethra and prostate[110]. PDE5 inhibition possibly increases tissue perfusion, modulates autonomic nervous system activity and inhibits the prostatic inflammatory process, all of which lead to an improvement in voiding symptoms[111]. Changes in uroflowmetry parameters are less clear; some studies show no change upon PDE5 inhibition[112], whereas others have documented an improvement[111]. A recent meta-analysis reported that the use of PDE5 inhibition alone was associated with a significant improvement in IPSS values as well as in International Index of Erectile Function scores but not Qmax[113]. This finding supports the use of PDE5 inhibitors in men with LUTS related to BPH who might or might not also have erectile dysfunction. The lack of improvement in Qmax in these men might be attributable to the PDE5 inhibitor tadalafil, which decreases detrusor pressure without profoundly changing Qmax[114].

Another possible treatment target is DHT levels in the prostate. Steroid 5α-reductase inhibitors (such as finasteride and dutasteride) block the conversion of testosterone to DHT, resulting in shrinkage of the prostate. The benefits of these drugs take 4–6 weeks to become evident; 3–6 months of treatment are needed for maximal effect[68].

With increasing BOO, the bladder can become unstable, leading to urinary urgency and frequency. In men with LUTS and small PVR volumes (FIG. 5), the use of muscarinic receptor antagonists can provide relief. Muscarinic receptors are involved in the modulation of detrusor contractility; inhibition of these receptors reduces smooth muscle tone and relieves symptoms. Although human detrusor has been shown to contain all five types of muscarinic receptors, M2 and M3 receptors predominate (with the M2 subtype outnumbering

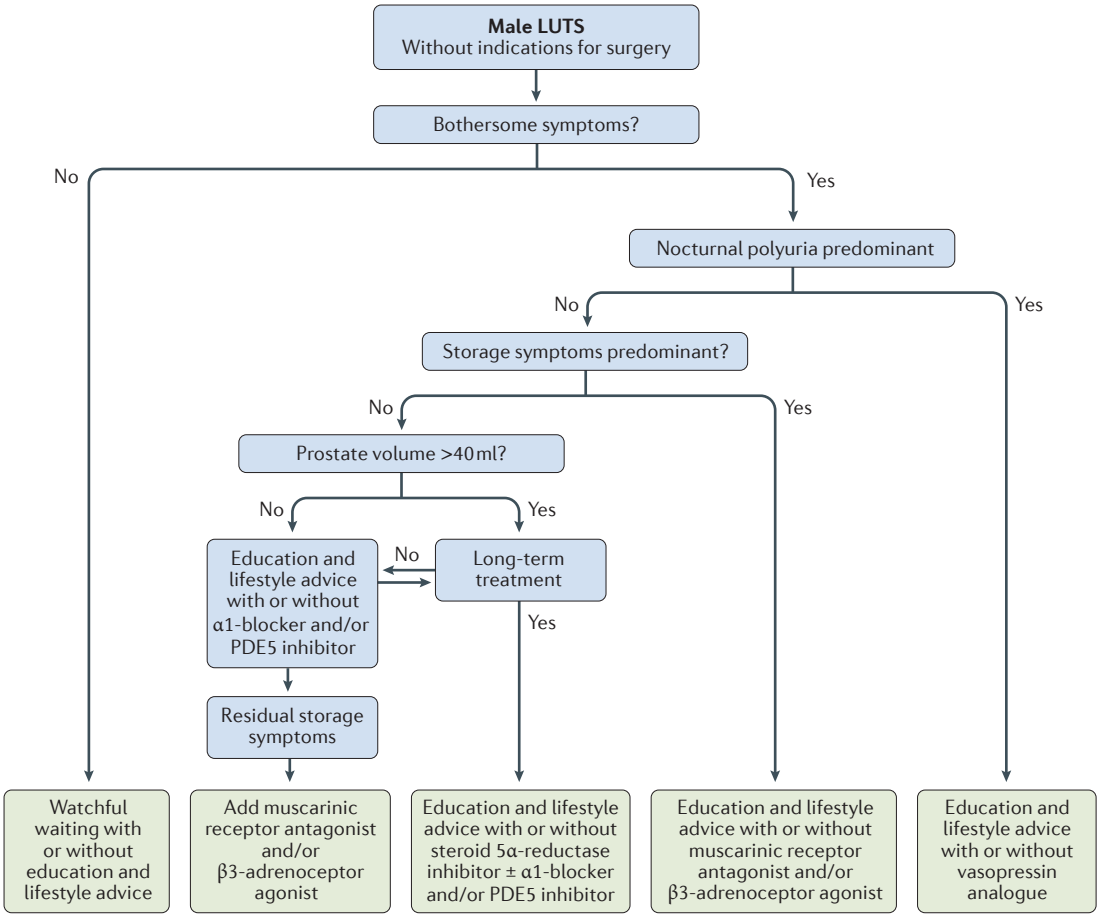

Figure 5 | **Management algorithm for men with lower urinary tract symptoms.** The large number of pharmaceutical agents available can cause confusion when selecting the best treatment option for men with benign prostatic hyperplasia and lower urinary tract symptoms (LUTS). Many treatment algorithms have been published, including from the European Association of Urology[68,70] and the American Urological Association[69]. Here, we provide a simple algorithm that captures the majority of patient and clinical findings, and reflects the consensus of the most recent (2016) European Association of Urology guidelines[68] on conservative and/or medical treatment. Patients can be observed with watchful waiting with advice on education and lifestyle or, if necessary, commenced on medication dependent on their symptoms. Those with predominant voiding symptoms can benefit from treatment with an α1-adrenergic receptor antagonist or possible combination treatment of an α1-adrenergic receptor antagonist with a steroid 5α-reductase inhibitor. Recent evidence has also suggested that treatment with a phosphodiesterase type 5 (PDE5) inhibitor might benefit those with predominant voiding symptoms. Patients with predominately storage symptoms might require an anti-muscarinic agent and/or a β3-adrenoceptor agonist. This algorithm also recommends identifying patients for whom nocturnal polyuria is the predominant symptom. In addition to conservative management, these patients might require medical treatment with a vasopressin analogue. Adapted with permission from REF. 147, Uroweb.

the M3 subtype by three to one)[115,116]; detrusor contraction is primarily controlled by M3 receptors[117]. Available agents include non-selective antagonists, such as oxybutynin, and selective antagonists, such as solifenacin and tolterodine. Solifenacin is more selective for the M3 receptor than the M2 receptor[118]. Tolterodine exhibits selectivity for the urinary bladder over salivary glands. For patients who have a poor response to anti-muscarinic drugs or who have previously experienced adverse effects with these drugs, agonism of the β3-adrenoceptor might be an alternative treatment option. Indeed, mirabegron (a β3-adrenoceptor agonist) has recently been made available for this indication in the United States and Europe[119]. Stimulation of the β3-adrenoceptor results in detrusor relaxation and relieves symptoms.

Combining agents that target different pathways can be useful (BOX 2). For example, the combination of dutasteride and tamsulosin has been shown to not only produce durable improvements in voiding symptoms but also results in a significant reduction in the risk of disease progression; in particular, the time to first episode of acute urinary retention or BPH-related surgery was significantly lower with combination therapy versus tamsulosin treatment alone[120]. Furthermore, one study showed that the combination of tamsulosin and tadalafil provided a significant improvement in IPSS, bladder storage and voiding symptoms over tamsulosin alone[114]. A meta-analysis on the use of PDE5 inhibition with α1-adrenergic antagonists showed improvements in IPSS, Qmax and the International Index of Erectile

Function score compared with α1-adrenergic antagonists alone[113]. Another meta-analysis reviewed the evidence combining α1-adrenergic antagonists with anti-muscarinic agents, concluding that combination therapy significantly improved storage symptoms compared with α1A-adrenergic antagonist therapy alone but was associated with a small risk of increased PVR volume, decreased Qmax and the development of urinary retention[121].

Surgery

Many surgical options are available for men with BPH and they can be classified into three main groups: compressing the prostate tissue, debulking of the adenoma and removal of the entire adenoma (adenectomy).

Compression. Compression procedures involve the insertion of a device that compresses the prostate laterally, widening the urethral channel. A treatment that has shown early clinical efficacy is the prostatic urethral lift known as the UroLift® system (NeoTract, Pleasanton, California, USA). This approach is relatively new and was approved by the US FDA in 2013 (REF. 122), is CE marked in Europe and is available for sale in the United States, Canada, Europe and Australia. Urethral lift is a non-ablative technique and can be performed under local anaesthesia as a day patient procedure[123]. Owing to its tissue-sparing approach, this procedure seems to be promising in minimizing the comorbidities of other BPH treatments and is able to considerably improve LUTS[124].

Furthermore, unlike ablation treatments, prostatic urethral lift has the added benefit of preserving sexual function[124]. Clinical studies conducted show statistically and clinically significant improvements in QOL and symptom scores in men with LUTS[123]. In comparison with a sham treatment, prostatic urethral lift showed an improvement in IPSS and Qmax[123]. After 2 years of follow up, prostatic urethral lift showed stability and durability with a mild adverse-effect profile — with postoperative dysuria, discomfort, urgency and haematuria resolving quickly[123]. However, research is ongoing to assess the long-term results.

Adenoma debulking. Debulking surgery involves the endoscopic removal of some of the adenomatous component that obstructs the outlet. Although transurethral resection of the prostate (TURP) is traditionally conducted with monopolar diathermy (in which a high-frequency electric current is delivered to generate heat to resect the tissue), several other options are now available (BOX 3) — including bipolar diathermy (Gyrus), laser (photoselective vaporization of the prostate (PVP)) and microwave. Bipolar diathermy has the advantage of enabling resection with saline irrigation. GreenLight laser vaporization[125], which also uses saline irrigation, has the additional advantages of being able to be performed while patients remain on anticoagulation therapy and is often performed as a day patient procedure. Microwave treatment can also be performed as a day patient procedure with minimal adverse events[126].

Despite these advances, standard monopolar diathermy TURP is still regarded as the gold-standard procedure for debulking. A meta-analysis reported that the efficacy of PVP was similar to TURP at 6 months with regards to Qmax, PVR volume and IPSS outcomes — making PVP a promising minimally invasive technique[127].

Adenectomy. The traditional approach and one of the oldest techniques to treat men with BPH and very large prostates (usually >100 ml) was open simple prostatectomy or adenectomy[68]. For this approach, the adenoma is enucleated (removed whole) off its capsule. Traditionally, adenectomy was an open surgical operation but can now be achieved with less morbidity with laser enucleation of the prostate transurethrally[128]. A meta-analysis showed that men treated with holmium laser enucleation of the prostate (HoLEP) had a better Qmax at 3 months and 12 months than those treated with TURP; PVR volume was also reduced at 6 months and 12 months and the IPSS was lower at 12 months with HoLEP. HoLEP and TURP had similar postoperative complications rates, but HoLEP had a lower blood transfusion rate[129]. However, HoLEP is regarded as a more difficult procedure for the surgeon to master and requires the appropriate technology to perform, and is not available at all centres.

Quality of life

BPH can have a considerable effect on the QOL of a patient and on determining the degree that impairment forms part of the initial evaluation of these patients and informs treatment decisions. Evaluation of QOL typically

Box 2 | **Medical therapies for BPH**

The below therapies are commonly used in the medical management of lower urinary tract symptoms in men with benign prostatic hyperplasia (BPH). Therapies can also be combined: α1-adrenergic receptor antagonists are often combined with steroid 5α-reductase inhibitors, phosphodiesterase type 5 (PDE5) inhibitors or muscarinic receptor antagonists.

α1-Adrenergic receptor antagonists
- Alfuzosin
- Doxazosin
- Silodosin
- Tamsulosin
- Terazosin

Steroid 5α-reductase inhibitors
- Dutasteride
- Finasteride

PDE5 inhibitor
- Tadalafil

Muscarinic receptor antagonists
- Solifenacin
- Tolterodine

β3-adrenoceptor agonist
- Mirabegron

involves the use of patient questionnaires. The American Urological Association Symptom Index questionnaire and the IPSS contain identical questions related to symptoms; however, the IPSS contains a specific question relating to QOL: "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" (REF. 130). From the current literature, the impact of BPH on a patient's QOL is clearly evident — with worsening symptoms resulting in an overall deterioration in QOL. From a patient's perspective, improvement of QOL and, in particular, the degree of bother they experience will probably form the main reason to seek treatment[131].

The effect that BPH has on QOL has been compared with other disease conditions. When comparing studies that used the EQ-5D™ general health questionnaire (EuroQoL), BPH had a similar influence on QOL as epilepsy requiring surgery and asthma[131]. By comparison, the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) questionnaire revealed that patients with BPH had a worse QOL in all domains except physical functioning than patients with chronic obstructive pulmonary disease[131]. The effect of BPH on QOL has also been reported in a multicentre observational study that included >800 patients 50–80 years of age. The study sought to investigate the relationship between different lifestyle factors, prostate-related variables and symptom severity[132]. It was concluded that the strongest association between the IPSS and all variables assessed was found for QOL. That is, patients with more-severe symptoms that affected activities of daily living ultimately had a lower QOL[132]. The partners of patients with BPH have also been shown to be affected; one survey of 50 couples for whom the male partner had BPH revealed that the female partner experienced morbidities such as sleep disturbance, disruption to social life and an increasing psychological burden[133]. Another study demonstrated that the degree of morbidity experienced by the partner was related to the severity of the patient's symptoms[134].

Various studies have supplemented the IPSS with questionnaires to demonstrate the effect of BPH on a patient's QOL. For example, the BPH Impact Index comprises four questions and was developed to assess the negative effect of BPH on health status as well as the effect on everyday life and daily activities[8]. It has been used in conjunction with the American Urological Association Symptom Index to show the improvement in QOL with medical treatment for BPH[135]. Hunter *et al.*[136] used the general SF-36 to demonstrate a deterioration in QOL as well as in general health status with increasing LUTS. In that study[136], 217 men ≥55 years of age with LUTS were surveyed; between 9% and 49% of those with moderate or severe urinary symptoms reported interference with some of their daily activities. The SF-36 has also been used to demonstrate that patients with severe symptoms awaiting surgical treatment for BPH experience a poor health-related QOL[137]. In a longitudinal observational trial, Thomas *et al.*[138] quantitatively compared the impact of admission for an episode of acute urinary retention with that of elective surgery for BPH and/or an emergency presentation to hospital with renal colic. Using various QOL instruments and parameters, acute urinary retention was deemed to impose high pain scores and substantial economic burden on patients[138].

Box 3 | **Surgical therapies for BPH**

Open prostatectomy
Open prostatectomy (complete or partial removal of the prostate) can be performed with a retropubic or suprapubic approach. Retropubic prostatectomy involves enucleation (whole removal) of the prostatic adenoma through a direct incision of the anterior prostatic capsule; the suprapubic approach involves enucleation through an extraperitoneal incision of the lower anterior bladder wall. Traditionally, these methods are used for large (usually >100 ml) prostates.

Transurethral resection of the prostate
The traditional standard transurethral resection of the prostate (TURP) procedure involves an electrical current 'loop' attached to a resectoscope used to cut the transitional zone of the prostate into small 'chips', which are then suctioned out.

Transurethral incision of the prostate
Using similar equipment to a standard TURP, transurethral incision of the prostate (TUIP) involves using an electrical current 'knife' to incise the prostate and widen the bladder outlet without removing any tissue.

Transurethral vaporization of the prostate
Instead of using an electrical current loop as in TURP, transurethral vaporization of the prostate (TUVP) uses a ball or a button to heat the prostate tissue so that it is reduced to vapour.

Photoselective vaporization of the prostate
Using a transurethral approach, the GreenLight™ laser (American Medical Systems, Minnetonka, Minnesota, USA) is used to vaporize excess prostate tissue to widen the urinary channel.

Transurethral holmium laser ablation of the prostate
Similar to photoselective vaporization of the prostate, transurethral holmium laser ablation of the prostate (HoLAP) uses a holmium laser to vaporize the excess prostate tissue.

Holmium laser resection of the prostate
Holmium laser resection of the prostate (HoLRP) also uses a holmium laser to precisely resect large pieces of the prostate. The laser is then used to cut the resected tissue into smaller pieces before their removal.

Transurethral holmium laser enucleation of the prostate
Using transurethral holmium laser enucleation of the prostate (HoLEP), the intact prostatic lobes obstructing the urethra are cut. Another instrument, a morcellator, is then used to chop the prostate tissue into small pieces that can be easily removed.

Prostatic urethral lift
A minimally invasive treatment that involves the placement of small implants that hold the enlarged prostate tissue out of the way, therefore, reducing the obstruction to flow.

BPH, benign prostatic hyperplasia.

Outlook

Although recent trials have looked into the effects of different combinations of existing medications to better manage BPH (and LUTS), surgery is arguably the most exciting developing area in BPH. Hitherto, the gold-standard treatment for BPH has been TURP[139]. Indeed, although TURP is the most investigated procedure and has been practiced for many decades, complication rates for patients following this intervention can be as high as 20% depending on the definition of complication[139]. To reduce the morbidity of TURP and maintain its benefits, other transurethral procedures are being developed to manage BPH by way of resection, compression, ablation or enucleation[139].

One of these procedures is Aquablation (PROCEPT BioRobotics®, Redwood Shores, California, USA), which is a novel technology that incorporates the use of a high-pressure water jet and surgical laser to treat BPH[139]. The water jet ablates the prostate tissue under mechanical control and high energy is delivered to the desired area to produce "an energy efficient and precise surface haemostasis" to ablate the tissue[139]. This technique enables physicians to preserve blood vessels and the prostate capsule while removing the obstructing tissue. Aquablation might be feasible with varying prostate sizes[139]. Faber *et al.*[139] tested the efficacy and safety of aquablation in a canine model; following treatment, a 6-week postoperative histological evaluation revealed no major change in cellular architecture, implying its safety for the prostatic urethra. In humans, a single-centre, prospective, non-randomized trial involving 15 men who reported having moderate-to-severe LUTS showed no adverse events for aquablation[140]. In that study[140], the mean age of the patients was 73 years (range: 59–86 years) and the mean prostate volume was 54 ml (range: 27–85 ml). Importantly, the mean procedure time was 48 minutes with the actual aquablation treatment used for 8 minutes. A significant reduction in IPSS was noted — from 23.1 at baseline to 8.6 at 6 months follow-up. Qmax also improved significantly from 8.6 ml per second at baseline to 18.6 ml per second at 6 months[140]. Furthermore, patients experienced a 31% reduction in prostate size at 6 months. Notably, the authors reported no cases of urinary incontinence or erectile dysfunction. These preliminary results demonstrate that aquablation is safe and comparable with existing surgical treatments.

Another therapy under development is prostate artery embolization (PAE), which is a minimally invasive procedure in which the inferior vesicle artery is ablated in a superselective manner using hydrophilic microcatheters and polyvinyl alcohol[141]. Polyvinyl alcohol consists of microparticles that, when released into the blood vessels, cause occlusion of the vascular bed, leading to ischaemic necrosis of the prostate. In turn, the prostate shrinks and LUTS are improved[142]. In a study of 255 men with BPH who underwent PAE, 98% technical success (that is, embolization of the prostatic artery) was achieved with bilateral PAE in 82% of patients, with unilateral PAE achieved in 18% of cases owing to tortuosity and atherosclerotic changes of the iliac arteries preventing bilateral embolization[143]. Clinical success was deemed as an IPSS reduction of at least 25% of the total score (<18 points overall) and a reduction of ≥1 point (or ≤3 points overall) in the QOL domains of the IPSS. Patients were followed up for a mean of 10 months (range: 1–36 months) with clinical success rates of 80.7%, 75.2% and 72% at 3, 12 and 36 months, respectively[143].

These treatments only highlight that a select few options are coming along the pipeline for the treatment of individuals with BPH. Time will tell which patients will benefit from these therapies as well as the durability of the different treatments.

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Author contributions
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