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Review

Pathophysiology of clinical benign prostatic hyperplasia



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Abstract A disease can be defined as an abnormal anatomy (pathology) and/or function (physiology) that may cause harm to the body. In clinical benign prostatic hyperplasia (BPH), the abnormal anatomy is prostate adenoma/adenomata, resulting in a varying degree of benign prostatic obstruction (BPO) that may cause harm to the bladder or kidneys. Thus clinical BPH can be defined as such and be differentiated from other less common causes of male lower urinary tract symptoms. Diagnosis of the prostate adenoma/adenomata (PA) can be made by measuring the intravesical prostatic protrusion (IPP) and prostate volume (PV) with non-invasive transabdominal ultrasound (TAUS) in the clinic. The PA can then be graded (phenotyped) according to IPP and PV. Multiple studies have shown a good correlation between IPP/PV and BPO, and therefore progression of the disease. The severity of the disease clinical BPH can be classified into stages from stage I to IV for further management. The classification is based on the effect of BPO on bladder functions, namely that of emptying, normal if post-void residual urine (PVRU) < 100 mL; and bladder storage, normal if maximum voided volume (MVV) > 100 mL. The effect of BPO on quality of life (QoL) can be assessed by the QoL index, with a score ≥ 3 considered bothersome. Patients with no significant obstruction and no bothersome symptoms would be stage I; those with no significant obstruction but has bothersome symptoms (QoL ≥ 3) would be stage II; those with significant obstruction (PVRU > 100 mL; or MVV < 100 mL), irrespective of symptoms would be stage III; those with complications of the disease clinical BPH such as retention of urine, bladder stones, recurrent bleeding or infections would be stage IV. After assessment, further management can then be individualised. A low grade and stage disease can generally be watched (active surveillance) while a high grade and stage disease would need more invasive management with an option for surgery. The final decision making would take into account the patient's age, co-morbidity, social economic

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background and his preferences/values. Proper understanding of pathophysiology of clinical BPH would lead to better selection of patients for individualised and personalised care and more cost effective management.

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1. Introduction

A disease is an abnormal pathophysiological state or condition that may cause harm to the organism. It is important to distinguish between the cause and consequence of a disease. For example, diabetes mellitus is caused by an abnormal insulin metabolism which results in an elevated postprandial sugar level. High blood sugar level by itself is not diabetes mellitus. Similarly in clinical benign prostatic hyperplasia (BPH), benign prostatic obstruction (BPO) [1] is the consequence rather than cause of the disease. What then is the abnormal anatomy (pathology) that causes abnormal functions (physiology) in clinical BPH and may eventually harm the patient? Our study showed that prostate adenoma/adenomata (PA) is the cause of clinical BPH, resulting in a varying degree of obstruction with or without symptoms [2]. If the obstruction is severe, it may eventually harm the bladder and the kidneys. Intervention would therefore be needed to prevent this.

In clinical practice, the need for intervention depends on whether the disease is: first, life threatening; second, affecting the functions of organs; and last, affecting the patient's quality of life (QoL), in order of priority. Though clinical BPH is seldom life threatening, severe obstruction leading to hydronephrosis, and infection in an immunocompromised patient may cause death. More commonly, bladder functions may be affected leading to poor voiding and back pressure changes in the kidneys, compromising their functions. When making the final decision on treatment modality (watchful waiting, medical or surgical intervention) for a particular patient, age, co-morbidity, social economic background, and patient preferences or values should also be considered. Thus experience and an understanding of the pathophysiology of the disease are important in reaching a final balanced clinical decision for personalised care of the individual patient [3].

2. Definition of clinical BPH

On histopathology, BPH is nodular hyperplasia and not diffuse hyperplasia, affecting the transitional and periurethral zones of the prostate [4]. Often the hyperplasia is multinodular, coalescing to form adenomata. Adenomata from the transitional zone form the lateral lobes while adenomata from the periurethral zone form the middle lobe in clinical disease [5]. BPH gives rise to obstruction by compression as well as by distortion of the bladder outlet. In flow dynamics, distortion causes more obstruction than compression. Using the analogy of a garden hose, it is easier to stop the water flow by distorting (bending) rather than

compressing the hose. At the prostate, the lateral lobes tend to compress the bladder outlet while the middle lobe tends to distort it.

A third factor which may play a part in bladder outlet obstruction (BOO) is the decrease in elastic system fibers and collagen in the prostatic urethra [6]. There may also be an increase in chondroitin sulphate proteoglycans in BPH [7]. These may affect the plasticity of the prostatic urethra, influencing the distortion and compression by the PA. This may explain why in some older patients, the prostate can grow to a large size with minimal obstruction, possibly because the prostatic urethra becomes more rigid or less elastic and therefore more difficult to bend or compress.

The degree of BOO depends more on where the PA is sited than its size. Adenoma sited at the bladder neck in the periurethral zone forming the middle lobe would distort the bladder outlet and cause severe obstruction even if small, while adenoma sited deep in the transitional zone forming the lateral lobes would need to grow to a much bigger size before causing compression of the prostatic urethra and obstruction (Figs. 1 and 2).

BPH progresses slowly and patients may accommodate to it, not having symptoms even though they may have severe obstruction. Thus clinical BPH can be defined as PA irrespective of size, causing a varying degree of obstruction, with or without symptoms [2].

3. Diagnosing clinical BPH

In a normal male, the bladder neck is inverted with the prostate less than 20 g and peak flow rate above 20 mL/s [2]; but in a patient with clinical BPH, the bladder neck is distorted by the PA, and where the PA is sited gives rise to its shape. This can be detected by measuring the intravesical prostatic protrusion (IPP) on transabdominal ultrasound (TAUS). IPP can be measured from the tip of the protruding prostate to the base of the gland at the circumference of the bladder, seen in the sagittal plane of the TAUS [8,9] (Fig. 3). It can be considered as a simple measure of the prostate shape, and can be graded accordingly: grade 1, ≤ 5 mm; grade 2, $>5-10$ mm; and grade 3, >10 mm [9]. IPP has 100% specificity and 100% positive predictive value in the diagnosis of clinical BPH [2]. Thus clinical BPH can be diagnosed with confidence by measuring IPP with TAUS and uroflowmetry [10].

In the family physician clinic, clinical BPH can be suspected on digital rectal examination if the prostate is more than 2 finger breadths and has a smooth firm consistency, and the patient has a poor average flow rate [11].

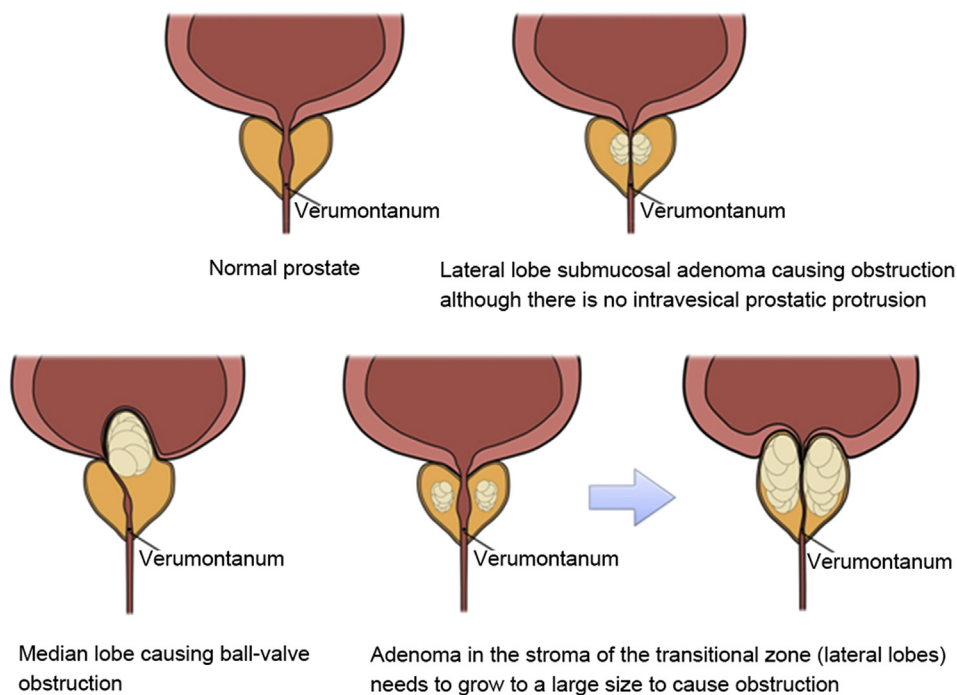


Figure 1 Bladder outlet obstruction depends on the site of the adenoma at the prostate.

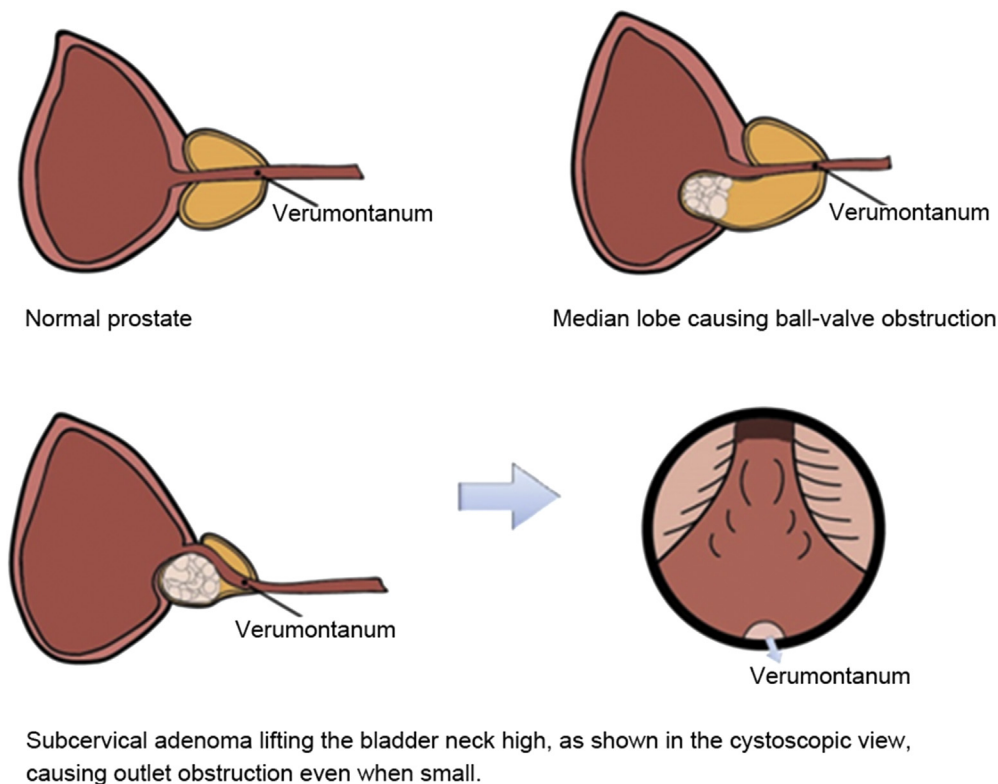


Figure 2 Sagittal view of the prostate adenoma.

4. Phenotyping clinical BPH for prognostication

The prostate adenoma can be phenotyped according to IPP and prostate volume (PV).

It has been shown and validated that the greater the IPP, the greater the obstruction and thus the more likely that the disease will progress [12,13]. IPP has also been shown to predict failure in trial off catheter in patients with acute

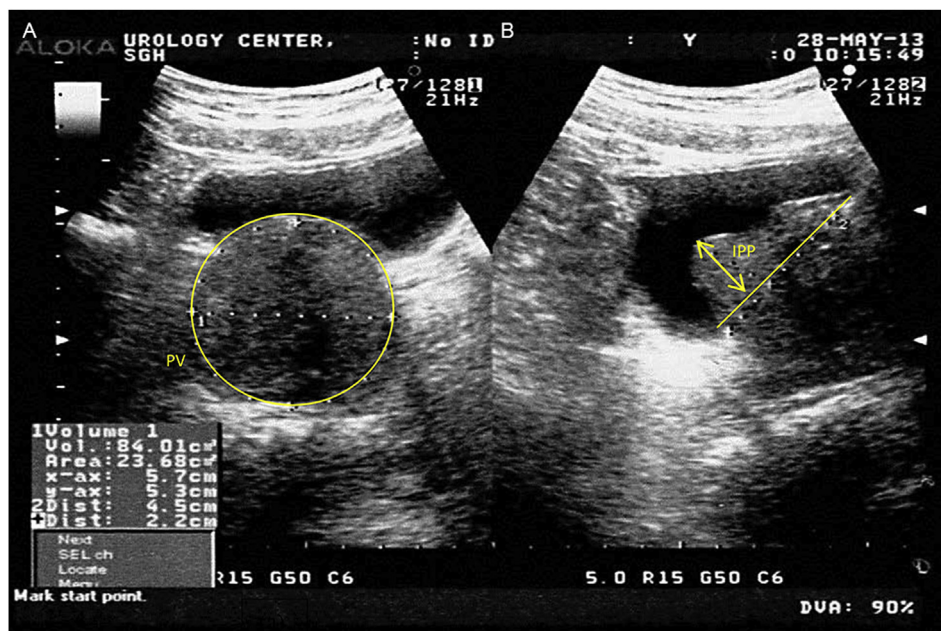


Figure 3 Transabdominal ultrasound (TAUS) measurements of prostate volume (PV) and intravesical prostatic protrusion (IPP). (A) Transverse view, (B) Sagittal view. PV is measured in grams by tracing the area of prostate in the transverse view to obtain the estimated size of the prostate using the ellipsoid formula and classified as follows: Grade a, ≤ 20 g; b, >20 – 40 g; c, >40 g. In the sagittal view, the IPP is measured in millimetres from the innermost protruding tip of the prostate adenoma to the base of the prostate at the circumference of the bladder and classified accordingly: Grade 1, ≤ 5 mm; 2, >5 – 10 mm; 3, >10 mm [9]. This ultrasound image is from a 62-year-old patient who first presented with raised prostate specific antigen (PSA) of $7.7 \mu\text{g/L}$ with no lower urinary tract symptoms at age 53 years. He had three negative transrectal biopsies. In spite of medical treatment, he eventually had transurethral enucleating and resection of the prostate adenomata weighing 54 g (TUERP), for episodes of urinary infection and deteriorating symptoms. He recovered well, had benign prostatic hyperplasia on histology, and a postoperative PSA level of $1 \mu\text{g/L}$.

retention of urine, with 36% of grade 1 and 67% of grade 3 IPP patients failing trial off catheter [9]. This was validated in another study in patients with acute urinary retention treated with Alfuzosin [14]. IPP was also found to be a better predictor of failure in trial off catheter than PV in patients with acute retention of urine in another study done in Edinburgh, UK [15].

PV measured on TAUS can be graded as follows: a, ≤ 20 g; b, >20 – 40 g; and c, >40 g. Thus the PA can be graded according to both prostate shape (IPP) and PV into nine categories, namely 1a, 1b, 1c; 2a, 2b, 2c; 3a, 3b, and 3c. IPP can be due to PA in the periurethral zone forming the middle lobe and/or PA in the transitional zone forming the lateral lobes. In general, IPP increases with PV but there can be important exceptions, namely the small prostates arising from the periurethral zone only. Our study showed that patients with grade 3a prostate (high IPP but small PV) were most likely to be obstructed (at 82%), with obstruction defined as a peak flow rate of less than 10 mL/s [16]. These are patients with a classical median lobe causing ball-valve obstruction. Patients with grade 1a prostate were least likely to be obstructed at 21% while 64% of patients with grade 3c prostate had obstruction. This suggests that prostate shape (IPP) is more important than PV, as distortion by IPP causes more obstruction than compression by large lateral lobes in the prostate.

This classification is of clinical importance in that patients with grade 3a PA would be better treated with surgery, while medications would be more suited for patients with grade 1c PA. Moreover it is not advisable to prescribe anti-muscarinic drugs to patients with a high grade IPP in view of the high probability of aggravating the obstruction and bladder emptying. There is also evidence to show that patients with grade 3 IPP respond less well to α blockers than those with grade 1 IPP [17].

5. Classifying severity of clinical BPH

For cost effective treatment, the basic principle is to treat patients according to the severity of the disease. The PA causes a varying degree of obstruction with or without symptoms. The severity of clinical BPH can be classified according to obstruction and symptoms, with obstruction being more important than symptoms as significant obstruction would lead to organ dysfunctions, first the bladder and then the kidneys. The two main functions of the bladder are that of emptying and storage. Impaired emptying function leads to persistent post-void residual urine (PVRU) whereas a small maximum voided volume (MVV) is observed when the storage function is affected.

A PVRU of more than 100 mL has been shown to be predictive of subsequent acute urinary retention. In a

pooled analysis of 11 controlled studies with Alfuzosin ($n = 953$), 6 out of 7 patients who subsequently developed acute urinary retention (AUR) had a PVRU of more than 100 mL at initial evaluation [18].

Therefore patients with a persistent PVRU of more than 100 mL can be classified as being significantly obstructed. In addition, patients with frequency and urgency symptoms with a MVV of less than 100 mL might have significant obstruction.

International Prostate Symptom Score (IPSS) has a poor correlation to obstruction and thus it should not be used alone for further management of male lower urinary tract symptoms (LUTS)/BPH. Rosier et al. [19], in a study of 717 patients, found that among patients with an IPSS of 0–7 (mild symptoms), 49% were not obstructed and 51% were obstructed. Of those with an IPSS of 20–35 (severe symptoms), 63% were obstructed but 37% were not obstructed. Various other studies have shown that the severity of the symptoms often does not correlate well with the presence of obstruction [20–22]. Using only IPSS/QoL to guide treatment could result in over- or under-treatment. The QoL is also more important than IPSS. Compared to a retiree who wakes up 4 times at night due to nocturia, a young executive who has nocturia twice a night might find his symptoms more bothersome and need treatment.

The severity of clinical BPH can therefore be classified according to whether there is significant obstruction (indicated by persistent PVRU > 100 mL or MVV < 100 mL) and bothersome symptoms (QoL ≥ 3), as follows:

- Stage I: Patients have no significant obstruction and no bothersome symptoms. They can generally be watched and counselled.
- Stage II: Patients have no significant obstruction but have bothersome symptoms. They can generally be treated symptomatically with medications such as α blockers.
- Stage III: Patients have significant obstruction irrespective of symptoms. They would need more aggressive treatment such as 5- α reductase inhibitors and be offered the option for surgical intervention.
- Stage IV: Patients have complications of clinical BPH such as retention of urine (acute or chronic), bladder stones, recurrent bleeding or recurrent urinary tract infection. They would generally need surgical intervention [23].

6. Clinical relevance

Similar to the grading and staging of malignant disease like prostate cancer and bladder cancer, generally there is good concordance between the grade of the PA and the stage of the disease clinical BPH. Patients with grade 1 or 2 IPP are associated with the lower stages I and II disease, whereas those with high stage III disease are mainly due to high grade 3 IPP. In our study of 408 patients with male LUTS/BPH, 44 patients were in stage III; 36 of them had IPP grade 3 and only seven had grade 1 or 2 IPP. Thus there was discordance in 16% (7/44) of the patients. If invasive procedure is considered for further management, only these patients would need more invasive assessment such as urodynamic studies or flexible cystoscopy [24]. This is to

assess the possibility of detrusor underactivity as a possible cause of high PVRU with low grade IPP.

Using the above grading and staging system for phenotyping and classification of severity of clinical BPH, majority of the patients (59%) in the above study of 408 patients were watched and counselled, 32% were managed medically while 9% required surgical intervention [24]. This is in agreement with a study done in 1981, on the natural history of prostatism (old term for male LUTS/BPH) which showed that of 107 patients followed up for 5 years, 32% improved, 52% remained stable and only 16% deteriorated of whom 9% required surgery [25]. What is significant now is that measuring IPP allows us to predict more accurately at initial evaluation which subset of patients would deteriorate and which would probably remain stable or improve.

The above definition of clinical BPH, phenotyping and classification of the severity of the disease BPH, are in line with the recommendations of the American Urological Association guidelines (2010) on future directions in clinical research on male LUTS/BPH, a common clinical problem worldwide [26].

7. Conclusion

The pathology of clinical BPH is essentially PA causing physiological changes: a varying degree of bladder outlet obstruction, with or without LUTS. Clinical BPH can be differentiated from other causes of male LUTS with non-invasive TAUS and uroflowmetry in the clinic. With IPP, PVRU and IPSS/QoL, the disease can be phenotyped and classified according to severity for more cost effective management.

Conflicts of interest

The author declares no conflict of interest.

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